Improvement of Ischemic Non-Healing Wounds Following Hyperoxygenation: The Experience at Rambam-Elisha Hyperbaric Center in Israel, 1998–2007

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ABSTRACT: **Background:** Wounds of the lower extremities are a significant public health problem, being severe and costly to treat. Adjunctive treatment with hyperbaric oxygenation (HBOT) has proven to be a useful and cost-effective means of treating ischemic wounds, mainly in diabetic patients.

Objectives: To describe patients with ischemic wounds treated at the Rambam and Elisha Hyperbaric Medical Center and their wound improvement following HBOT.

Methods: We conducted a retrospective cohort study of all patients (N=385) treated in the center during 1998–2007 for ischemic non-healing wounds in the lower extremities.

Results: The mean age of the patients was 61.9 years (SD 13.97). Most of them were diabetic (69.6%) and male (68.8%). Half of the subjects had a wound for more than 3 months prior to undergoing pre-HBOT transcutaneous oximetry ($TcPO_2$) testing. Most of the wounds were classified as Wagner degree 1 or 2 (39.1% and 46.2% respectively). The median number of treatments per patient was 29. Only 63.1% of patients had continuous treatments. Approximately 20% of patients experienced mild side effects. An improvement occurred in 282 patients (77.7%) following HBOT: 15.2% fully recovered, 42.7% showed a significant improvement (and were expected to heal spontaneously), and 19.8% a slight improvement.

Conclusions: HBOT can benefit the treatment of non-healing ischemic wounds (especially when aided by pretreatment $TcPO_2$ evaluation; data not shown). Our experience shows that this procedure is safe and contributes to wound healing.

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KEY WORDS: hyperbaric oxygenation, ischemic wound, non-healing wound, diabetic wound, transcutaneous oximetry

Wounds in the lower extremities represent a significant problem, with implications for both the individual and the health care system [1]. Prevalence rates among western elderly populations (aged > 65) are increasing, and range from 3% to 5% [2]. In 1998, the long-term cost of treating a patient with an ischemic wound was $27,203. The estimated resultant rates of amputation – a procedure associated with high mortality – ranged from 2.8 to 43.9 per 100,000/year [1].

Hyperbaric oxygenation treatment involves the use of 100% oxygen breathed in a chamber with ambient pressure above 1 atmosphere absolute (ATA). The beneficial effects of HBOT include intermittent correction of wound hypoxia, reduction of tissue edema, enhanced host immune response, improved wound metabolism, prevention of reperfusion injury, and induction of cytokine and cytokine receptors [3]. Since tissue hypoxia is the key feature in many patients with non-healing wounds, the marked increase in tissue oxygen gradient from blood to ischemic tissue under hyperbaric oxygen conditions is the main mechanism whereby HBOT can improve cellular oxygenation. This occurs even when the tissue perfusion rate is low. Thus, HBOT can make a major contribution to the treatment of non-healing wounds. Detailed descriptions of HBOT and its rationale for treating non-healing wounds have been reported previously [4,5].

Complications of HBOT are minor when trained personnel are involved; they include ear barotrauma, transient myopia and claustrophobia. Central nervous system oxygen toxicity is very rare. The only absolute contraindication for HBOT is tension pneumothorax [3].

Adjunctive HBOT has been demonstrated to be useful and cost-effective mainly in diabetic patients [6,7]. It has been recommended by health agencies and organizations worldwide and has been included in Israel's 'basket of health services' since 1986 [8,9]. The present article describes the patients with ischemic wounds who were treated at the Rambam and Elisha Hyperbaric Medical Center and their wound improvement following HBOT.

HBOT = hyperbaric oxygenation treatment

PATIENTS AND METHODS

We conducted a retrospective cohort study at Rambam and Elisha Hospitals' Hyperbaric Medical Center. This center is the only facility in northern Israel that treats patients with chronic indications for HBOT. Candidates for HBOT undergo large vessel assessment, physical examination by a physician at the center, and an assessment of wound ischemia by transcutaneous oximetry. Patients receive daily HBO treatments 5 days a week. Each treatment takes 90 minutes after which a nurse dresses the wound. The number of HBO treatments is determined for each patient individually based on clinical findings and progress, usually after 15 treatments. In addition, patients are examined by a plastic surgeon once a week and the wounds are photographed and sketched.

The study group comprised all 385 patients with lower extremity ischemic non-healing wounds who were treated in our center during a 10 year period: 1 January 1998 to 1 March 2007. The study was approved by the ethics committee of Rambam Medical Center, the largest university-affiliated hospital in northern Israel.

DATA COLLECTION AND VARIABLES DEFINITION

Data collection was based on the patients' medical and nursing records in the hyperbaric center. Records were reviewed by one of the study investigators (Y.F.I.), a nurse from the center, who used a specifically designed study questionnaire.

DEMOGRAPHIC FACTORS

Data on age, gender, ethnicity, socioeconomic status and employment status were gathered. Socioeconomic status was determined using the Israel Bureau of Statistics classification of local authority clusters [10]. Clusters 1–5 were considered low socioeconomic status, 6–7 moderate and 8–10 high. Employment status was based on whether the patient was documented as employed or not.

CLINICAL FACTORS

Clinical variables included documentation of diabetes, its duration (long/short) and treatment (diet/medication/insulin). The duration was considered short if the patient had diabetes for less than 5 years or if no complications were documented. In cases where a patient received more than one type of diabetes therapy, the more invasive one was recorded.

Additional factors were presence or absence of neuropathy, hypertension, heart disease, previous stroke, hyperlipidemia, peripheral artery disease, kidney disease, hypercoagulability, anemia, pain and mobility. Smoking status was categorized as never smoked, formerly smoked, or currently smoked. Body mass index was calculated based on weight and height (kg/m^2).

WOUND ASSESSMENT

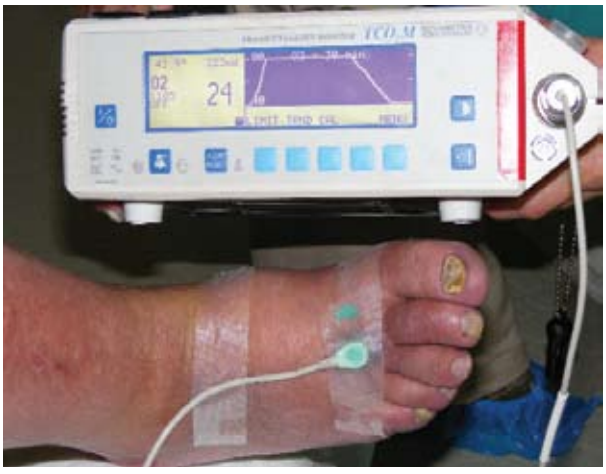
- Ischemic non-healing wound was defined as a radionecrosis wound or a wound with osteomyelitis, or if the patient had $TcPO_2$ values < 40 mmHg while breathing air at sea level. If the patient had more than one wound, the most severe one was selected.
- $TcPO_2$ was measured by a Novametrix 860 device with a singe electrode attached near the patient's wound [Figure 1]. The values were recorded in three consecutive conditions: breathing air at sea level, breathing oxygen at sea level (10 min) and breathing oxygen at 2 or 2.4 ATA (at 0, 5, 10 and 15 min after reaching that pressure).

The following wound characteristics related to the period beginning 2 weeks before the first HBOT administration and ending 1 week thereafter:

- Wound infection was noted if antibiotics were taken following signs of infection or positive culture results
- Wound osteomyelitis was defined based on the presence or suspicion of bone infection or positive biopsy, bone scan, X-ray or magnetic resonance imaging findings
- Wound appearance was classified based on the plastic surgeon's examination: a) wound covered with scar, b) wound covered with good granulation tissue, c) partial granulation, d) no granulation and/or wound covered with fibrin, e) necrosis at the base of the wound or wound covered with an escar
- The depth of the wound was determined according to the Wagner grading scale of six categories: 0 – no open wound,

$TcPO_2$ = transcutaneous oximetry

Figure 1. $TcPO_2$ criteria for HBOT in the Rambam and Elisha Hospitals' Hyperbaric Center



Breathing air at sea level: $TcPO_2$ < 40 mmHg
Breathing 100% oxygen: 10% increase in $TcPO_2$ values after 10 min
Breathing 100% oxygen at 2–2.4 ATA: $TcPO_2$ > 200 mmHg

ATA = atmosphere absolute

1 – superficial involving skin only, 2 – involving bones or tendons, 3 – involving bones or tendons with infection, 4 – necrosis at digit or foot requiring local amputation, 5 – extensive gangrene requiring amputation below the knee. The depth of the wound was used to determine wound severity

- Surface area of wounds was the sum of all the patient's wounds (cm^2) measured at admission and based on medical data
- Additional wound parameters documented were: wound location, presence of edema, secretion, duration of wound until $TcPO_2$ testing (months), history of past wounds (yes/no), number of wounds, amputation and vascular surgery.

TREATMENT CHARACTERISTICS

The number of treatments and continuity of treatments were recorded. Treatments were defined as non-continuous when the following interruptions occurred: the patient missed 5 consecutive days of HBOT or the patient received fewer than four treatments per week for two or more consecutive weeks [11].

OUTCOME MEASURES

- Wound improvement was determined at the end of the HBO treatments (a week before and up to 2 weeks after the last treatment). Wound improvement was classified as 'full recovery', 'significant improvement', or 'slight improvement'. Full recovery was documented when the wound was completely epithelialized or had been successfully closed with a skin graft. Significant improvement was documented when the wound was covered with granulation tissue or had a demarcation line, and a physician's note stating that it was expected to heal spontaneously. Another scenario included a note that it was expected to heal completely following a skin graft. Slight improvement was documented when there had been an improvement in the wound's characteristics (i.e., depth, appearance, area, secretion), when the wound was partially closed by a skin graft, or when a demarcation line was present but the wound was not expected to heal spontaneously. Wounds described as 'no change', 'worsened' or 'amputated' were classified as 'not improved'.
- Direct side effects of the HBO recorded during a treatment session included barotrauma, oxygen poisoning, hypoglycemia, lung edema, sinus crush, visual disturbances, anxiety and arrhythmia.
- Outcomes related to the lower extremities included the occurrence of new wounds, infections or osteomyelitis a week after starting HBOT and up to a week following its completion.

STATISTICAL ANALYSIS

A pretest was initially conducted on 30 randomly selected records. After completing the data collection, logic and reliability tests were run. Reliability was checked by a blinded data collection of nine randomly selected records. Kappa and intra-class correlation was calculated for categorical and continuous variables respectively.

Categorical data are presented by numbers and percentages, and continuous variables by range, mean and standard deviation. The median is presented when appropriate. Analyses were performed using SPSS, version 13.0.

RESULTS

The study population treated in our facility (1998–2007) and who met our research criteria numbered 385 patients. The mean age of the population was 61.9 years (SD=14.0) and most of them were males (68.8%). Additional sociodemographic characteristics are shown in Table 1.

The majority of patients were diabetic (69.6%), had long disease duration (63.8%), and were treated with diet (5.7%), hypoglycemic agents (50.9%) and insulin (43.4%). About half the patients had peripheral artery disease (45.5%) and most of them were either non-smokers or former smokers (43.4%, 38.2% respectively). Most of the patients were overweight (29.5%) or obese (28.5%). Almost half the patients (45.5%) needed assistance in mobility and 60.0% reported pain. Additional clinical characteristics are presented in Table 2.

At admission the total number of lower extremity wounds for each patient was one or two (a median of one wound). The surface area of wounds per patient ranged from 0.25 to 187 cm^2 (median 9.5 cm^2). In about 85% the wounds were classified as Wagner grade 1 or 2. In half the patients the most severe wound prevailed for at least 3 months prior to $TcPO_2$ testing. At admission, a third of the patients (32.3%)

Table 1. Sociodemographic characteristics of the study population (N=385)*

Variable	Category	No.	%
Age (yrs)	< 50	67	17.4
	50–64	118	30.6
	65–74	139	36.1
	≥ 75	61	15.8
Gender	Male	265	68.8
	Female	120	31.2
Ethnicity	Jewish and other	334	86.8
	Arab	51	13.2
Socioeconomic status**	Low	194	50.7
	Moderate	180	47.0
	High	9	2.3
Employment**	Employed	96	25.4
	Unemployed	282	74.6

*Missing values are excluded
**See definitions in study methods

Table 2. Medical conditions of the study population (N=385)*

Variable	Category	No.	%
Diabetes	Yes	268	69.6
	No	117	30.4
Hypertension	Yes	279	72.5
	No	106	27.5
Heart disease	Yes	191	49.6
	No	194	50.4
Previous stroke	Yes	54	14.0
	No	331	86.0
Hyperlipidemia	Yes	161	41.8
	No	224	58.2
Peripheral artery disease	Yes	175	45.5
	No	210	54.5
Kidney disease	Yes	84	21.8
	No	301	78.2
Hypercoagulability	Yes	19	4.9
	No	366	95.1
Anemia	Yes	156	40.5
	No	229	59.5
Neuropathy	Yes	79	20.5
	No	306	79.5

*Missing values are excluded

had a history of amputation at the lower extremity with the most severe wound (the index extremity). Approximately a quarter (21.4%) of the patients underwent vascular surgery in the index extremity, 34.3% had an infection and 16.1% had osteomyelitis.

Most of the $TcPO_2$ measurements were conducted near a foot wound (78.1%), whereas the rest of the measurements were conducted near a leg wound. The median value of $TcPO_2$ near the wound, with the patient breathing air at sea level, was 20.0 mmHg, and while breathing pure oxygen at 2 or 2.4 ATA, after 10 min, was 515 mmHg. Other wound characteristics are shown in Table 3.

The number of treatments ranged from 1 to 115. The median number of treatments was 29 per patient. Only 63.1% of patients had continuous treatments.

Overall, 363 of 385 patients (94.3%) had a documented outcome: 282 (77.7%) showed improvement following HBOT, of whom 15.2% fully recovered, 42.7% showed a significant improvement and 19.8% a slight improvement. The rest of the patients had no change (6.1%), a worse outcome (4.1%), or underwent an amputation (12.1%). Most of the patients did not exhibit any side effects of HBOT (79.2%) and did not develop any new infection, wound or osteomyelytis (60.5%) during the treatment course.

Table 3. Clinical characteristics of wound and extremities at admission (N=385)*

Variable	Category	No.	%
Wound appearance**	Good granulation	19	5.1
	Partial granulation	132	35.1
	No granulation and/or the wound is covered with fibrin	153	40.7
	The base of the wound is full with necrotizing tissue	72	19.1
Wound depth**	Superficial, without subcutaneous tissue	148	39.1
	Involvement of tendons or bones	175	46.2
	Involvement of tendons or bones with infection	45	11.9
	Digit gangrene with digit requiring local amputation	11	2.9
	Foot gangrene requiring below-knee amputation	0	0
Edema**	Yes	251	79.7
	No	64	20.3
Secretion**	No	7	2.6
	Low	51	19.2
	Moderate	121	45.7
	High	86	32.5
Past wounds	Yes	156	45.5
	No	187	54.5
Amputation**	Yes	124	32.3
	No	261	67.8
Amputation (other extremity)	Yes	63	16.4
	No	322	83.6
Vascular surgery**	Yes	82	21.4
	No	301	78.6
Infection**	Yes	132	34.3
	No	253	65.7
Osteomyelitis**	Yes	62	16.1
	No	323	83.9

*Missing values are excluded

** At the index extremity

DISCUSSION

The present study describes the characteristics of Israeli patients who underwent HBOT for ischemic non-healing wounds in our facility during a 10 year period. The advanced age of the population (mean 61.9 years) receiving therapy is due to the higher incidence and prevalence rates of wounds in older people [2]. Similarly, in other studies on ischemic non-healing wounds, the age range was 60–68.9 years [8,12-14]. This finding mandates that the medical staff at the center address the special needs of older patients, such as improving accessibility, adjusting the medical and nursing care to patients' chronic illnesses and medications, providing clear guidance and careful monitoring with regard to side effects, assessing self-efficacy and giving emotional support.

The proportion of women receiving HBOT was significantly lower (P = 0.000, binomial test) than the proportion of women aged 50+ in the general population (31.2% vs. 54.3%, respectively) [15]. This lower proportion of women on HBOT was also reported elsewhere, with Fife et al. [11] documenting 42% and Faglia et al. [16] 27%. This finding is surprising given the known higher rates of chronic lower extremity wounds in women [17]. It might be the result of different medical care given to women (resulting in higher recovery rates, or higher amputation or death rates) and/or the result of different accessibility to HBOT.

As shown in Table 2, more than 70% of our patients suffered from various chronic illnesses that are known to affect wound healing. Artery and vein diseases, hypertension, hyperlipidemia, heart disease, diseases of lung, liver and kidney, hematologic and rheumatologic diseases, malignancies, immune deficiencies and drugs (chemotherapy) are documented risk factors for impaired healing [18]. Some of these factors are modifiable, such as anemia and smoking, and should be considered by primary care physicians prior to HBOT. It is not surprising that diabetic patients constitute the majority (69.6%) of our sample, since HBOT was previously demonstrated to be effective for ischemic non-healing wounds primarily in diabetic patients [12,19].

Our patients underwent on average 33.5 (SD 22.5) HBO treatments. Despite the similarity to findings and recommendations in the literature, our range of treatments was much wider (1–115), although a similar treatment range (15–108) was found by Wattel et al. [14]. This finding could be attributed to the different insurance policies in various countries. The optimal number of HBO treatments for ischemic non-healing wounds remains to be determined [3].

A large number of treatments is usually associated with a high risk of side effects, mainly transient myopia. Nevertheless, no such relationship was found in our study (P = 0.142, Mann-Whitney), with only 20.8% of patients demonstrating HBOT side effects, the most common being hypoglycemia (14.9%), barotrauma (12.5%, mostly very mild), anxiety (2.9%) and worsening of heart failure (2.1%, not related to hyperoxygenation). Only two patients (0.5%) had seizures, one due to hypoglycemia and the other to oxygen poisoning. The latter occurred when 2.4 ATA pressure was used; today the pressure employed at our facility is only 2 ATA. In other studies seizures were reported in up to 10% of patients [20]. In our study barotrauma was found in the lower limit of the range reported in other studies (3.8–37%) [12,21]. Other studies reported pneumothorax, vision disturbances and death due to seizures or lung edema, side effects that were absent in our patients [20]. It is important to note that the side effects of HBOT have a similar prevalence to that of other procedures [22]; of the 57 studies reporting serious side effects of therapy only 9 (15.8%) described wounds treated with HBOT [20]. Some researchers reported absence of side effects [19]. Overall, HBOT is considered a safe procedure.

$TcPO_2$ values and their rate of increase under hyperbaric conditions are routinely used in our center to predict the response to HBOT since these measures reflect the microcirculatory support at the tissue level [23]. $TcPO_2$ values that do not reach 200 mmHg within 10 minutes of administering HBOT (a median value of 515 mmHg in the study) indicate insufficient microcirculatory support. It is difficult to compare our $TcPO_2$ results with those reported elsewhere, since many studies reported $TcPO_2$ values after their stabilization regardless of the time it took to reach these values. The high $TcPO_2$ values at entry are expected to predict healing success, and indeed, about 78% of our patients showed improvement.

Improvement following HBO treatments occurred in 282 (77.7%) of 363 patients with available outcome data. This positive outcome, manifested by slight improvement up to full wound recovery, relates, however, also to 20 patients with $TcPO_2$ values below 200 mmHg (after 10 minutes under hyperbaric conditions). According to the literature the latter patients are not candidates for HBOT since their chance of healing following treatment is relatively low [11]. They were given HBOT in an attempt to prevent amputation of the remaining leg (after a previous amputation). Only 12 (60%) of these 20 patients showed improvement. HBOT tends to be beneficial after at least 10 treatments. Twenty-seven of our patients received fewer than 10 treatments. Since these patients discontinued HBOT before achieving the beneficial effect, it is not surprising that only 15 (40.7%) improved. In a univariate logistic regression model, a one unit increase in the number of treatments was associated with a 1.04-fold increase in the rate of wound improvement (P = 0.000). The improvement rate among patients (N=261) who had $TcPO_2$ values above 200 mmHg and who had at least 10 HBO treatments was 81.2%.

We found two studies, similar in methodology to ours, that reported slightly lower rates of wound improvement (73.8%, 70.4%) [8,13]. However, there are differences in the populations studied that make the comparison between improvement rates difficult.

It should be noted that wound severity in our study was relatively low in comparison to wounds described by others: wounds with Wagner grade 1 and 2 were prevalent in 39.1% and 46.2% of our patients, respectively. The parallel proportions among patients described by Fife and co-authors [8] were 60.1% and 16.8%. We believe, however, that ischemic wound, as proven by $TcPO_2$ values, will probably not heal spontaneously, regardless of its Wagner grade. Ischemia that is corrected in the early stage may prevent further wound deterioration. Our analysis shows that the median pre-entry wound duration was 3 months. The Israel Ministry of Health recommends treating non-healing wounds within 2 months

of standard therapy failure [9]; we posit that ischemic wounds be treated with HBOT as soon as possible, especially when using $TcPO_2$ results.

Although the present study was not a randomized controlled clinical trial on the effectiveness of HBOT, it seems that patients undergoing this adjunctive therapy have a good chance for wound improvement. Additional adjunctive therapies are suggested in the literature, such as ultrasound, electric stimulation, shock wave therapy, hydrotherapy, macrophages and vacuum-assisted closure [4,24,25]. The only adjunctive therapy that was reported to be effective in a randomized controlled clinical trial was vacuum-assisted closure [25]. Since the various studies on these therapies were conducted in different populations, on different types of wounds and used different definitions of healing or improvement, comparing their effectiveness is difficult.

LIMITATIONS

This study was based on good quality data, indicated by high Kappa and intra-class correlation values when reexamining records. It should be mentioned that in order to achieve accurate $TcPO_2$ measurements using one electrode only, the participation of clinically experienced professionals was required. The external validity of the study is compromised because the study was conducted in one center only.

CONCLUSIONS

HBOT can make a major contribution to the treatment of ischemic non-healing wounds (especially when aided by pretreatment $TcPO_2$ evaluation; data not shown). Our experience demonstrates that this procedure provides a good chance for wound improvement and is safe.

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"Parkinson's Fourth Law: The number of people in any working group tends to increase regardless of the amount of work to be done"

C. Northcote Parkinson (1909-1993), British historian and author

Iron Deficiency in Children with Attention Deficit Hyperactivity Disorder

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ABSTRACT: **Background:** Several studies have suggested that iron deficiency may be related to the pathophysiology of attention deficit hyperactivity disorder (ADHD) due to the role of iron in the production of dopamine and noradrenaline.

Objectives: To evaluate the status of iron deficiency in ADHD children, using ferritin levels, a reliable measure of iron storage in body tissue, as an iron status marker, and to investigate a possible correlation between ferritin levels and the diagnosis of ADHD.

Methods: The study group included 113 newly referred ADHD children aged 5–15 years (mean age 8.8 ± 2.7).

Results: Ferritin levels were below 20 ng/ml in 67 children (59%) and above 20 ng/ml in 46 (41%). There was a very low inverse statistical correlation between scores on Conners' Rating Scale and ferritin levels, probably without clinical significance.

Conclusions: Our findings suggest that low iron stores may be related to ADHD pathophysiology; therefore, ferritin should be included in the overall evaluation of children with ADHD.

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KEY WORDS: attention deficit hyperactivity disorder (ADHD), iron, ferritin

Attention deficit hyperactivity disorder, the most prevalent neuropsychiatric disorder worldwide, affects between 5% and 10% of school-aged children and was found to persist through adolescence and adulthood in 30%–50% of these individuals [1,2]. The disorder is characterized by developmentally inappropriate inattention, hyperactivity and impulsivity, with onset before age 7 years and impaired functioning in two or more settings (school, home, etc.) [3].

The pathophysiology of ADHD is complex and not completely understood. No specific etiology has been identified for ADHD, and findings are consistent with a multifactorial hypothesis. Indeed, all neuropsychiatric disorders are thought to be caused by a complex combination of environmental, genetic and biological factors. Therefore, the proposed etiologies related to prenatal and perinatal risk factors, genetics and neurobiological deficits may all be involved in the pathophysiology of ADHD in different individuals [2]. However, many studies using different methodologies have indicated that dopamine is a key element of ADHD pathophysiology. The association between ADHD and the genes regulating dopamine, norepinephrine, serotonin and gamma-aminobutyric acid (GABA) has been studied [3,4]. Of these neurotransmitters, dopamine may play a central role because of its association with the modulation of psychomotor activity and executive functions, which are the main clinical features of individuals with ADHD. Several molecular genetic studies of ADHD have concentrated on the genes involved in dopaminergic function, and special attention was focused on the association of both the dopamine D4-receptor gene and the dopamine transporter gene (DAT1) with ADHD [5,6].

The association of the dopamine transporter with ADHD is of particular importance because this site is the main target for medications that are widely used by individuals with ADHD, such as methylphenidate, pemoline and dexamphetamine. Iron is a cofactor of tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis [7]. Therefore, brain iron stores may influence dopamine synthesis and subsequently affect various behavioral features, in particular those described in people with ADHD.

Several studies were performed in recent years [8-12] to define the role of serum ferritin levels as a reliable measure of iron stores in body tissues, including the brain, in the absence of anemia in children with ADHD. Only a few of these found a correlation between low ferritin levels and the presence of ADHD [8-11] and one study was unable to confirm this observation [12].

Our hypothesis was that depleted iron stores measured by ferritin levels in the serum may have a causative role in children with ADHD. The purpose of the present study was to investigate a possible correlation between iron stores as measured by serum ferritin and the diagnosis of ADHD.

SUBJECTS AND METHODS

The study was prospective and included all new consecutive patients during a 6 month period who were referred to the

ADHD = attention deficit hyperactivity disorder

Pediatric Neurology Clinic at Asaf Harofeh Medical Center, Zerifin, Israel, with a diagnosis of suspected ADHD, following their agreement to participate.

The children were diagnosed according to the DSM-IV TR criteria confirming the presence of symptoms in two settings, using Conners' Parents Rating Scale (CPRS) and Conners' Teachers Rating Scale (CTRS). The inclusion criteria were children aged 6–16 years, attending regular schools, and not taking any stimulant medications. The exclusion criteria were chronic medical problems requiring medical treatment, such as asthma, epilepsy, etc., and hemoglobin below 10 g/dl.

Blood samples for hemoglobin, iron and ferittin were obtained from all the children. The range of assumed normal values of ferritin in our laboratory was 20–165 ng/ml; therefore, values < 20 ng/ml were recorded as low.

After taking a detailed history, examining the patients and evaluating all available data, a treatment plan was suggested to the family based on the clinical features of ADHD symptoms. Treatments included behavioral modification, academic support, and medication. The ethics committee of our facility approved the study.

Statistical analysis was performed using SPSS software. The Pearson test was used for correlations between symptom severity and serum ferritin levels.

RESULTS

The number of children eligible to be included in the study was 146, of whom 33 were excluded because of refusal by their parents to participate. The study group thus comprised 113 children: 87 (75.6%) boys and 26 (24.4%) girls aged 6–15 years (mean age 8.8 ± 2.7), all of whom met the above mentioned criteria.

Table 1 shows the hemoglobin, ferritin and iron levels and Conners' scores of the study group. There were no significant statistical differences between the age groups for these values. Sixty-seven children (59%) had ferritin levels below 20 ng/ml and 46 (41%) had ferritin levels above 20 ng/ml.

Table 1. Hemoglobin, iron and ferritin levels, and Conners' scores in the study group

	All subjects
No. of children	113
Males (%)	87 (75.6%)
Mean age (SD, yrs)	8.8 (2.7)
Mean hemoglobin (SD, g/dl)	12.9 (0.84)
Mean iron (SD, ng/ml)	70.5 (31)
Mean ferritin (SD, ng/ml)	20.8 (12.3)
Mean Conners' score (SD)	18 (4.4)

Table 2. Comparison of factors in children diagnosed with ADHD and grouped according to low and high serum ferritin levels

	Low ferritin (< 20 ng/ml)	High ferritin (> 20 ng/ml)	*P* value
No. of children	67	46	
Males (%)	55 (82.1%)	32 (69.6%)	0.18
Mean age (SD, yrs)	8.6 (2.7)	9.2 (2.6)	0.2
Mean hemoglobin (SD, g/dl)	12.86 (0.85)	12.88 (0.84)	0.93
Mean iron (SD, ng/ml)	74.6 (33)	64.9 (26)	0.11
Mean ferritin (SD, ng/ml)	13.6 (3.5)	31.2 (13.2)	
Median ferritin (range, ng/ml)	14 (4–19)	25 (20–79)	
Mean Conners' score (SD)	17.5 (4.5)	18.7 (4.2)	0.15

Table 2 compares these two groups (< 20 and > 20 ng/ml) in terms of several factors, including gender, mean age distribution, and mean hemoglobin, iron and ferritin levels. No statistical difference was found between the groups, except for a very weak inverse correlation between Conners' scores and ferritin values, which most likely had no clinical significance.

DISCUSSION

The role of iron deficiency has been demonstrated in various neurologic and developmental disorders in both laboratory and clinical studies [13]. The relationship of iron deficiency to developmental delay and cognitive deficits with and without anemia has been a focus of many studies in both developed and developing countries [14,15]. Serum ferritin reflects the status of iron stores in the body: only when the level is below 10 ng/ml are bone marrow stores depleted and anemia develops [16].

In 1997, Sever et al. [8] presented a preliminary report on 14 boys aged 7–11 years with ADHD who were treated with an iron preparation, 5 mg/kg/day, for 30 days. Blood samples of ferritin, as well as their parents' and teachers' reports were obtained before and after treatment. The results showed a significant increase in serum ferritin levels (from mean ± SD 25.9 ± 9.2 to 44.6 ± 18 ng/ml) and a significant decrease in symptoms according to the parents' reports only. In 2004, Konofal et al. [9] compared iron levels in 53 ADHD children, aged 4–14 years, with iron levels in a control group matched for age and gender. Serum ferritin levels were used as a parameter for iron stores, and Conners' scores were used to measure ADHD symptom severity. The results showed that the mean serum ferritin levels were low in 84% of the children with ADHD (mean 23 ± 13 ng/ml) as compared to 18% of controls (mean 44 ± 22 ng/ml). In addition, low serum ferritin levels correlated with more severe ADHD symptoms and greater cognitive deficits. The authors concluded from their results that low iron stores

may contribute to ADHD and that children with ADHD may benefit from iron supplementation.

Millichap and colleagues [12] investigated the role of iron deficiency in ADHD by including serum ferritin in a battery of laboratory tests performed in 68 consecutive children aged 5–16 years seeking treatment at a clinic for attention deficit disorder. Serum ferritin levels ranged from a low of 7.7 ng/ml to a high of 150 ng/ml. The mean serum ferritin level in children with ADHD (39.9 ± 40.6 ng/ml) was not different from that of the control group (44 ± 22 ng/ml) reported by Konofal et al. [9] or the U.S. national control data. However, 74% of the patients in Millichap's study [12] had serum ferritin levels below 50 ng/ml, 44% had levels below 30 ng/ml, and 18% had serum ferritin levels below 20 ng/ml. None of the children showed evidence of iron deficiency anemia.

In our study, a comparison of the clinical characteristics of the 12 children with the lowest serum ferritin levels (< 20 ng/ml) and the 12 with the highest levels (> 60 ng/ml) revealed no significant difference in severity or frequency of ADHD and comorbid symptoms, or in response to medications. In this patient cohort study, a causative role for low serum ferritin was not confirmed. Nevertheless, because therapy with iron has been beneficial for some neurologic disorders despite the absence of anemia, a controlled trial of ferrous sulphate supplement may be justified in ADHD children with ferritin levels below 20 ng/ml.

In another recently published controlled case study from India [10], serum ferritin levels were measured in children newly diagnosed with ADHD and compared with those of controls. A correlation was sought between serum ferritin levels and ADHD symptom severity as determined by Conners' Rating Scale. Serum ferritin was found to be significantly lower in children with ADHD (mean ± SD 6.04 ± 3.85 ng/ml) as compared to controls (mean ± SD 48 ± 41.64 ng/ml). There was also a significant inverse correlation between serum ferritin levels and oppositional subscores on Conners' Rating Scale.

The assumed low normal values of ferritin suggesting the presence of iron deficiency are variable in different studies investigating its relationship to ADHD, ranging from 12 ng/ml [10,17,18] to 30 ng/ml [12]. The value of 20 ng/ml as a low normal in our study represents an average of the values that were used in the other studies.

Recently, a new computerized continuous performance functions test [19], which includes a multitask approach, was found to be a valid and reliable tool for the diagnosis of ADHD in children and may be used for better assessment in future studies.

Our results support the assumption that iron status may play a role in the pathophysiological processes underlying ADHD. The majority of the children (59%) had ferritin levels below 20 ng/ml with no significant difference between the age groups. Moreover, hemoglobin and iron values were also similar in all age groups. There was no strongly significant statistical correlation between ferritin levels and symptom severity, as described by Mllichap and co-researchers [12] and in contrast to the results of Konofal et al. [9] and Juneja et al. [10].

The variability of the results in the different studies may reflect differences in age, gender, race/ethnicity and nutritional status due to socioeconomic conditions as well as the contribution of other factors, such as type of symptoms and associated comorbidity, that may have some influence on ADHD features.

Only one study [11] examined the effects of iron supplementation on ADHD in children. In this study 23 non-anemic children aged 5–8 years with serum ferritin levels below 30 ng/ml were randomized (3:1 ratio) to treatment with either oral iron supplements (ferrous sulphate, 80 mg/day, n=18) or placebo (n=5) for 12 weeks. There was a significant progressive decrease in the ADHD rating scale after 12 weeks on iron, but not in the placebo group; however, improvement on Conners' Parent Rating Scale and Conners' Teacher Rating Scale with iron supplementation therapy failed to reach significance. The limitations of this study was the small sample, particularly that of the placebo group.

The results of most studies, including the present one, support the hypothesis that depletion of iron stores, although not so severe as to cause anemia, may be related to the pathophysiological processes underlying the development of ADHD symptoms. Other studies [17,18] have suggested that lower ferritin levels are associated with higher rates of behavioral problems and that the presence of comorbid conditions might increase the effect of lower iron stores on behavioral measures.

The absence of a control group and the size of the study group are points of weakness in the design of the present study. Larger samples are required to investigate the possibility that in the population at large, the same proportion of normal children without ADHD have low levels of ferritin as found in the different study groups of children with ADHD.

Recently, it was suggested that low levels of iron and zinc might be associated with ADHD since both are related to dopamine metabolism [20]. Since ADHD constitutes a heterogeneous group of conditions with different features and clinical expressions, it may be assumed that depleted iron stores, as reflected by a significant low level of ferritin, are not a constant finding in every child with ADHD.

In conclusion, we suggest that ferritin, as a marker for iron stores, be included in all baseline evaluations of children with clinical presentation of ADHD. Furthermore, children with ferritin levels below 20 ng/ml should be required to undergo a careful dietary iron evaluation, followed by a diet that features appropriate amounts of iron sources. Additional larger controlled double-blind trials are necessary to demonstrate

the value of iron supplements in treating ADHD children with depleted iron stores as reflected by low ferritin levels.

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Capsule

Pericytes in neuronal scarring

Scarring can serve the valuable purpose of reestablishing tissue integrity after damage. This immediate response to damage can, however, interfere with slower but more effective tissue repair processes. In the central nervous system, the scars left after damage to neuronal tracts have been thought to be derived from astrocytes, a type of glial cell. Göritz et al. identified pericytes as important contributors to scars in neural tissue. Pericytes, usually found wrapping small blood vessels, are already known for their contributions to scars in dermal and kidney tissues. A subgroup of pericytes formed the core of scars after spinal cord damage in the mouse, and when the contribution of pericytes was reduced, the lesion was more likely to remain unclosed.

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Eitan Israeli

Capsule

Optineurin in autophagic bacterial clearance

Autophagy receptors bind both ubiquitin and autophagy markers, including microtubule-associated protein light chain 3 (LC3), and promote the specific clearance of protein aggregates, defective organelles, and intracellular pathogens. Wild and co-researchers describe optineurin (OPTN) as an autophagy receptor whose function is regulated by phosphorylation of its LC3-interacting motif. Phosphorylation by the protein kinase Tank binding kinase 1 (TBK1) increased the affinity of OPTN for autophagy modifiers by 13-fold. OPTN is also a ubiquitin-binding protein and was recruited to cytosolic *Salmonella* to promote bacterial clearance via the autophagy pathway. Thus, TBK1 and OPTN represent critical components of the cell defense system for restricting the growth of bacteria in the cell.

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Eitan Israeli

Comparative Study of the Pathological Characteristics of Gastric Stump Carcinoma and Carcinoma of the Upper Third of the Stomach

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ABSTRACT: **Background:** Gastric stump cancer is often described as a tumor with a poor prognosis and low resectability rates.

Objectives: To compare the pathological characteristics of gastric stump cancer patients with those of patients with proximal gastric cancer.

Methods: This retrospective study was based on the demographic and pathological data of patients diagnosed with gastric cancer and treated at Assaf Harofeh Medical Center during an 11 year period. The patients were divided into two groups: those undergoing proximal gastrectomy for proximal gastric cancer and those undergoing total gastrectomy for gastric stump cancer.

Results: Patients with gastric stump cancer were predominantly male, older (P = 0.202, not significant), and had a lower T stage with less signet-ring type histology, fewer harvested and fewer involved lymph nodes (P = 0.03, statistically significant) and less vascular/lymphatic involvement than patients with proximal gastric cancer.

Conclusions: The lower incidence of involved lymph nodes and lymphovascular invasion in gastric stump cancer as compared to proximal gastric cancer in this study may imply that the prognosis of gastric stump cancer may be better than that of proximal gastric cancer. However, to verify this assumption a study comparing patient survival is required.

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KEY WORDS: gastric stump cancer (GSC), gastric remnant cancer (GRC), proximal stomach cancer (PSC), pathological characteristics

The definitions of gastric remnant cancer and gastric stump cancer are somewhat confusing. While Thorban et al. [1] and Safatle-Ribeiro et al. [2] define GSC as a carcinoma developing in the gastric stump at least 5 years following gastric resection that was performed for ulcer disease, Tanigawa et al. [3] define GRC as cancer developing in the remnant stomach at least 10 years after distal gastrectomy, without taking into account whether gastric resection was performed for benign or malignant disease. Reviewing the literature, it becomes evident that different authors mix both definitions for tumors occurring after gastric resection that was performed for either benign or malignant disease [1,3,4]. GSC and GRC are rare, the incidence ranging between 1.1% and 10% [1-7] of all gastric cancer patients. The incidence of primary proximal gastric cancer is reported to be around 3%–4% [1,8]. To simplify the nomenclature, we united GSC and GRC under one term – GSC.

GSC is often described as a tumor with a poor prognosis and low resectability rates in the range of around 38% to 40%, because of extended lymph node metastases and infiltration of adjacent organs [1,5,6,9]. The reported 5 year disease-specific overall survival rate for patients undergoing gastrectomy for GSC ranges from 7% to 20% [1,5-7,9]. The aim of our study was to compare the pathological characteristics of GSC patients with those of patients with PGC.

PATIENTS AND METHODS

This retrospective study, approved by the Institutional Review Board of Assaf Harofeh Medical Center, is based on demographic and pathological data retrieved from a computerized database of all patients with gastric cancer treated at Assaf Harofeh Medical Center during an 11 year period.

The patients were divided into two groups: Group I – patients undergoing proximal gastrectomy for PGC (Siewert type II and III) [1,10], and Group II – patients undergoing completion total gastrectomy for GSC that developed following distal gastrectomy for benign disease (duodenal ulcer) or for distal gastric cancer.

The following parameters were documented: gender, age, T stage, overall number of lymph nodes harvested, percentage of lymph nodes involved by the tumor, tumor differentiation, tumor morphology, and American Joint Committee

GSC = gastric stump cancer
GRC = gastric remnant cancer

PGC = proximal gastric cancer

on Cancer stage. All pathological slides were re-reviewed by a senior pathologist (J.S.).

Statistical analysis was performed at the Department of Statistics of Tel Aviv University (*t*-test for age, Mann-Whitney test for positive lymph nodes). Other parameters could not be studied due to the limited number of patients in group II.

RESULTS

Group I comprised 48 patients with the tumor located in the cardia – Siewert type II and III. Of these 48 patients, 34 underwent proximal gastrectomy and 14 total gastrectomy [Table 1]. Group II consisted of 9 patients who developed GSC. All nine patients underwent total gastrectomy. There were 29 males and 19 females with a mean age of 64.0 years in Group I, and 6 males and 3 females with a mean age of 70.1 years in Group II ($P = 0.202$, not significant) [Table 1].

The mean number of lymph nodes harvested per patient was 16.7 in Group I as compared to 8.3 in Group II. However, the mean number of metastatic lymph nodes per patients was 3.7 in Group I versus 0.7 in Group II ($P = 0.03$, statistically significant) [Table 1].

DISCUSSION

GSC or GRC are synonyms for the same clinical entity, where gastric cancer develops in the stump or remnant stomach many years after gastrectomy either for benign or malignant disease [1-9,11-13]. The incidence of GSC following distal subtotal gastrectomy for peptic disease increases logarithmically with the years and specifically from the 5th postoperative year onwards [1,4-8]. Hence, this particular group of patients requires gastroscopic surveillance [1,4-7,9,14].

It is believed that once developed, GSC or GRC carries a grave prognosis. Is this really so? Different studies report conflicting results, with some describing the aggressive behavior of these tumors and others a less aggressive clinical course [1-9,11-14]. Different studies compared the pathological features of GSC or GRC to those of gastric cancer located in the cardia [1-9,11,12,14].

We used the same model for our study. We compared nine patients with GSC to 48 randomly selected patients with Siewert type II and III gastric cancer [1,10]. As was the case in other studies [1,4,5,7,9,12], the overall number of patients with GSC was small. Nevertheless, the differences in the various pathological features of tumor aggressiveness are clear. All tumor parameters – such as T stage and N stage; tumor differentiation; vascular, lymphatic or neural invasion; and the presence of signet-ring differentiation – had better prognostic indexes in the GSC group as compared to the PGC group. These findings are shown clearly in the study by Han and coauthors [12] in contrast to the studies by others [4,11].

Table 1. Comparative data on pathological characteristics of the groups studied

		Group I (primary PGC) 48 patients	Group II (GSC + GRC) 9 patients
Mean age (yrs)		64.0 (33–85)	70.1 (51-86)
T stage	In situ	2 (4.1%)	0 (0%)
	T1	3 (6.25%)	2 (22.2%)
	T2	12 (25.0%)	3 (33.3%)
	T3	30 (62.5%)	4 (44.5%)
	T4	1 (2.0%)	0 (0%)
AJCC stage	IA	2 (4.1%)	2 (22.2%)
	IB	10 (20.8%)	3 (33.3%)
	II	8 (16.6%)	2 (22.2%)
	IIIA	13 (27.0%)	1 (11.0%)
	IIIB	6 (12.5%)	0 (0%)
	IV	7(14.6%)	1 (11.0%)
Overall lymph nodes harvested		777 (16.7 per patient)	75 (8.3 per patient)
Positive lymph nodes		169 (3.7 per patient)	7 (0.7 per patientt)
Pathologic features			
Differentiation			
Well differentiated		4 (8.3%)	0 (0%)
Moderately differentiated		24 (50.0%)	3 (33.3%)
Poorly differentiated		20 (41.7%)	6 (67.0%)
Macroscopic features (Borrmann's classification)			
Ulcer type		24 (50.0%)	2 (22.0%)
Polyp type		11 (22.9%)	3 (33.3%)
Fungating		11 (22.%)	3 (33.3%)
Not reported		2 (4.5%)	1 (11.0%)
Microscopic features (Lauren's classification)			
Diffuse type		12 (25.0%)	4 (44.5%)
Intestinal type		15 (31.25%)	3 (33.3%)
Both types		3 (6.25%)	0 (0%)
Unclassified/indeterminate		18 (37.5%)	2 (22.2%)
WHO classification			
1. Intestinal type:	Papillary	1 (2.0%)	1 (11.0%)
	Tubular	Not reported	Not reported
2. Diffuse type:	signet-ring cells	16 (33.3%)	2 (22.0%)
Mucin production tumors		4 (8.4%)	0 (0%)
Vascular invasion		26 (54.0%)	2 (22.0%)
Neural invasion		18 (37.5%)	2 (22.0%)

PGC = proximal gastric cancer, GSC = gastric stump cancer, GRC = gastric remnant cancer, AJCC = American Joint Committee on Cancer

A point of interest was the number of lymph nodes harvested: 16.7 per patient undergoing primary surgery but only 8.3 per patient undergoing surgery for GSC. The explanation is probably based on the fact that a substantial number of nodes had been harvested during the primary resection.

As the prognosis of patients with gastric cancer depends on the T and N stages, which determine the stage of the disease, it can be clearly seen that in the PGC group most of the patients had stage IIIA, IIIB or IV cancer (54.1%) vs. 22% in the GSC group. Moreover, lymphovascular invasion, another ominous prognostic factor, was again found in 54% of the patients with PGC as compared with 22% in the GSC group. Only poorly differentiated tumors were surprisingly more frequent in the GSC group (67%) as compared to the PGC group (41.7%).

In conclusion, patients with GSC were predominantly male, older ($P = 0.202$, NS), and had a lower T stage with less signet-ring type histology, fewer harvested and fewer involved lymph nodes, and less lymphatic/vascular involvement ($P = 0.03$, statistically significant) than patients with PGC. These data demonstrate the somewhat better pathological characteristics of the patients in Group II.

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Capsule

Control of T_H17 cells occurs in the small intestine

Interleukin (IL)-17-producing T helper cells (T_H17) are a recently identified $CD4^+$ T cell subset distinct from T helper type 1 (T_H1) and T helper type 2 (T_H2) cells. T_H17 cells can drive antigen-specific autoimmune diseases and are considered the main population of pathogenic T cells driving experimental autoimmune encephalomyelitis (EAE), the mouse model for multiple sclerosis. The factors that are needed for the generation of T_H17 cells have been well characterized. However, where and how the immune system controls T_H17 cells in vivo remains unclear. By using a model of tolerance induced by CD3-specific antibody, a model of sepsis and influenza A viral infection (H1N1), Esplugues and collaborators show that pro-inflammatory T_H17 cells can be redirected to and controlled in the small intestine. T_H17-specific IL-17A secretion induced expression of the chemokine CCL20 in the small intestine, facilitating the migration of these cells specifically to the small intestine via the CCR6/CCL20 axis. Moreover, the authors found that T_H17 cells are controlled by two different mechanisms in the small intestine: first, they are eliminated via the intestinal lumen; second, pro-inflammatory T_H17 cells simultaneously acquire a regulatory phenotype with in vitro and in vivo immune-suppressive properties (rT_H17). These results identify mechanisms limiting T_H17 cell pathogenicity and implicate the gastrointestinal tract as a site for control of T_H17 cells.

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Eitan Israeli

Capsule

A pharmacological approach to first aid treatment for snakebite

Snake venom toxins first transit the lymphatic system before entering the bloodstream. Ointment containing a nitric oxide donor, which impedes the intrinsic lymphatic pump, prolonged lymph transit time in rats and humans and also increased rat survival time after injection of venom. This pharmacological approach should give snakebite victims more time to obtain medical care and antivenom treatment.

Nature Med 2011; 17: 809

Eitan Israeli

"Be polite to all, but intimate with few"

Thomas Jefferson (1743-1826), third U.S. president and author of the Declaration of Independence

Intensification of Diabetes Treatment with Long-Acting Insulin Shows no Benefit over Other Diabetes Treatment

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ABSTRACT: **Background:** Control of diabetes is challenging, and frequent treatment changes are needed.

Objective: To study the effect of the recommendation to start insulin glargine or insulin determir (long-acting insulin treatment, LAI) at discharge from hospital, on glucose control in the community setting.

Methods: Included were type II diabetes patients who were referred to and received a consultation from the hospital diabetes clinic during their hosptialization, as part of a routine consultation for diabetes management. During the visit, all patients were recommended long-acting insulin-based treatment, as inpatient treatment and at discharge. Follow-up was done by the primary physician in the community or by a community-based diabetes clinic. Glycosylated hemoglobin, glucose levels and other laboratory tests were obtained from the community health records before hospitalization and 6–12 months later. Medical treatment was ascertained by reviewing the actual usage of prescriptions.

Results: Eighty patients (58% males, mean age 64.1 ± 12.7 years) were included in the analysis. HbA1c levels were 10.1 ± 2.4% before admission, but improved significantly at follow-up (8.6 ± 2.2%, $P < 0.001$). Seventy-one percent of the patients were taking the LAI treatment and the rest were using non-LAI medications. Changes in diabetes control were similar between the LAI and non-LAI groups (HbA1c was reduced by 1.5 ± 3.2% and 1.9 ± 3.1% respectively). The rate of repeated admissions was also similar, averaging at 1.3 admissions for both groups, the minority of which were related to glucose control.

Conclusions: Insulin glargine or determir-based treatment does not show any superiority over other anti-diabetes treatment. It is our opinion that this treatment should be used as tailored therapy and should not be recommended routinely to all patients.

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KEY WORDS: diabetes control, long-acting insulin, glycosylated hemoglobin

With the increasing prevalence of diabetes mellitus worldwide, the treating physicians are faced with the challenge of how to achieve optimal glucose control. While the benefit of lowering blood glucose and HbA1c levels is unquestionable and was shown repeatedly to reduce diabetes complications [1], obtaining this elusive goal remains difficult [2]. The progressive nature of this disease, with the ongoing decline in the mass and function of beta cells, requires strict follow-up and relatively frequent treatment adjustments [3].

Many new glucose-lowering medications have been added to the arsenal of treatment during the last decade, both in the tablet and injection form. However, the addition of the new long-acting insulins has changed significantly the way we view insulin treatment in diabetes patients. Whereas previously, insulin treatment was the 'last stand' of treatment and preferably avoidable, today the addition of insulin glargine (Lantus®, Sanofi-aventis) and determir (Levemir®, Novo Nordisk) has become more frequent in the early stages of diabetes treatment [4]. These treatments were shown in clinical trials to be efficacious and also to have lower rates of serious treatment side effects (such as hypoglycemia) [5,6]. Current practice is often based on long-acting insulin as basal insulin, with additional oral agents as add-ons [7].

Because of these advantages, since August 2007 long-acting insulin-based treatment is recommended to all hospitalized diabetes patients in our center, regardless of their prior diabetes treatment. The purpose of this study was to examine the effects of this strategy on diabetes control in the community. Since our experience taught us that between 30% and 80% of the patients continue in the community the treatment that was recommended at hospital discharge, we assumed that the patients not receiving the recommended treatment could serve as controls. The hypothesis of the study was that LAI-based treatment is superior to other anti-diabetes medications for diabetes treatment intensification. The aim of the study was therefore to examine the effects of the recommendations for LAI-based treatment on glucose control and rehospitalization in the community setting.

*The first two authors contributed equally to this study

LAI = long-acting insulin

PATIENTS AND METHODS

The study was approved by the Institutional Review Board. Since the long-acting insulin protocol is recommended to almost all inpatient diabetes patients in our medical center, the patients included in this study did not have to sign an informed consent. Audit of the medical records of patients in the community setting was possible because all health management organizations responsible for the health insurance of Israeli citizens have electronic health records.

INCLUSION AND EXCLUSION

Included in this analysis were all inpatients who were referred to the hospital diabetes clinic during their hospitalization between 1 January and 31 December 2008. These patients were referred to the clinic by physicians of the different hospital departments and units, as part of a routine inpatient diabetes consultation, for the purpose of instructing patients how to inject themselves with insulin. We excluded from the analysis any patients (either inpatients or outpatients) who had type 1 diabetes mellitus, outpatients who had not been hospitalized during the study period, and patients who were not recommended LAI. One additional patient was excluded since the diagnosis of diabetes was not confirmed. The referring physicians responsible for the inpatient treatment and the family practitioners responsible for the treatment following the hospitalization were not aware that the patients' data had been collected.

DATA COLLECTION

- *General information and additional diseases:* The EHR of each patient was reviewed, and the data included general information (age, gender and marital status), evidence of atherosclerotic vascular disease (ischemic heart disease, stroke, any coronary intervention) and information about atherosclerosis risk factors (hypertension, hyperlipidemia, smoking).
- *Blood test information:* The control status of diabetes was ascertained by reviewing the HbA1c and fasting plasma glucose levels before and after the hospital admission. The date of reference was regarded as the date of the visit to the hospital diabetes clinic. Pre-DOR data were the FPG and HbA1c levels that were the last values measured in the HMO community clinic (Clalit Health Services) within the 12 months that preceded the DOR. If HbA1c levels were not performed, the patient was withdrawn from the study, unless he/she was diagnosed with diabetes during the current admission. Post-admission data included the first HbA1c and FPG levels measured between 6 and 12 months after the DOR. If HbA1c levels were not measured during this time frame, data were searched for an additional period of 2 months before and after the time frame, but not less than 4 months and not more than 14 months after the DOR. If HbA1c levels were not measured during this time frame, the patient was withdrawn from the study.
- The electrolyte levels (sodium and potassium) and the kidney function tests (urea and creatinine) that were reviewed in this analysis were measured during the same time frame as the HbA1c levels (for both pre- and post-DOR). The lipid levels included in this analysis were measured before the DOR.
- *Repeated admissions, diabetes-associated admissions and diabetes clinic follow-up:* This refers to the number of admissions during a follow-up period of 12 months after the DOR was elicited from the EHR. If the reason for admission was related to glucose control (either hypersomolar state or hypoglycemia), the admission was considered a diabetes-associated admission. Additional reasons for hospitalization, including diabetic foot, congestive heart failure and any cardiovascular event, were not considered a diabetes-associated admission and were counted only as repeated admissions. If a patient had two or more visits with a diabetes specialist within 12 months after the DOR, he/she was considered as "diabetes clinic follow-up."
- *Medication and compliance:* The EHR was reviewed for each of the diabetes drug classes, and the number of prescriptions drawn from the pharmacy was obtained. The patient was considered 'treated' with a specific medication if he/she used at least two prescriptions within the 12 months before the DOR and/or at least two prescriptions within the 12 months after the DOR. If the number of used prescriptions for a specific drug class was 0 or 1 during any specific time frame, the patient was considered as not using that specific drug for that time frame.

STATISTICAL ANALYSIS

The present study was designed to have 80% power to detect a true, between-group difference of 1.0 ± 1.5% in HbA1c, using the *t*-test for independent samples and assuming a two-sided alpha of 0.05. The paired sample *t*-test was used to ascertain significant changes between pre- and post-DOR laboratory values (except lipid levels). Patients were then categorized as long-acting insulin users (LAI) or non-users (non-LAI) based on the actual treatment with long-acting insulin (either insulin glargine or determir) after the DOR. The Student *t*-test was used to compare between LAI and non-LAI patients. Comparisons of the non-quantifiable data were done using the chi-square test. All quantifiable data are presented as mean ± standard deviation, and the non-quantifiable data are presented as the number (%).

EHR = electronic health record
DOR = date of reference
FPG = fasting plasma glucose
HMO = health management organization

RESULTS

Included in this study were 137 patients who fulfilled the inclusion criteria. The EHRs of 32 patients (23%) were not obtained because they were not registered members of the local Clalit Health Services clinic and access to the data was not permitted. The records of 24 patients (18%) were missing HbA1c levels at pre-DOR, post-DOR or both, and these patients were therefore excluded. One patient died during the follow-up period and was omitted from the analysis. The final database included 80 patients (58%).

DEMOGRAPHICS, CHRONIC ILLNESSES AND REASON FOR ADMISSION

Of the 80 patients, 46 (58%) were males (mean age 64.1 ± 12.7 years) and 54 (68%) were married. Additional diseases, cardiovascular risk factors and basic laboratory results are presented in Table 1.

The reasons for admission to hospital varied and were mostly not related to direct glucose control (data not shown). However, 14 patients (18%) were admitted due to a hyperosmolar state and 5 (6%) because of hypoglycemia that was attributed to diabetes treatment. In addition, 5 patients (6%) were hospitalized with new-onset diabetes mellitus that presented as a hypersomolar state.

DIABETES CONTROL BEFORE AND AFTER THE DOR

The status of diabetes control was poor. Before admission, mean HbA1c was 10.1 ± 2.4% and the FPG 13.6 ± 7.6 mmol/L. These levels were measured on average 160 ± 106 days before the DOR. Seventy-six patients (95%) had a HbA1c level above 7% (53 mmol), and 44 of them (60%) had a level above 9%. After the DOR, diabetes control improved significantly. HbA1c levels were reduced by an average of 1.5 ± 3% and the FPG levels by 4.4 ± 9.6 mmol/L. These levels were measured on average 258 ± 96 days after the DOR. Still, 53 (72%) of the patients had a HbA1c level above 7% but only 27 (37%) had a level above 9%. The laboratory results and medication profile of the patients before and after the DOR are shown in Table 2.

Table 1. Baseline information of the 80 patients included in the analysis

Demographics	
Age (yrs)	64.1 ± 12.7
Male sex (n, %)	46 (58%)
Married status (n, %)	64 (68%)
Additional cardiovascular risk factors and diseases	
Hypertension (n, %)	56 (70%)
Hyperlipidemia (n, %)	67 (84%)
Smoking (n, %)	14 (18%)
Ischemic heart disease (n, %)	31 (39%)
Congestive heart failure (n, %)	13 (16%)
Cerebrovascular disease (n, %)	7 (9%)
Post-coronary intervention (n, %)	16 (20%)
Baseline (pre-DOR) laboratory data	
Total cholesterol (mmol/L)	4.92 ± 1.32
LDL cholesterol (mmol/L)	3.11 ± 1.24
HDL cholesterol (mmol/L)	1.09 ± 0.28
Triglycerides (mmol/L)	2.57 ± 2.57
Sodium (mmol/L)	138 ± 4
Potassium (mmol/L)	4.5 ± 0.4
Urea (mmol/L)	17.5 ± 12.9
Creatinine (mmol/L)	97.2 ± 44.2

Quantifiable data are presented as mean ± SD
LDL = low density lipoprotein, HDL = high density lipoprotein

DIABETES CONTROL ACCORDING TO TREATMENT

Of the 80 patients who were recommended for the LAI-based therapy, 57 (71%) continued the recommended treatment and 23 (29%) received treatment that did not include the new LAIs. The comparison between the groups showed that the groups were comparable in all aspects, except for the rate of hypoglycemia on admission, history of congestive heart failure, past coronary intervention, and a tendency for a reduction in kidney function – all of which increased the chances of the patient to receive the LAI-based therapy in the community setting. On the other hand, a newly diagnosed diabetes mellitus status reduced the chances of being treated with LAI in the community. Demographic information, additional diseases and the pre-DOR laboratory results and treatment profile are given in Table 3. The LAI-based treatment did not show any superiority over non-LAI based treatment post-DOR. Mean HbA1c had decreased from 10.2 ± 2.6 to 8.7 ± 2.2% in the LAI group ($P < 0.001$) and from 10.2 ± 2.3 to 8.2 ± 2.3 % in the non-LAI group ($P = 0.004$). Mean FPG had decreased from 13.8 ± 7.5 to 9.5 ± 4.5 mmol/L in the LAI group ($P = 0.001$) and from 13.5 ± 7.3 to 9.7 ± 4.6 mmol/L in the non-LAI group ($P = 0.04$). Among the

Table 2. Laboratory results and medication profile before and after the DOR

	Pre-DOR	Post-DOR	*P* value
Laboratory data			
HbA1c (%)	10.2 ± 2.5	8.6 ± 2.2	< 0.0001
Mean of difference (%)	1.6 ± 3.2		
Fasting plasma glucose (mmol/L)	13.7 ± 7.4	9.6 ± 4.5	< 0.001
Mean of difference (%)	4.4 ± 9.5		
Sodium (mmol/L)	138 ± 4	139 ± 3	0.016
Potassium (mmol/L)	4.5 ± 0.4	4.6 ± 0.5	0.09
Urea (mmol/L)	17.5 ± 12.9	18.9 ± 12.1	0.047
Creatinine (mmol/L)	97.2 ± 44.2	97.2 ± 44.2	0.44
Diabetes medication profile			
Sulphonyl urea (n, %)	32 (40%)	12 (15%)	< 0.0001
Metformin (n, %)	39 (49%)	30 (38%)	0.020
Rosiglitazone (n, %)	5 (6%)	2 (3%)	0.016
Sitagliptin (n, %)	0	3 (4%)	0.048
Repaglinide (n, %)	7 (9%)	14 (18%)	0.021
Total Insulin (n, %)	27 (34%)	61 (76%)	< 0.0001
Long-acting insulin (n, %)	8 (10%)	57 (71%)	< 0.0001

DOR = date of reference: the date of the diabetes clinic visit when long-acting insulin treatment was recommended

Table 3. Demographic information, additional diseases and the pre-DOR laboratory results and treatment profile according to post-DOR treatment

	LAI (n=57)	No LAI (n=23)	*P* value
Demographics			
Age (mean ± SD)	65.5 ± 12.4	60.4 ± 13.2	0.11
Male sex (n, %)	32 (56%)	14 (61%)	0.34
Married status (n, %)	36 (63%)	18 (78%)	0.002
Cardiovascular risk factors and diseases			
Hypertension (n, %)	41 (72%)	15 (65%)	0.14
Hyperlipidemia (n, %)	48 (84%)	19 (83%)	0.66
Smoking (n, %)	10 (18%)	4 (17%)	0.97
Ischemic heart disease (n, %)	23 (40%)	8 (34%)	0.26
Congestive heart failure (n, %)	12 (21%)	1 (4%)	< 0.0001
Cerebrovascular disease (n, %)	5 (9%)	2 (9%)	0.98
Post-coronary intervention (n, %)	13 (23%)	3 (13%)	0.02
Reasons for admission and follow-up			
Hyperosmolar state	9 (16%)	5 (22%)	0.10
Hypoglycemia	5 (9%)	0	0.002
New-onset diabetes mellitus	2 (4%)	3 (13%)	< 0.0001
Diabetes clinic follow-up	29 (51%)	6 (26%)	< 0.0001
Pre-DOR Laboratory data			
HbA1c (%)	10.2 ± 2.6	10.2 ± 2.3	0.96
Fasting plasma glucose (mmol/L)	13.8 ± 7.5	13.5 ± 7.3	0.90
Sodium (mmol/L)	138 ± 3	137 ± 4	0.24
Potassium (mmol/L)	4.6 ± 0.5	4.5 ± 0.2	0. 41
Urea (mmol/L)	19.3 ± 14.3	12.5 ± 5.7	0.04
Creatinine (mmol/L)	101 ± 48	80 ± 25	0.06
Pre-DOR diabetes medication profile			
Sulphonyl urea (n, %)	22 (39%)	10 (43%)	0.32
Metformin (n, %)	29 (51%)	10 (43%)	0.14
Rosiglitazone (n, %)	5 (9%)	0	0.002
Repaglinide (n, %)	6 (11%)	1 (5%0	0.044
Total insulin (n, %)	22 (39%)	5 (22%)	< 0.001
Long-acting insulin (n, %)	7 (12%)	1 (5%)	< 0.015

DOR = date of reference: the date of the diabetes clinic visit when basal insulin-based treatment was recommended

LAI = long-acting insulin-based treatment, i.e., long-acting insulin that the patients were taking

non-LAI patients, 4 patients (17%) were taking insulin treatment that was not glargine or determir (either mixed insulin or NPH – neutral protamine Hagedorn, also known as isophane insulin). Results remained the same after omitting these patients from the analysis.

REPEATED HOSPITALIZATIONS FOLLOWING DOR

Thirty-three patients (41%) were readmitted during the 12 month follow-up after the DOR, and 25 of them were readmitted more than once (31%, average number of readmissions during follow-up 1.4 ± 2.4). Reasons for the admission varied, but in six patients it was diabetes-associated (8% of the database and 18% of the patients who required readmission). When analyzing the admission data of the two treatment groups, long-acting insulin-based therapy had no effect on the number of readmissions after the DOR. Of the 57 patients receiving long-acting insulin, 23 required readmission (40% compared to 43% in the non-LAI group) and 18 required more than one readmission (32% compared to 30% in the non-LAI group). The average number of readmissions in the LAI group was 1.3 ± 2.5 compared to 1.3 ± 2.5 in the non-LAI group ($P = 0.98$). In four patients receiving LAI treatment (7% in the LAI group and 17% in the readmitted LAI group) the admission was diabetes-associated, as compared to two patients in the non-LAI group (9% of the non-LAI group and 20% of the readmitted non-LAI group) ($P = 0.49$).

DISCUSSION

During the last decade the use of insulin in the early stages of diabetes has become more frequent. Common practice suggests adding a once-a-day insulin injection for treatment intensification of uncontrolled diabetes [8], but there is no consensus regarding the optimal insulin to be used, and the type of insulin is a subject of ongoing debate. In the literature the data are equivocal, with some studies showing superiority of the new long-acting insulins over other insulins [9] and others showing no such difference [10,11].

Our data suggest that basal insulin-based treatment using insulin glargine or determir is not superior to other medications when upgrading diabetes treatment. We found that HbA1c and FPG levels decreased to the same extent regardless of the treatment. We also found no improvement in all-cause readmissions and diabetes control-associated readmissions of patients treated with new long-acting insulin. Based on prior experience, we assumed that the between-group difference would be 1 ± 1.5% in HbA1c; however, in this study sample the between-group difference was much smaller, and the standard deviation was more than twice our estimates. We propose that the improved reduction in HbA1c levels observed in the patients treated with non-LAI does not signify superiority of non-LAI based treatment and is clinically insignificant. Therefore, the data shown here refute our baseline hypothesis on the superiority of the new long-acting insulin compared to other treatments for diabetes treatment intensification.

The effect of treatment selection on the number of readmissions is an important issue. Our data suggest that the number of readmissions of severely diabetic patients with very high baseline HbA1c levels is extremely high. In our database, many of the participants required more than one readmission during 12 months of follow-up. Most of the reasons for the admissions were not directly related to glucose control, and most were attributed to diabetes complications such as diabetic foot. It is therefore logical to assume that any effect on glucose control-related admissions is too small to be noticeable in this study group and may be obscured by the high readmission rate in our study population.

Our study is not without limitations. A major limitation was the lack of randomization of treatment. Like all non-randomized studies, our study too could be subject to biases that may have impaired our results. Since the decision regarding the treatment prescribed was made by the community clinic physician, the allocation of patients to the different treatment groups (LAI vs. non-LAI) may have been subject to variables that could by themselves influence the quality of treatment (such as disease severity, where the severe cases were allocated to LAI and the non-severe cases to non-LAI based treatment). With that in mind, we recommend that additional larger randomized studies be undertaken to confirm our results. Another major limitation of our study was the sample size. Some might argue that the small sample size prevents us from reaching our conclusions. Despite a relatively high flow of patients in our hospital clinic, we managed to obtain complete data and included fewer than 100 patients over a period of 12 months. Nevertheless, our study was powered to detect a clinically meaningful difference and, therefore, we claim that our results are valid. However, again, we stress the importance of larger randomized studies regarding this issue as well. Additional limitations of our study include the lack of information on disease duration, the dosage of pre-DOR treatment and other parameters that may influence the treatment change. These parameters were unavailable in the EHRs and were therefore not analyzed. This important information on each patient will definitely help in tailoring treatment intensification to each patient; however, our study was designed to answer the question whether the new LAIs should be given to all diabetes patients regardless of the disease duration, prior medical treatment, etc. Our answer to this question is a resounding no: There is no rationale to use the new LAIs for *all* diabetes patients, and we recommend (and currently practice) tailoring treatment to each patient. In this context we suggest that the new LAIs may still have superior results when used to intensify diabetes treatment in patients with evidence of hypoglycemia episodes. Despite the lack of data in our study, this treatment (insulin glargine and determir) probably does reduce the occurrence of hypoglycemic events as well as hypoglycemia-associated admissions.

An additional point worth mentioning is the undisputed difficulty in controlling diabetes. More than 90% of the patients in our database had HbA1c levels above 7% at study entry, and more than half had a level above 9%. This may be used as a sign of severe diabetes, and may also be associated with low beta cell function and/or poor compliance with treatment and diet. We believe the latter may be responsible for the fact that almost 20% of diabetes patients do not measure their HbA1c level on a regular basis (these patients were excluded from the analysis), and this may also explain the increased variance of time between tests. Regardless of the reason for the difficulty in controlling diabetes, the mere admission of a diabetes patient and the recommendations to change treatment had a positive effect on the quality of treatment in the community setting. It is our belief that the collaboration of efforts between hospital and community doctors to improve the treatment of diabetes (and probably all other cardiovascular risk factors) is likely to be beneficial for the patient.

It is our belief that the new long-acting insulins should not be routinely recommended to all diabetes patients in the attempt to intensify treatment. We propose that this treatment be used as tailored therapy, and that changing the oral hypoglycemic medication profile and/or adding an insulin that is not long acting is an equivalent option for diabetes control.

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Benign Liver Masses and Lesions in Children: 53 Cases over 12 Years

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ABSTRACT: **Background:** Primary liver masses in children may require intervention because of symptoms or concern about malignant transformation.

Objectives: To review the management and outcome of benign liver masses in children.

Methods: We conducted a retrospective chart review of children with liver masses referred to our institution during the period 1997–2009.

Results: Benign liver masses were identified in 53 children. Sixteen of these children (30%) had hemangioma/infantile hepatic hemangioendothelioma (IHH) and 15 (28%) had focal nodular hyperplasia. The remainder had 6 cysts, 4 hamartomas, 3 nodular regenerative hyperplasia, 2 adenomas, 2 vascular malformations, and one each of polyarteritis nodosa, granuloma, hepatic hematoma, lymphangioma, and infarction. Median age at presentation was 6 years, and 30 (57%) were female. Masses were initially noticed on imaging studies performed for unrelated symptoms in 33 children (62%), laboratory abnormalities consistent with liver disease in 11 (21%), and palpable abdominal masses in 9 (17%). Diagnosis was made based on characteristic radiographic findings in 31 (58%), but histopathological examination was required for the remaining 22 (42%). Of the 53 children, 27 (51%) were under observation while 17 (32%) had masses resected. Medications targeting masses were used in 9 (17%) and liver transplantation was performed in 4 (8%). The only death (2%) occurred in a child with multifocal IHH unresponsive to medical management and prior to liver transplant availability.

Conclusions: IHH and focal nodular hyperplasia were the most common lesions. The majority of benign lesions were found incidentally and diagnosed radiologically. Expectant management was sufficient in most children after diagnosis, although surgical intervention including liver transplant was occasionally necessary.

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KEY WORDS: hemangioendothelioma, focal nodular hyperplasia

Primary liver masses constitute the third most common group of solid abdominal tumors of childhood [1,2], with an incidence of 0.4 to 1.9 per million children each year [3]. Liver masses in children can be malignant, benign, or indeterminate [4]. Although improved radiographic modalities facilitate the identification of benign and malignant liver masses [2], differentiation of masses is still complex, and biopsy or resection for histological diagnosis sometimes becomes necessary [5-8]. Serum tests of alpha-fetoprotein level may be elevated in children with malignant lesions such as hepatoblastoma (90%) and hepatocellular carcinoma (50%), but cautious interpretation is warranted as alpha-fetoprotein level is frequently elevated in premature and/or normal infants up to 6 months of age and may be slightly elevated with benign tumors and with hepatic insult or regeneration [5,9].

Benign primary liver masses described in children include hemangioma/infantile hepatic hemangioendothelioma, focal nodular hyperplasia, simple hepatic cysts, mesenchymal hamartomas, adenomas, nodular regenerative hyperplasia, hematomas, arterial venous malformations, granulomas, and lymphangiomas [1-5,10,11]. Hemangiomas and hemangioendotheliomas are the most common vascular tumors in children and are the most frequent benign hepatic tumor seen in infants [5,11]. In small children hamartomas have been seen and are composed of mesenchymal and epithelial components often arranged to form a multicystic mass [6]. More commonly seen in older children and adolescents, focal nodular hyperplasia comprises stellate lesions of proliferating epithelial derived cells forming malformed bile ducts centrally circumscribed by a thin fibrous network of tissue that contains supplying blood vessels [3,5,12]. The diagnostic challenge is often to distinguish focal nodular hyperplasia non-invasively from an hepatic adenoma, which requires preemptive surgical resection as adenomas are at significantly higher risk for malignant transformation and/or spontaneous rupture and hemorrhage [5,7,11,12]. Nodular regenerative hyperplasia is characterized histologically by small hyperplastic nodules without a fibrous rim centered around portal tracts compressing adjacent, frequently atrophic, liver cells and sinusoids and is considered to be non-specific tissue adaptation to a heterogeneous distribution of blood flow [13,14]. Unfortunately, vascular contrast to demonstrate such features as

rim enhancement on computed tomography or magnetic resonance imaging does not conclusively distinguish focal nodular hyperplasia or nodular regenerative hyperplasia from malignant fibrolamellar hepatocellular carcinoma [5,9,12].

While the majority of benign masses may be of little consequence, morbidity and mortality can occur from benign masses [5,6]. Mass effect from a tumor can cause pain, biliary obstruction and inferior vena cava obstruction, limit lung capacity, or cause feeding difficulty [2,5,6]. Furthermore, malignant degeneration has been described from adenomas [5,12], rarely from hamartomas [6] or IHH [6,15], and possibly focal nodular hyperplasia [5]. Both IHH and hamartomas can result in fatal hemorrhage, high-output heart failure, thrombocytopenia, and disseminated intravascular coagulation (Kasabach-Merritt syndrome) [2,5,6,8]. The aim of this study was to review the clinical features, management and outcome of children diagnosed with benign liver masses at our center. These data may help illuminate an approach for the management of benign liver masses in the current era.

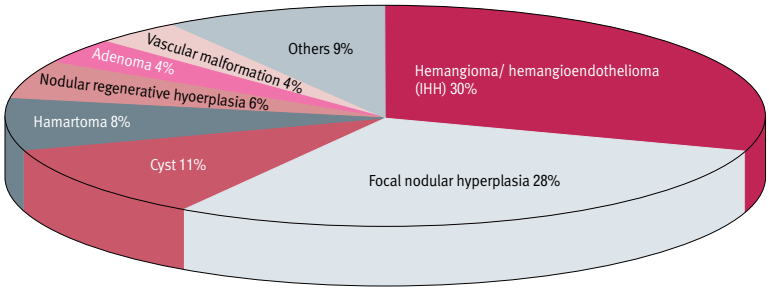
PATIENTS AND METHODS

A retrospective review of the records of all children with liver masses seen by the Pediatric Liver/Liver Transplant Program, a quaternary referral center for children with liver diseases, from 1997 to 2009 was undertaken after obtaining Institutional Review Board approval. Malignancy was excluded by evaluation of liver tumor markers and by interpretation of typical signal and enhancement characteristics seen on imaging. Histopathology, when available, was the gold standard of diagnosis. Children with preexisting chronic liver disease associated with developing benign and/or malignant liver masses such as hepatitis B or C, metabolic syndromes such as tyrosinemia, autoimmune hepatitis and/or sclerosing cholangitis, or chronic cholestatic syndromes such as progressive familial intrahepatic cholestasis were excluded from this study [5,11]. Children with indeterminant lesions, lesions without definitively benign imaging characteristics or available histopathology, were also excluded from this study. Database and statistical calculations were compiled with Excel (Microsoft, 2002).

RESULTS

Over the 10 year period 1997–2009, benign masses were diagnosed in 53 children referred to our pediatric liver program. Figure 1 illustrates the various types of benign masses by frequency. The most common were IHH and focal nodular hyperplasia, which together accounted for 58% of benign masses. Table 1 presents the demographics and clinical features of children with benign masses; the mode of diagnosis, management, and length of follow-up from presentation are detailed in Table 2.

Figure 1. Pie-chart illustrating the etiology of benign liver lesions



Diagnosis	n (%)	Diagnosis	n (%)
IHH	16 (30)	Nodular regenerative hyoerplasia	3 (6)
Focal nodular hyperplasia	15 (28)	Adenoma	2 (4)
Cyst	6 (11)	Vascular malformation	2 (4)
Hamartoma	4 (8)	Others	5 (9)
		Total benign	**53 (100)**

IHH = infantile hepatic hemangioma/hemangioendothelioma, FNH = focal nodular hyperplasia, NRH = nodular regenerative hyperplasia, Others = one each of polyarteritis nodosa, granuloma, hepatic hematoma, lymphangioma, and infarction

Sixteen children had IHH, 11 were incidentally found and were between 1 and 6 cm in size, including two infants with multiple IHH. The remaining five with symptomatic IHH were less than 5 months of age and had multiple masses up to 11 cm in size. Two infants developed congestive heart failure. Six children with IHH were treated with steroids. Four were listed for liver transplantation as they were refractory to treatment with steroids and/or vincristine. Three infants were transplanted by age 10 months, while the fourth died of congestive heart failure at age 4 months prior to availability of a liver graft. The fifth was a newborn with abdominal distension; evaluation with Doppler ultrasound and MRI revealed multiple IHH up to 11 cm in largest dimension. The masses responded to medical therapy with steroids, vincristine and aminocaproic acid and did not require surgical intervention. Four of 16 (25%) children with IHH demonstrated spontaneous resolution radiologically by 4 years of age.

Children with vascular lesions in the liver that were not IHH were classified as vascular malformation. An 11 year old with a dissecting pseudoaneurysm underwent transplantation and a newborn had a 3 cm venous malformation which regressed on follow-up imaging.

Fifteen children had focal nodular hyperplasia ranging in size from 2 to 13 cm (median 6 cm); 10 of these were incidentally found, 4 were discovered because of laboratory abnormalities, and one was secondary to an abdominal mass. The children with focal nodular hyperplasia who came to medical attention secondary to laboratory abnormalities or abdominal mass

IHH = infantile hepatic hemangioendothelioma

Table 1. Demographics and reason for presentation in children diagnosed with benign liver masses

Diagnosis	n (%)	Median age at Px (yrs) (range)	Gender F	Gender M	Px with abdominal mass	Px with lab abnormality	Incidental finding
IHH	16 (30)	0.4 (neo–18)	8	8	4	1	11
Focal nodular hyperplasia	15 (28)	14 (neo–17)	12	3	1	4	10
Cyst	6 (11)	2 (neo–17)	4	2	0	1	5
Hamartoma	4 (8)	2 (neo–16)	1	3	1	0	3
Nodular regenerative hyperplasia	3 (6)	16 (3–19)	2	1	1	1	1
Adenoma	2 (4)	12 (10–14)	0	2	1	1	0
Vascular malformation	2 (4)	6 (neo–11)	0	2	0	2	0
Others*	5 (9)	1 (neo–19)	3	2	1	1	3
Total benign	**53 (100)**	**6 (neo–19)**	**30**	**23**	**9**	**11**	**33**

Px = presentation, IHH = infantile hepatic hemangioma/hemangioendothelioma, neo = neonate (birth–60 days)
*Others includes one each of polyarteritis nodosa, granuloma, hepatic hematoma, lymphangioma, and infarction

Table 2. Mode of diagnosis and treatment of children with benign liver masses

Diagnosis	Total	Diagnosed by imaging	Diagnosed by biopsy	Diagnosed at resection or transplant	Observed	Medical treatment	Surgical treatment (includes Tx)	Median follow-up (mos) (range)
IHH	16	15	1	0	9	7	3	8 (1–81)
Focal nodular hyperplasia	15	6	4	5	8	0	7	16 (4–48)
Cyst	6	5	0	1	5	1	1	4 (2–60)
Hamartoma	4	0	0	4	0	0	4	30 (4–68)
Nodular regenerative hyperplasia	3	2	1	0	3	0	0	9 (2–25)
Adenoma	2	0	0	2	0	0	2	3 (2–3)
Vascular malformation	2	2	0	0	1	0	1	16 (12–20)
Others*	5	1	1	3	1	1	3	5 (1–40)
Total benign	**53**	**31**	**7**	**15**	**27**	**9**	**22**	**9 (1–81)**

IHH = infantile hepatic hemangioma/hemangioendothelioma
*Others includes one each of polyarteritis nodosa, granuloma, hepatic hematoma, lymphangioma, and infarction

detection were younger at presentation (median age 11 years) compared to those with incidentally found focal nodular hyperplasia (median age 14 years). The median size of focal nodular hyperplasia masses was 7 cm (range 5–12 cm) for symptomatic children compared to 5 cm (range 3–13 cm) in incidentally found focal nodular hyperplasia. A 3 year old with esophageal variceal bleeding and history of premature birth and umbilical line placement was found on imaging to have portal vein thrombosis. He had nodular regenerative hyperplasia on histology and a subsequent MRI demonstrated numerous 1 cm lesions in the liver. The child is stable after undergoing a splenorenal shunt. A 15 year old girl with Turner syndrome and supplementation with progesterone and growth hormone had multiple lesions up to 5 cm in size and absence of the portal vein; the lesions were diagnosed as nodular regenerative hyperplasia on histology.

The tumor was an incidental finding in 33 (62%) of the 53 children imaged for other reasons. Reasons for these imaging investigations included acute non-hepatic gastrointestinal processes (e.g., appendicitis) suspected in 12 cases, urinary issues such as infection or hematuria (n=7), suspected non-hepatic congenital abnormalities (n=6), investigation for ovarian cysts or torsion (n=3), and routine prenatal screening (n=2); further cases were identified for one each of viral respiratory process, monitoring of a cardiac transplant patient, and screening in a child with a family history of adrenal cancer, respectively. In none of these cases were the symptoms related to the tumors.

A male infant had an enlarged liver noted on prenatal ultrasound, and on postnatal imaging a suspicion for multifocal hepatoblastoma was raised. A resection at age 4 weeks revealed mesenchymal hamartoma and this boy was thriving at 4 months of age. Three children of various ages with a history of hydronephrosis, hematuria, and a sibling with adrenal tumor respectively, had hepatic lesions 2–6 cm in size uncovered during imaging investigations. Upon resection they had ciliated cystic hamartomas that did not recur. A 16 year old boy underwent ultrasonography for investigation of a urinary

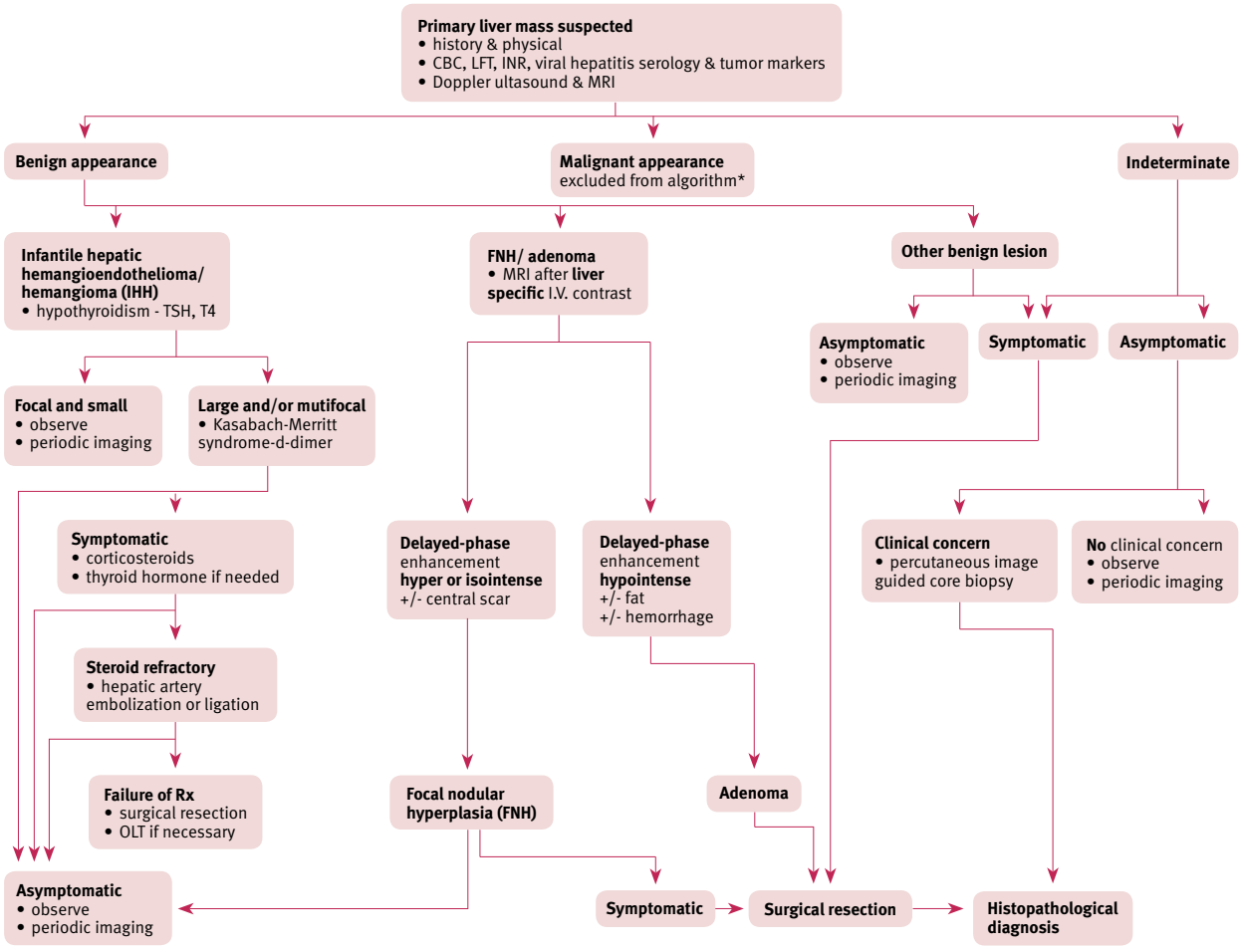
tract infection and was found to have a 12 cm hepatic cyst. Suspicion for echinococcal infection prompted treatment with albendazole. Surgical resection and pathological examination was not specific for an echinococcal origin of the cyst.

Laboratory abnormalities prompted abdominal imaging in 11 children (21%); 10 children had imaging done for abnormal liver function tests and one had thrombocytopenia. Radiographic findings were diagnostic in 31 (58%) of the 53 children. Definitive histological diagnosis was made in the remaining 22 (42%), either from imaging guided/laparoscopic biopsies in 7 children (13%) or from surgical resection (including liver transplantation) in 15 (28%). Of the 53 children with benign liver lesions, 27 were under observation while 17 had masses resected. Medications targeting masses were used in nine and liver transplantation was performed in four (three IHH, one vascular malformation). The only death occurred in a child with multifocal IHH unresponsive to medical management and prior to liver transplant availability.

For the 27 children whose benign liver lesions were observed without intervention, clinical follow-up information was available for a median duration of 9 months (range 1 month to 5 years). Four children who were observed without intervention had complete resolution of their tumor, while 3 had imaging studies showing tumor regression, and 14 children had lesions that were unchanged. None of these observed lesions were known to increase in size, although for six children no follow-up imaging information was available.

Almost all of our patients were referred from the New York/New Jersey regional area and ethnicity was representative of the diversity of the region, with no predominance for a particular tumor. Based on our experience, we devised an algorithm for the management of suspected benign pediatric liver masses [Figure 2] to better guide management at other regional referral centers with expertise in the diagnosis and management of pediatric liver lesions.

Figure 2. Algorithm demonstrating clinical approach to benign pediatric liver lesions



*The evaluation of lesions presumed to be malignant is excluded. FNH = focal nodular hyperplasia, OLT = orthotopic liver transplant

DISCUSSION

The present study is the largest single-center study documenting the clinical features, diagnosis, management and outcome in children with benign liver masses. Although rare in children, benign tumors affect approximately 20% of the U.S. population [10] and constitute a significant number of outpatient referrals annually in pediatric practice. In the present work, an approach to managing these lesions as non-invasively as possible, using the latest imaging techniques is presented and an algorithm developed to illustrate our approach.

The majority of benign masses in our series were incidentally found and asymptomatic, compared to the presence of symptoms in over 70% in other reported series [1,2]. This may be secondary to the increased use of improved imaging modalities detecting masses on studies performed for unrelated indications. In a study examining 155 adults with benign liver tumors [7], nearly half were symptomatic and only 10% had abnormal liver function tests in comparison to 22% children in our study. There is a report of more than 300 children with histologically diagnosed benign liver tumors, but this was pathology based and unfortunately no information on clinical presentation or outcome was provided in that series [16]. The other major study describing benign lesions in children is from more than two decades ago, and given that radiological methods of examination were not that advanced between 1950 and 1981, many of the 48 children had their lesions diagnosed after developing major complications and 13 of the 48 were diagnosed postmortem [1].

IHH was the most common benign liver lesion in our series. It may be suggested by visible cutaneous strawberry hemangiomas in an infant with a liver mass [9]. Associated hypothyroidism may also suggest that the mass is IHH, and previous reports suggest screening for hypothyroidism [11,17,18] as shown in our algorithm. All four of the infants listed for liver transplantation had evidence of hypothyroidism. A large rapidly growing IHH can cause high output heart failure, arteriovenous shunting, massive hepatomegaly and Kassabach-Merritt syndrome [2,8]. The latter refers to a localized intravascular coagulopathy with thrombocytopenia [2]. Elevated liver enzymes with or without jaundice may result from biliary and/or vascular obstruction by the lesion [9]. Diagnostic options to identify IHH include Doppler-enhanced sonography and contrast-enhanced CT or angiographic techniques [5,17]. Ultrasound without Doppler might only differentiate cystic masses from solid ones, and in one series IHH appeared as if solid in all six children [1]. MRI with contrast enhancement may provide the best identification of flow characteristics and surrounding vascular structures [17], with lower false positive rates for hepatocellular carcinoma and less ionizing radiation risk than CT [11]. For pediatric liver masses where a definitive diagnostic characterization by Doppler ultrasound is not achieved, our algorithm [Figure 2] suggests that referral to a center where MRI is available be strongly considered secondary to the superiority of MRI over CT [11]. Radiological findings may not always reflect true liver pathology, and in a study that initially identified 62 children with radiological diagnoses of IHH, 3 had malignant tumors based on tissue pathology [17].

Corticosteroids are the mainstay of treatment of IHH [5,17]. More recently propranalol has been used successfully in the initial treatment of IHH [18]. Second-line therapy includes hepatic artery ligation and transcatheter embolization [5,17], surgical excision [1,2,5,17], and rarely liver transplantation [5,11,19]. Observation with periodic re-imaging may be appropriate for asymptomatic IHH [9], as was utilized for the majority of 16 cases of IHH in our series [Table 2], with 4 (25%) demonstrating spontaneous resolution by age 4 years. Complete spontaneous regression of benign liver tumors can occur, including small focal IHH [5,20], inflammatory pseudotumor/myofibroblastic tumor [20] and peliosis hepatic [21].

Oral contraceptives are associated with the development of focal nodular hyperplasia, adenomas and nodular regenerative hyperplasia [2,5,20]. Only two of the patients in this series were on hormonal supplementation. This included a 14 year old adolescent female on a low dose oral contraceptive pill, with a 2 cm lesion diagnosed as focal nodular hyperplasia based on imaging characteristics. The oral contraceptive was stopped and the lesion has been managed expectantly without any significant enlargement. The other adolescent on hormonal supplementation, a 15 year old girl with Turner syndrome and supplementation with progesterone and growth hormone, had multiple lesions up to 5 cm in size and absence of the portal vein; the lesions were diagnosed as nodular regenerative hyperplasia on histology. In focal nodular hyperplasia many masses, but not all, demonstrate the classic finding of a central scar [5,12]. Adenomas frequently display a heterogeneous appearance due to intralesional fat and/or hemorrhage [12]. Accurate diagnostic differentiation of adenoma from focal nodular hyperplasia is important because adenomas may rupture and bleed or undergo malignant transformation into hepatocellular carcinoma, while focal nodular hyperplasia may usually be observed with expectant management [3,12].

MRI with gadobenate dimeglumine (MultiHance, Bracco Diagnostics, Princeton, NJ, USA) intravenous contrast provides accurate differentiation of focal nodular hyperplasia from adenoma for at least 97% of adults, as focal nodular hyperplasia enhances at 1–3 hours on delayed imaging phase because of the presence of bile ductules [12]. The telangiectatic type of focal nodular hyperplasia has multiple dilated blood spaces near the center of the lesion without significant fibrosis; it may have an increased potential for malignant deterioration and hemorrhage similar to adenomas and possibly should be managed aggressively [22]. Although adenomas may spontaneously disappear [20], our algorithm recommends surgical resection

of adenomas due to the risks of malignant degeneration [9,12] or hemorrhage after rupture [5,12].

Hamartomas are the second most common benign tumors in infants and are thought to be the result of ductal plate malformations, vascular insult, toxic injury or neoplasia [6]. Lesions may either be predominantly stromal or cystic with imaging studies showing a multilocular, multicystic mass with low density cysts separated by dense septae [5,6]. Similar to our experience in all four children with hamartoma, imaging findings are usually inconclusive, with the hamartoma diagnosed only after biopsy or resection to exclude the possibility of malignancy [5,6,9]. Solitary cystic lesions have previously been described to occur in children of all ages, are best demonstrated by ultrasound, and are usually asymptomatic [6] – all findings that are consistent with our series.

Histological differentiation can be difficult, and core biopsy, rather than fine needle aspiration, is recommended [6]. Lesions should be at least 2 cm in diameter and well visualized by the imaging modality used to facilitate biopsy. Major vascular structures may prevent safe passage of the needle in image-guided biopsy and make operative biopsy or resection difficult [23]. In a study of 36 pediatric liver lesions that underwent CT or sonographically guided fine needle aspiration, 53% had histopathology consistent with malignancy, 36% initially were classified as benign, and 11% had indeterminate pathology [4]. Of the 53 children with benign liver tumors followed by our center, 4 (8%) were transplanted, 3 for IHH and one for vascular malformation. While this high percentage may reflect that children referred to a quaternary referral center frequently require more advanced care, cases of benign liver tumors requiring transplantation are well documented. A recently published review mentions that in the United Network for Organ Sharing database during the 20 year period 1987–2007, there are 39 reported cases of liver transplant for IHH, 7 for adenoma, 2 for arteriovenous malformation and 2 for hamartoma [11]. Details of 29 pediatric and adult patients with benign tumors who have undergone liver transplantation have also been published [10,19,24,25]. An additional 112 pediatric and adult patients have had liver transplantation for polycystic liver disease [10].

The spectrum of benign liver lesions in pediatrics is similar to that seen in adults. Benign liver masses are of diverse etiologies and are often found incidentally. IHH and focal nodular hyperplasia were the most common lesions in the present series. Diagnosis was made radiologically in over 50% and histologically in the rest. The devised algorithm may be helpful in the management of children presenting with benign liver masses. Advanced imaging modalities together with improved surgical techniques, intensive care facilities, and the option of liver transplantation have led to a substantial improvement in the diagnosis and treatment of benign liver masses occurring in children.

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Hypercoagulation in Chronic Post-Traumatic Stress Disorder

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ABSTRACT: **Background:** Whereas procoagulation abnormalities in acute stress are well established, little is known about the mechanism of hypercoagulation in chronic stress, such as post-traumatic stress disorder (PTSD). This is crucial, given the fact that chronic coagulation disturbances have been associated with increased morbidity and premature mortality due to thromboembolism and cardiovascular disorders, complications recently described in PTSD patients.

Objectives: To explore the mechanisms of hypercoagulation in chronic PTSD.

Methods: Thirty patients diagnosed with chronic PTSD were enrolled and compared with a control group matched for age, gender and ethnicity. Hypercoagulation state was evaluated by levels of fibrinogen, D-dimer, prothrombin fragment F 1+2, von Willebrand factor (vWF) antigen, factor VIII activity, activated protein C resistance, ProC Global assay, and tissue factor antigen. Psychiatric evaluation was performed using the Mini-International Neuropsychiatric Interview and Clinician Administered PTSD Scale (CAPS).

Results: vWF antigen levels were significantly higher in patients with chronic PTSD compared with the controls (121.3 ± 42 vs. 99.7 ± 23, respectively, $P = 0.034$). Higher levels of vWF antigen and factor VIII activity were found in patients with severe chronic PTSD (CAPS › 80), compared to controls and patients with chronic PTSD and less severe symptoms (CAPS ≤ 80). However, no differences were observed in any other studied coagulation parameters between patients and controls.

Conclusions: Increased levels of vWF antigen and factor VIII activity were documented in severe chronic PTSD. These findings suggest that the higher risk of arterial and venous thromboembolic events in PTSD patients could be related to endothelial damage or endothelial activation.

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KEY WORDS: chronic post-traumatic stress disorder (PTSD), hypercoagulation, von Willebrand factor, factor VIII, thromboembolic events

Acute stress has been extensively studied and is known to correlate with procoagulant changes such as increased levels of fibrinogen, clotting factors VII, VIII, XII and von Willebrand factor [1], especially in the elderly. However, the data on chronic psychological stress and coagulation are still contradictory. This information is particularly important, since chronic stress diseases, such as post-traumatic stress disorder, may affect 8% of the population [2] and persist for a lifetime in the vast majority of cases. PTSD was recently described as a concurrent psychiatric and somatic disorder [3], given the common cardiovascular complication, which could be partially explained by possible coagulation disturbances. PTSD may develop as a result of life-threatening traumatic events and is diagnosed by the presence of three clusters of symptoms: re-experiencing, avoidance, and hyperarousal for at least 1 month [2]. In acute PTSD the duration of symptoms is limited to 3 months; after this period it is considered to be chronic [2]. In a recent study, PTSD-like symptoms were found in approximately 10% of Israelis exposed to a long wave of terrorist attacks in 2002 [4]. Chronic PTSD has been associated with poor physical health [5] and premature mortality due to venous and arterial thromboembolism, even when depression is controlled [3,6]. In PTSD, biological factors such as lower cortisol levels, increased sympathetic activity [7] and resting mean blood pressure [8] have been shown to be related to a hypercoagulable state, reflected by an increased amount of procoagulant molecules, providing a plausible biopsychological link to coronary artery disease [9]. Patients with PTSD develop a low grade systemic inflammatory state [10], suggesting a mechanism that could contribute to coronary heart disease. The mediators of this mechanism could be stress hormones (norepinephrine) producing a cascade of inflammatory reactions (interleukin 6, IL-1, C-reactive protein, tumor necrosis factor-alpha, leptin, resistin and angiotensin II) [11], which may culminate with the metabolic syndrome, elevated blood pressure, obesity, dyslipidemia, diabetes, heavy smoking and low physical activity level that are associated with PTSD and are major risk factors for coronary artery disease [12].

*** The first two authors contributed equally to this study**

PTSD = post-traumatic stress disorder
IL = interleukin

Inflammation can induce local thrombosis which, in turn, can amplify inflammation and this cross-talk contributes to atherosclerosis progression [13]. A positive and partially independent correlation was revealed between the severity of acute PTSD and plasma levels of both factor VIII and fibrinogen [14]. In addition, markers of endothelial dysfunction, i.e., soluble tissue factor, and vWF were found to be associated with acute PTSD and partly affected by psychobiological distress [15]; however, the data concerning a possible link between chronic PTSD, its symptom severity and hypercoagulation are relatively limited.

The aim of the current study was to assess the levels of hypercoagulation parameters in patients with chronic PTSD compared to matched controls who were exposed to the same trauma.

PATIENTS AND METHODS

The study group included 30 civilians diagnosed as suffering from chronic PTSD after the Second Lebanon War in summer 2006. Study participants were recruited at the Center for Anxiety and Trauma Disorders of the Rambam Health Care Campus between October and December 2007 and were diagnosed by senior psychiatrists as suffering from chronic PTSD for more than a year. The study was approved by the Rambam Institutional Review Board and all patients signed an informed consent form.

Inclusion criteria were age 18–70, diagnosis of chronic PTSD, and the ability to give informed consent. Participants were excluded from the study if they had a history of psychiatric disorder, major cardiac or thromboembolic events, evidence of acute infectious disease, a diagnosis of cancer, or if they were pregnant, drug abusers, or receiving anticoagulant therapy. The control group included 30 healthy civilians matched for age, gender and ethnicity, exposed to the same war trauma, who had not developed PTSD or other psychiatric disorders.

PSYCHIATRIC ASSESSMENT

All study participants were invited for one clinic visit during which they underwent psychiatric assessment to confirm the diagnosis of chronic PTSD and its severity. Assessment instruments included the MINI and the CAPS. The MINI (Mini-International Neuropsychiatric Interview) is an abbreviated psychiatric structured interview evaluating major adult Axis I disorders using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and International Classification of Diseases-10 (ICD-10). MINI elicits all the symptoms listed in the symptom criteria for DSM-IV and for ICD-10 for 15 major Axis I diagnostic categories, one Axis II disorder and for suicidality. Its diagnostic algorithms are consistent with DSM-IV and ICD-10 diagnostic algorithms. The CAPS (Clinician Administered PTSD Scale) is a structured interview assessing PTSD diagnostic status, symptom severity, core and associated symptoms. It evaluates the frequency and intensity of each symptom using standard prompted questions and explicit, behaviorally anchored rating scales [16]. In the current study, a CAPS score > 80 corresponded to severe PTSD, and a CAPS score ≤ 80 corresponded to mild PTSD.

MINI = Mini-International Neuropsychiatric Interview

COAGULATION STUDIES

During the same visit, venous blood samples of patients and controls were collected by venipuncture into tubes with 3.2% sodium citrate for coagulation studies. Blood samples were centrifuged at 2000 g for 15 minutes. Prothrombin time, activated partial thromboplastin time, fibrinogen, ProC Global assay and activated protein C resistance tests were performed on fresh plasma samples. All other coagulation assays were performed on thawed frozen plasma samples. Plasma samples were frozen after a second centrifugation at 2000 g for 15 minutes in aliquots at -70 ± 5°C. Prior to testing, plasma aliquots were thawed in a 37 ± 0.5°C water bath for 15 min. PT, PTT, fibrinogen, ProC Global assay and APC-R were performed on the STA-R evolution analyzer (Diagnostica Stago, Gennevilliers, France). Recombinant human thromboplastin Dade Innovin® (Dade Behring Marburg GmbH, Germany) was used for PT assay. STA-PTT®, STA-FIBRINOGEN and STA-LIATEST® D-DI kits were employed for PTT, fibrinogen and D-dimer assays, respectively (Diagnostica Stago). The ProC Global assay kit (Dade Behring) and Coatest APC resistance kit (Chromogenix – Instrumentation Laboratory SpA Milan, Italy) were used for the relevant tests.

Levels of coagulation factor VIII activity were determined by one-stage assay using factor VIII deficiency plasma (Diagnostica Stago). Levels of vWF antigen were evaluated using the STA-LIATEST® vWF:ag kit (Diagnostica Stago). Prothrombin fragment F1+2 concentration, as a marker of prothrombin activation, was measured by an enzyme-linked immunosorbent assay using Enzygnost® F1+2 (monoclonal) (Dade Behring). Tissue factor antigen levels were determined with the IMUBIND® Tissue Factor ELISA kit (American Diagnostica Inc., Stamford, CT).

STATISTICAL ANALYSIS

Data were analyzed using the SPSS statistical software package. Differences between the two groups in coagulation parameter levels and other continuous variables (age, years of education) were estimated with the *t*-test. Differences

CAPS = Clinician Administered PTSD Scale
PT = prothrombin time
PTT = partial thromboplastin time
APCR = activated protein C resistance
vWF = von Willebrand factor
F1+2 = fragment F1+2

between the two groups in categorical demographic variables (gender, marital status, employment status and CAPS) were checked by Pearson chi-square or Fisher's exact test. Linear correlation between CAPS scores and the level of each of the coagulation factors as well as between CAPS scores and education duration was analyzed using Pearson correlation. $P < 0.05$ was considered significant.

RESULTS

Table 1 shows key demographic and ethnic characteristics of the two groups. The patients with chronic PTSD and the controls were matched in all criteria apart from education duration and employment status. Patients had higher PTSD symptom scores compared with controls; the mean CAPS score was 89 ± 25 for patients and 0.9 ± 1.4 for controls. In addition, PTSD patients had higher symptom levels of anxiety, suicidal thoughts and depression; almost 73% of PTSD patients had comorbid major depression and 26% had suicidal thoughts.

vWF antigen levels were found to be significantly higher in patients with chronic PTSD as compared with controls. No differences were documented in other studied coagulation factor levels between the two groups [Table 2]. Significantly higher levels of vWF antigen and factor VIII activity were observed in patients with severe chronic PTSD (CAPS > 80) compared with controls and 10 patients with mild chronic PTSD (CAPS ≤ 80) [Table 3].

Factor VIII levels correlated with those of vWF antigen in both patient and control groups ($r = 0.7$, $P < 0.0001$). However, factor VIII levels correlated with F1+2 only in the patient group ($r = 0.4$, $P = 0.04$), and with fibrinogen levels only in the control group ($r = 0.4$, $P = 0.02$). No correlation was found between the CAPS scores and the level of any of the coagulation factors, or education duration.

Among patients with chronic PTSD, no differences were found in any of the studied coagulation parameters between subjects with comorbid major depression or suicidal thoughts and those with PTSD only, or between employed and unemployed individuals. In the patient group, no correlation was observed between education duration and the CAPS score ($r = -0.005$, $P = 0.979$). In addition, no significant correlation was demonstrated between vWF and education duration or between factor VIII activity levels and education duration either in patients ($r = -0.12$, $P = 0.52$ or $r = -0.16$, $P = 0.38$, respectively) or in controls ($r = -0.04$, $P = 0.81$ or $r = -0.01$, $P = 0.95$, respectively).

Table 1. Demographic characterization of PTSD patients and controls

	Patients (n=30)	Controls (n=30)	*P* value
Gender (male/female)	11/19	11/19	NS
Age (yrs, mean ± SD)	39.63 ± 11	39.93 ± 10.9	NS
Marital status (married/not married)	15/15	14/16	NS
Ethnicity (Jewish/Arabs)	14/16	12/18	NS
Employment status (employed/unemployed)	18/12	30/0	< 0.001
Education (yrs, mean ± SD)	12 ± 1.6	16.43 ± 2.2	< 0.001

NS = not significant

Table 2. Plasma coagulation parameters in PTSD patients compared with controls

Plasma parameters (mean ± SD)	Patients (n=30)	Controls (n=30)	*P* value
PT (sec)	9.8 ± 1	9.9 ± 1	0.651
PTT (sec)	33.7 ± 3	34.8 ± 3	0.178
D-dimer (mg/L)	0.4 ± 0.4	0.35 ± 0.3	0.842
Fibrinogen (mg/dl)	322.8 ± 60	343.1 ± 66	0.324
Protein C global assay (PCAT-NR)	0.77 ± 0.13	0.78 ± 0.11	0.796
APC sensitivity ratio**	2.43 ± 0.23	2.42 ± 0.25	0.8
vWF antigen (u/ml)	121.3 ± 42	99.7 ± 23	0.034
Factor VIII activity (u/ml)	123.8 ± 31	111.3 ± 28	0.208
Tissue factor (pg/L)	36.4 ± 21	39.8 ± 20	0.279
Prothrombin F1+2 (pmol/L)	208.7 ± 109	191.3 ± 71	0.734

PCAT-NR = protein C activation time-normalized ratio, APC = activated protein C sensitivity ratio, vWF = von Willebrand factor

P < 0.05 considered significant

Table 3. Levels of FVIII activity and vWA antigen in severe PTSD compared with mild PTSD and controls

	CAPS > 80	CAPS ≤ 80	*P* value
Patients (n)	20	10	–
Controls (n)	0	30	–
vWF antigen (u/ml)	130.4 ± 32	111.1 ± 27	0.043
FVIII activity (u/ml)	128.5 ± 48	101.5 ± 21	0.022

CAPS = clinician administered PTSD scale

CAPS > 80 = severe PTSD, CAPS ≤ 80 = mild PTSD

DISCUSSION

The lifetime prevalence of PTSD is estimated to be about 8% in the general population, although an additional 5–15% may experience subclinical forms of the disorder [2]. The symptoms are chronic and often life-lasting, disabling people and causing a financial burden on society. PTSD patients are at increased risk of mortality, especially from cardiovascular disease and thromboembolic events that could be associated with hypercoagulation [2,5,17].

The aim of the current study was to assess the levels of hypercoagulation parameters in patients with chronic PTSD compared to matched controls who were exposed to the

same trauma. Among all the hypercoagulation parameters evaluated, including D-dimer, F1+2, tissue factor levels and protein C pathway activity, only levels of vWF antigen were found to be significantly higher in the patient group compared to the controls. These results suggest that the higher risk of arterial thrombosis in PTSD patients may be related to endothelial damage or endothelial activation and is not associated with coagulation activation or decreased activity of the protein C pathway. In patients with severe PTSD (CAPS > 80), elevated levels of vWF were accompanied by high FVIII activity levels.

vWF plays an important role in hemostasis and thrombosis, both as a cofactor in platelet adhesion and aggregation and as a circulating carrier protein for factor VIII [18]. Meta-analyses of prospective studies have suggested that increased circulating vWF levels are associated with a high risk of CAD [19,20], and elevated plasma levels of factor VIII are related to an increased risk of venous thrombosis [21,22].

Von Kanel et al. [14] found a positive and partially independent association between dimensional aspects of acute PTSD and plasma levels of both factor VIII and fibrinogen, suggesting a correlation between the severity of acute PTSD symptomatology and concentration of these procoagulant factors. Their data also suggest that traumatic stress could increase levels of factor VIII [14]. Factor VIII and fibrinogen are known to be acute-phase reactants [23-25]; however, in our study no differences were found in fibrinogen levels between patients and controls, but the high levels of factor VIII were associated with elevated levels of vWF. These findings may imply that fibrinogen levels return to normal in the chronic stress state and that higher levels of factor VIII and vWF are associated with chronic endothelial cell activation, but this should be further investigated.

In a later study, von Kanel and co-authors [15] revealed elevated levels of soluble tissue factor, which is another endothelial marker, in 14 patients with acute PTSD developed after an accident compared to 14 controls who did not have PTSD. In this study, no differences were documented in the levels of vWF antigen. In our study, the levels of soluble tissue factor, measured by the method used by von Kanel et al., did not differ between the study and control groups. Differences in the results of endothelial marker evaluation might stem from chronic versus acute state, variations in study populations and the type of trauma that patients were exposed to.

The aim of this study was to explore hypercoagulation parameters in a chronic stress disorder (PTSD). Our findings of elevated levels of vWF and FVIII activity support the hypothesis that hypercoagulation persists after an acute period in PTSD, which could contribute to the morbidity and mortality in these patients and should be addressed in the treatment program.

Compared to previous studies [14,15], the current trial included larger cohorts of patients with chronic PTSD (duration ≥ 1 year) and controls who were exposed to the same trauma. However, the limitation of our study is related to the small size of the group with severe chronic PTSD (CAPS > 80). Another limitation is associated with the higher education and employment levels found in the control group compared to the patient group.

Levels of vWF and factor VIII were not found to be affected by any concomitant psychiatric illness (e.g., depression, suicidal thoughts), education duration or employment status; however, they were associated with the incidence and severity of chronic PTSD.

CONCLUSIONS

Severe chronic PTSD is associated with high levels of vWF and factor VIII, which may explain the increased risk of developing arterial and venous thrombosis among patients with this disorder. These findings could contribute to the improvement of PTSD diagnosis and treatment. The results obtained in the current study may be considered preliminary. To assess their significance, prospective clinical trials larger cohorts of patients with severe chronic PTSD are warranted. It is also crucial that follow-up of arterial and venous thrombosis be incorporated in protocols of these studies.

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Capsule

Milk drinkers may be thinner

Researchers at Ben-Gurion University of the Negev in Beer Sheva, Israel, say that milk contains key nutrients – such as calcium and vitamin D – that help in weight loss. They tracked 300 overweight or at-risk men and women aged 40–65 who were either on a low fat Mediterranean or low carbohydrate diet for two years. They found that participants on either diet with the highest dairy calcium intake 6 months into the study – averaging about 580 mg per day, or the amount in about two glasses of milk – lost about 5.4 kilos at the end of the two years compared to about 3.1 kilos for those with the lowest dairy calcium intake – about 170 mg or about half a glass. The study, published in the *American Journal of Clinical Nutrition*, also found that at 6 months each additional 177 ml serving of milk or milk products – about three-quarters of a glass of milk – was associated with successful weight loss 4.5 kilos above the average.

Israel High-Tech & Investment Report

Capsule

Structure-based design of non-natural amino acid inhibitors of amyloid fibril formation

Many globular and natively disordered proteins can convert into amyloid fibrils. These fibrils are associated with numerous pathologies as well as with normal cellular functions, and frequently form during protein denaturation. Inhibitors of pathological amyloid fibril formation could be useful in the development of therapeutics, provided that the inhibitors were specific enough to avoid interfering with normal processes. Sievers and collaborators show that computer-aided, structure-based design can yield highly specific peptide inhibitors of amyloid formation. Using known atomic structures of segments of amyloid fibrils as templates, the authors have designed and characterized an all-d-amino-acid inhibitor of the fibril formation of the tau protein associated with Alzheimer's disease, and a non-natural l-amino-acid inhibitor of an amyloid fibril that enhances sexual transmission of human immunodeficiency virus. These results indicate that peptides from structure-based designs can disrupt the fibril formation of full-length proteins, including those, such as tau protein, that lack fully ordered native structures. Because the inhibiting peptides have been designed on structures of dual-β-sheet 'steric zippers', the successful inhibition of amyloid fibril formation strengthens the hypothesis that amyloid spines contain steric zippers.

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Eitan Israeli

"Eat food. Not too much. Mostly plants"

Michael Pollan (b. 1955), American author, journalist, activist, and professor of journalism at the University of California, Berkeley. A 2006 *New York Times* books review describes him as a "liberal foodie intellectual"

Factors Associated with Hypertensive Patients' Compliance with Recommended Lifestyle Behaviors

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ABSTRACT: **Background:** A crucial element in controlling blood pressure is non-pharmaceutical treatment. However, only a few studies specifically address the question of hypertensive patients' compliance with physicians' recommendations for a healthy lifestyle.

Objectives: To explore factors associated with hypertensive patients' compliance with lifestyle recommendations regarding physical activity, smoking cessation and proper diet.

Methods: We performed a secondary data analysis of a representative sample of 1125 hypertensive patients in Israel's two largest health funds. Data were collected in 2002–2003 by telephone interviews using structured questionnaires. The response rate was 77%. Bivariate and multivariate analysis was conducted.

Results: About half of the hypertensive patients reported doing regular exercise and adhering to a special diet; 13% were smokers. About half reported receiving counseling on smoking cessation and diet and a third on physical exercise. A quarter reported receiving explanations regarding self-measurement of blood pressure and signs of deterioration. Multivariate analysis revealed that patients' beliefs about hypertension management, their knowledge on hypertension and its management, and physician counseling on a healthy lifestyle and self-care, have an independent effect on compliance with recommended lifestyle behaviors.

Conclusions: The low counseling rates suggest that there may be a need to improve physicians' counseling skills so that they will be more confident and effective in delivering this service to their patients. A model based on educating both physicians and patients may contribute to improving the care of hypertensive patients.

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KEY WORDS: hypertension, patient compliance, patient adherence, lifestyle, risk reduction behavior

*Deceased

An integral and crucial element in controlling blood pressure is non-pharmaceutical treatment, which includes smoking cessation, weight reduction, proper diet, and regular physical activity. However, the level of patients' compliance with medical and non-medical treatment recommendations is low. Consequently, blood pressure is controlled in only about a third of hypertensive patients [1,2].

Patients' education, their knowledge of cardiovascular risk factors, their perception of the benefits and potential risks of treatment, and their active participation in treatment decisions have been found to affect their compliance with treatment recommendations [3]. Physicians play an important role in helping patients modify unhealthy lifestyles and behaviors [4,5], but they do not always routinely advise their hypertensive patients to change their behavior [6].

Most research on patient compliance with hypertension-control guidelines focuses on medication, adverse events of the medication, and the patients' sense of well-being. There are only a few studies that specifically address the issue of compliance with recommendations for a healthy lifestyle, none of which were conducted in Israel. The objective of the present study was to explore factors associated with the compliance of hypertensive patients with lifestyle recommendations regarding physical activity, smoking cessation and proper diet.

PATIENTS AND METHODS

This is a secondary data analysis of a study on the implementation of hypertension and diabetes guidelines in primary care [7]. The study was approved by the Institutional Review Board of HaEmek Medical Center. The study population included hypertensive patients of primary care physicians affiliated with the two largest health funds in Israel (Clalit Health Services and Maccabi Healthcare Services), insuring over 80% of the population.

The sample was drawn in two stages. In the first stage, a representative stratified sample of 997 primary care physicians was drawn from the health funds' lists. Of these, 743 physi-

cians were interviewed, yielding a response rate of 78%. In the second stage, we sampled 1775 patients with hypertension and/or diabetes listed with these primary care physicians. A total of 1369 participants completed the patient questionnaire (77% response rate). Each participant was assigned a weight based on the probability of being sampled. The secondary data analysis presented in this article is based on the 1125 weighted cases of patients with hypertension.

DATA COLLECTION

Between December 2002 and June 2003, telephone interviews, using structured questionnaires, were conducted with hypertensive patients. The questions were constructed by the research team based on the health funds' guidelines for treating hypertension. A pretest was conducted with 300 patients and the questions were tested for face and construct validity. The interviews lasted an average of 20 minutes and were conducted by trained interviewers. The questionnaires were translated into Russian and Arabic to include significant segments of Israel's population that do not speak Hebrew fluently.

MEASURES

The outcome variable of the study was health behaviors. Patients responded yes vs. no/sometimes to questions on physical activity, whether they followed a special hypertension diet (e.g., caloric restriction, no salty foods, etc.), and whether they smoked. A measure was built by counting the number of times participants reported healthy health behaviors. The 20% with the highest health behavior compliance scores were defined as "high" in the measure. Independent variables in the study were:

- *Sociodemographics:* gender, age, education, family status and country of origin
- *Body mass index:* calculated according to self-report of height and weight, and categorized into normal (19–25), overweight (26–29) and obese (30 and over)
- *Level of blood pressure:* self-report of numerical blood pressure level last time tested, and response to the question: "is your blood pressure controlled nowadays?" (yes vs. sometimes/no)
- *Medication:* self-report on taking prescription medicines regularly for blood pressure patients (yes vs. sometimes/no)
- *Counseling on lifestyle behaviors and self-care:* We used seven questions (yes vs. no) to ascertain whether or not participants received counseling from medical staff regarding appropriate diet, body weight, smoking cessation, physical activity, risks and complications of hypertension, self-measurement of blood pressure, and signs of deterioration in the patient's medical condition. Respondents who answered "yes" to 5–7 items were defined as "high" in this measure
- *Knowledge on hypertension:* Respondents were asked whether they thought the following statements were true or false: "High blood pressure can damage blood vessels and lead to heart attacks and strokes," "Being overweight affects blood pressure," "Salt consumption raises blood pressure," "Physical activity helps reduce blood pressure," and "Medication is all that is needed to treat hypertension." The measure counted the number of correct answers ranging from 0 to 5. Those with 0–2 correct answers were defined as "low"
- *Beliefs about hypertension management:* The respondents were asked to respond "yes" or "no" to the following statements: "I believe that medication to reduce hypertension will help me feel better," "I believe that a diet to reduce hypertension will help me feel better," "A patient diagnosed with hypertension has to continue treatment whether or not his/her condition improves," "I believe that it is possible to control my blood pressure." The measure counted the number of constructive beliefs from 0 to 4. Those with 0–2 constructive beliefs were defined as "low"
- *Perceived responsibility for hypertension management:* We evaluated perceived responsibility for hypertension care based on patients' reports as being "primarily or solely of the patient" vs. "primarily of the medical team."

STATISTICAL ANALYSIS

Statistical analyses were conducted using the SPSS Version 11.5 computer package. We first ran descriptive statistics. We then conducted chi-square tests to establish bivariate correlations with the outcome variables. All variables significant at the 0.05 level were examined for multi-colinearity and then entered into multivariate logistic regression models as potential predictors of compliance with recommended lifestyle behaviors. We found no multi-colinearity effects among the various indices entered into the regression models.

RESULTS

The characteristics of the study population are shown in Table 1. Fifty percent of the patients were men, and 78% of the sample was 61 years old and over; 56% were born outside Israel, 73% were married, and 34% had more than 12 years of education. Regarding their medical condition, 41% were overweight (BMI 26–29) and 24% were obese (BMI 30 and above); 69% reported that their blood pressure was controlled. When asked about numerical values, 52% reported that their blood pressure was lower than 140/90 mmHg at the last measurement. Taking prescription medication was reported by 95%.

About half the current smokers reported receiving counseling on smoking cessation. About half of all respondents reported receiving counseling on diet and a third on physi-

BMI = body mass index

Table 1. Sociodemographic and medical characteristics of patients

	(n=1125)
Age (yrs)	
24–60	244 (22)
61–72	384 (35)
73+	464 (43)
Gender	
Male	560 (50)
Female	565 (50)
Country of origin	
Israel	478 (44)
Other countries	613 (56)
Family status	
Married/living with partner	790 (73)
Divorced/separated	44 (4)
Widowed	229 (21)
Single	26 (2)
Education (last institution attended)	
Post-high school/college or university	364 (34)
Other	713 (66)
BMI	
Normal	335 (35)
Overweight	388 (41)
Obese	233 (24)
Systolic and diastolic blood pressure when last checked	
Healthy, below 140/90	405 (52)
140/90–159/99	197 (25)
160/99–179/109	139(18)
Over 180/110	39(5)
Is your blood pressure controlled?	
Yes	729 (69)
Sometimes	210 (20)
No	111 (11)
Has your physician prescribed medication for hypertension	
Yes	1054 (95)
No	52 (5)

The numbers in parentheses represent the percentage of patients with a valid answer for each field

Table 2. Patients' reports on lifestyle and self-management counseling by medical staff

	(n=1125)
Lifestyle counseling	
Current physician recommended physical activity Yes	338 (31)
Current physician discussed smoking cessation (current smokers only) Yes	(n=143) 77 (54)
Current physician discussed the need for a suitable diet – what you may and may not eat Yes	581 (54)
Current physician discussed your desirable weight Yes	532 (50)
Self-management counseling	
Current physician explained the risks and complications of high blood pressure Yes	57 (641)
Current physician explained how to measure blood pressure by yourself Yes	24 (270)
Current physician explained about signs for deterioration Yes	25 (281)

The numbers in parentheses represent the percentage of patients with a valid answer for each field

cal exercise. A quarter reported receiving explanations about self-measurement of blood pressure and about signs of deterioration they should watch out for [Table 2].

About half of the patients reported doing regular exercise and adhering to a special diet to reduce hypertension. Overall knowledge rates were high on most items but 37% of the patients believed that treating the disease only with medication was sufficient. Most people believed that high blood pressure can be treated [Table 3].

A multivariate logistic regression analysis to predict patients' compliance with a healthy lifestyle shows that age under 60 (odds ratio 0.62, $P < 0.05$), low scores on the "positive beliefs about hypertension management" scale (OR 0.44, $P < 0.05$) and on the "knowledge about hypertension and its management" scale (OR 0.28, $P < 0.05$) predicted low scores on healthy lifestyle behavior. Reported counseling by the primary care physician on a healthy lifestyle and self-care (OR 1.59, $P < 0.05$) predicted high scores on healthy lifestyle behavior. Other demographic variables in the model (gender, education, language) did not have a statistically significant effect on compliance with a healthy lifestyle.

OR = odds ratio

DISCUSSION

The results of the study show that the majority of hypertension patients are informed and have knowledge about both hypertension and the effect of a healthy lifestyle on controlling blood pressure. Furthermore, most believed that their disease could be managed. However, we found that many patients did not lead a healthy lifestyle. Only two-thirds of the respondents reported that they exercise and 13% of the respondents still smoke. Furthermore, only one-third of the respondents have a body mass index within normal levels, while others are overweight or obese. Finally, only 52% of the respondents reported that they had normal blood pressure levels (< 140/90 mmHg) at their last checkup and 95% were prescribed medication. These findings suggest that patients' lifestyle behaviors may contribute to their elevated blood pressure levels. Data from the U.S. National Health and Nutrition Examination Survey for 1999–2004 show that 65% of hypertensive patients do not have their blood pressure controlled to levels below 140/90 mmHg, which is attributed to poor management of elevated systolic blood pressure [8].

The non-optimal results among hypertensive patients in Israel could stem from the fact that in addition to the great difficulty in lifestyle adjustment [2,9], only a third to half of

Table 3. Patients' reported health behaviors, knowledge and beliefs about hypertension and its management

	(n=1125)
General Behavior	
Do you exercise regularly?	
Yes	537 (48)
No	588 (52)
Do you smoke, or have you in the past?	
I smoke	143 (13)
I used to smoke	410 (36)
I have never smoked	572 (51)
Do you follow a special diet for your hypertension (low calorie, low fat, salt-free, etc.)?	
Yes	500 (45)
Sometimes	230 (21)
No	379 (34)
Knowledge	
Unbalanced blood pressure can damage blood vessels and lead to heart attacks and strokes	
True	997 (91)
False	5 (1)
Don't know	97 (8)
Being overweight does not affect blood pressure	
True	154 (14)
False	799 (73)
Don't know	148 (13)
Salt consumption raises blood pressure	
True	975 (88)
False	26 (2)
Don't know	106 (10)
Physical exercise helps reduce blood pressure	
True	853 (78)
False	60 (5)
Don't know	184 (17)
Medication is all that is needed to treat hypertension	
True	410 (37)
False	600 (54)
Don't know	93 (9)
Beliefs	
I believe that medication to reduce hypertension will help me feel better	
Agree	933 (88)
Don't entirely agree	69 (6)
Disagree	40(4)
Don't know	18 (2)
I believe that a diet to reduce hypertension will help me feel better	
Agree	827 (77)
Don't entirely agree	70 (6)
Disagree	101 (10)
Don't know	74(7)
A hypertension patient has to be treated constantly, whether or not his/her health improves	
Agree	978 (90)
Don't entirely agree	26 (3)
Disagree	25 (2)
Don't know	53 (5)
I believe that it is possible to control my blood pressure	
Agree	821 (76)
Don't entirely agree	88 (8)
Disagree	55 (5)
Don't know	111(11)
Who is responsible for ensuring your blood pressure is balanced?	
Full/main responsibility is with the doctor and/or nurse	207 (21)
Full/main responsibility is with the patient	823 (79)

The numbers in parentheses represent the percentage of patients with a valid answer for each field

Table 4. Multivariate logistic regression: predictors of healthy lifestyle behavior

	OR	CI 95%
Age (up to 60)	0.62*	0.41–0.94
Language (Hebrew)	1.24	0.67–2.30
Gender (male)	1.05	0.75-1.45
Education (high)	1.34	0.95–1.90
Believes responsibility for balanced blood pressure is primarily of medical team	0.79	0.49–1.27
Constructive beliefs about hypertension management (low)	0.44*	0.25–0.79
Knowledge about hypertension and its management (low)	0.28*	0.12–0.64
Received counseling about lifestyle & self-care (high)	1.59*	1.06–2.34

$P < 0.05$*
Hosmer and Lemshow test chi-square 5.69, $P = 0.68$

the hypertensive patients reported receiving counseling from their physician on the necessity of smoking cessation, correct diet, desired weight, and regular exercise in the treatment of blood pressure. Previous studies suggest that knowledge transferred from medical staff is an important factor in inducing patients to comply with lifestyle recommendations [10]. Nevertheless, similar low counseling rates were reported in studies conducted abroad [11-13].

The main finding of the multivariate analysis was that patients' beliefs about hypertension management, patients' knowledge about hypertension and its management, and physician counseling on a healthy lifestyle and self-care each have an independent effect on hypertensive patients' reported compliance with the recommended lifestyle behaviors.

The effect of beliefs and knowledge about hypertension and its management is concordant with the known theoretical model relating attitudes to changes in lifestyle behaviors [14], as well as findings of former studies reporting that patient education about hypertension and lifestyle modification improved blood pressure control [2,3]. Apparently, such patients can play a more active role in their treatment and therefore are more effective in controlling their condition. The role of physician counseling in patient's compliance with lifestyle changes is also concordant with previous empiric studies [5,10]. Low counseling rates are attributed to a lack of time, knowledge, skills and training in lifestyle counseling, leading to physicians' low self-confidence in performing this role [15-17].

One of the greatest challenges facing medical systems is finding effective strategies for convincing and helping patients with chronic disease, including those with hypertension, to change their lifestyle and to play an active part in their treatment. The predominant theory is that there is a need to understand what motivates each patient and what affects his/her motivation and to convince him/her to make the change accordingly [18,19]. This can be achieved by organizing patient-centered workshops, for example, to teach about hypertension and to enhance patients' motivation to play an active role in their treatment. This will result in empowering patients and making them partners in the management of their condition.

This study has several limitations. First, the study was based on self-reporting by patients regarding their lifestyle behaviors and physician recommendations. These may be inaccurate because of "social desirability" responses or recall difficulties. Nevertheless, patients are considered a reliable source of information [20] on such topics. Furthermore, there is no alternative source of information regarding patients' behaviors and physicians' lifestyle counseling as this is not recorded in the medical files. Second, as in previous studies on these topics, the cross-sectional nature of the design prohibits conclusions about cause and effect, and therefore we refer only to an association between lifestyle behaviors and the independent variables in the multivariate regression model.

In conclusion, our study showed that receiving counseling from a physician about a healthy lifestyle and self-care, being informed about hypertension and its management, and having positive beliefs with regard to managing this condition led to maintenance of a healthy lifestyle. However, the low counseling rates found in the study suggest that there may be a need to improve physicians' counseling skills so that they will be more confident and effective in delivering this service to their patients. A model based on educating both physicians and patients may contribute to improving the care of hypertensive patients.

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"There is more to life than increasing its speed"

Mohandas Karamchand Gandhi (1869-1948), political and ideological leader of India who through mass civil disobedience and total non-violence led India to independence and inspired civil rights and freedom movements across the world

"A society grows great when old men plant trees whose shade they know they shall never sit in"

Greek proverb

Shortage of Surgeons, Fragmentation of General Surgery, and the Need for a General Surgery Specialty

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KEY WORDS: surgery, resident, shortage, fragmentation

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General surgery residency and practice have changed dramatically over the last years due to three major trends in surgical training. These are: a) the proliferation of fellowships in subspecialties of general surgery, b) efforts to recognize subspecialties of surgery as specialties in their own right, and c) pressure to reduce and even eliminate the traditional residency period in general surgery prior to subspecialization [1]. These trends have resulted in a shortage of surgeons who choose general, emergency, and trauma surgery as their future career.

The severe shortage of general surgeons exists throughout the world. The current scene in the United States unfortunately represents the worldwide occurrence. In the U.S., of an estimated 21,500 surgeons, 6000 perform very few surgeries and work primarily in administration; many of them are semi-retired, and 705 surgeons die or retire annually. Of the 1000 general surgeons who are certified annually, 100 never practice surgery, 60% elect further subspecialty training, and 500 are practicing general surgery. The current annual demand for young surgeons in the United States is 1875. With 705 graduates needed for general surgery positions, there is an annual shortage of 205 general surgeons. The situation in Israel is not very different. The number of residents entering residency programs is declining. Interns' perceptions of the heavy workload borne by general surgery residents have lessened interest in this discipline, creating a vicious cycle that has progressively diminished the glory of general surgery as a leading field in medicine.

The small financial compensation for the practice of medicine in Israel and changes in ideal prioritization among medical school graduates have added to the shortage of general surgery residents. The latter is not a new phenomenon and was anticipated and extrapolated from the slow but constant decline in medical school graduates. This coincided with an increasing demand for physicians to serve the growing population in Israel, despite the lack of proper planning and compensation for such.

In the past, long rotations of residents from related specialties increased the pool of young enthusiastic manpower in general surgery. These residents gained experience and practice in general surgery, and due to the length of the rotation period were considered true team members, sharing calls and duties. They created a bulwark, steadfast and dependable, for all surgical activities in the hospital. Not long ago, a resident in general surgery could be called upon to assist in a pediatric surgical case and that same night be called to operate on a laceration of the femoral artery. In parallel, the orthopedic surgeon on general surgery rotation was handling surgical cases in the emergency surgery department. In Israel, the rotation in general surgery for residents other than categorical general surgery has been reduced so drastically that residents in rotation are barely noticed in general surgery clinical practice. Unfortunately, this longstanding trend has been promoted by administrators and unit directors, consequent to demands on their own services.

The large gap between the demand for general surgery residents and the availability of young physicians results, among other factors, from longstanding negligence of the specific needs of general surgeons compared to other surgical professionals in Israel. Lack of centralization in residency programs has led to deficiencies in manpower in departments of general surgery, alongside prosperity and excess on demand in surgical related specialties.

This difficulty has been partially alleviated by persistent efforts of heads of general surgery departments to attain more resident positions through outsourcing of services, recruitment of non-surgical medical manpower and providing extra-budgetary salary payments. The attraction of residency programs that offer high income post-training positions has added to the current shortage of general surgery residents and to the slow but constant decline in the governmental and pivotal role of general surgery as the basic training domain of most surgical specialties. As in other countries, the shortage of residents in general surgery in Israel and the interest in subspecializations have resulted in a gradual decrease in the number of young surgeons willing to continue practicing basic surgery, previously termed general surgery. Based on the findings of a recent national study, Herbert R. Freund claimed that poor interrelations among surgeons are the strongest deterrent from choosing surgery as a career among pregraduates in Israel [2]. Students' negative perceptions of the relationships between

surgeons should be carefully scrutinized. Strong ego personalities, obstinacy, the need to delve into small details and perfection, dedication as well as competitiveness have been the halo of our profession since surgery has become known as a profession. This has not changed. Rather, the change is in the young generation's perception of our profession and in their expectations. Further, students' unfavorable perception should be examined in relation to other specialties in medicine and elsewhere. The change is in the decreased desire to join those "freaks" and not in their "freakiness." The young generation's (the Y generation) different perception of general surgery residency is a matter of extensive research and debate. Only residency programs willing to adopt demands of this new generation with its special needs based on their different personality structure will further succeed.

The paper published in this issue on the fragmentation of general surgery by Herbert R. Freund [3] raises concern for the future of this discipline. As the author espouses, experience in general surgery is fundamental to the practice of specialized surgeries, and essential for the health of patients and the wounded. Freund claims that general surgery will continue to be the core of surgical education. He suggests that surgeons who choose general surgery practice will be considered "general surgery specialists," and those seeking advanced training in the surgery of "selected organs" or "selected diseases" will form the body of specialized surgeons. The author has delineated a new residency program that would eliminate aspects of the rotation period imposed on residents and amount to a 5 year categorical residency program.

The shortage of general surgeons, as well as the loss of appeal of general surgery, should be combated in a number of ways. The geographical basis of this problem, specifically, its acuteness in peripheral hospitals, should be addressed when considering solutions.

The duration of general surgery residency is 72 months, including 6 months allocated as vacation time and 2 months for medical board examination preparation. Fifteen months (25%) of the residency is devoted to rotations in surgery subspecialties. If a resident works eight night shifts a month, then by law he or she is eligible for about 84 "days off" per year (equivalent to 2.8 months per year, 18 months per residency). Already included in the 15 month rotation in the surgery subspecialties is 3.75 months of post-night shift leaves (25% of 15 months of post-call vacation). Accordingly, only 40.75 months are available for true general residency training. It is obvious from this calculation that a thorough reorganization in the Israeli general surgery residency is mandatory. The author recommends shortening residency duration to 60 months. Applying the above calculation to a shortened residency program will result in a pure general surgery practice of 40.5 months. The numbers presented in Table 1 clearly indicate that shortening the residency program by eliminating unnecessary rotations would not significantly affect the time allocated for general surgery training.

The shortage of general surgery residents and the uncertain future of the general surgery specialty will eventually affect all surgical subspecialties. Thus, regrouping of all related surgical subspecialties and regaining the traditional role of general surgery as preparatory training for all subspecialties is of paramount importance.

To return the diadem to general surgery, some of the recently developing residences (e.g., vascular, pediatric, thoracic) should be returned to the realm of general surgery as basic training. A further two years fellowship in these subspecialties, followed by one or two years of training in a foreign country will yield proficient specialized surgeons. Central control of the number of surgeons training in each subspecialty in Israel will help to maintain an adequate number in the new specialty of general surgery and restrain an overwhelming desire to gain education in other sophisticated surgical fields. However, this is not enough. The general surgery specialist should be acknowledged and respected the same as his or her peers in the 'more sophisticated' surgery subspecialties. Further training in trauma, surgical intensive care, burns, and disaster medicine will raise the starting point of young physicians who choose general surgery as their future career to that of their colleagues. The dedication to this specialty, a truly hospital-based practice, should be appreciated and properly compensated.

In an era of innovation and rapid developments in surgical instrumentation and technologies, the general surgery specialist could be considered a low "tech" surgeon in comparison to other surgeons. It is our responsibility to ensure that this discipline maintains its high level of proficiency, credibility, and central role and position.

Table 1. Comparison of time allocation during general surgery training for a 6 and 5 year residence period

	72 months residency	60 months residency
Vacations (mos)	6	5
Examination leave (mos)	2	2
Calls per month (days)	8	8
Post-call days off (days) After Friday/holiday – no leave	7	7
Post-calls days off per residency/months	504/18	480/16
Rotations (mos)	15	3
Total months free for pure residency	37+ 3.75 = 40.75	39 + 3.5 = 40.5

The updating of a general surgery residency program, the creation of a new specialty for non-organ, non-disease related surgery, including emergency and trauma – the general surgery specialist, and regrouping of all "lost professions," are rescue measures that will return the laurel to our profession. General surgery as a profession should be nurtured and kept alive. I applaud Dr. Freund for his timely paper and call upon all surgeons to raise our profession from the ashes.

I further raise the question: Is your residency program ready for the Y generation?

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Capsule

Fatty food in the mouth signals the brain and induces endocannabinoid synthesis

Unfortunately for modern humans, we are adapted to pounce all over high-fat foods, presumably because the essential nutrients they provide were often scarce for our ancestors. In modern society, such preference for fatty foods in the face of their ample availability is a recipe for a major societal health problem. DiPatrizio et al. explored the mechanism by which the presence of fatty foods in the mouth stimulates the appetite of rats for more by surgically shunting ingested food from the stomach so that the rest of the digestive system was not affected. Surprisingly, the presence of fat in the mouth increased the synthesis of endocannabinoids (neurotransmitters related to the active substance in marijuana) in the small intestine. Severing the vagus nerve blocked the effect, showing that the signal must travel from the mouth to the brain and then to the intestine. Endocannabinoid blockade in the gut diminished the "feed-forward" effect of oral fat on further fat ingestion. The authors suggest that a strategy that diminishes endocannabinoid signaling in the gut could help reduce an excessive drive for fat intake without side effects on the brain, where endocannabinoids also function in reward pathways.

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Eitan Israeli

Capsule

C-reactive protein is related to memory and medial temporal brain volume in older adults

Recent research suggests a central role for inflammatory mechanisms in cognitive decline that may occur prior to evidence of neurodegeneration. Limited information exists, however, regarding the relationship between low grade inflammation and cognitive function in healthy older adults. Bettcher and associates examined the relation between inflammation, verbal memory consolidation, and medial temporal lobe volumes in a cohort of older community-dwelling subjects. Subjects included 141 functionally intact, community-dwelling older adults with detectable (n=76) and undetectable (n=65) levels of C-reactive protein (CRP). A verbal episodic memory measure was administered to all subjects, and measures of delayed recall and recognition memory were assessed. A semiautomated parcellation program was used to analyze structural MRI scans. On the episodic memory task, analysis of covariance revealed a significant CRP group by memory recall interaction, such that participants with detectable levels of CRP evidenced worse performance after a delay compared to those with undetectable levels of CRP. Individuals with detectable CRP also demonstrated lower performance on a measure of recognition memory. Imaging data demonstrated smaller left medial temporal lobe volumes in the detectable CRP group as compared with the undetectable CRP group. These findings underscore a potential role for inflammation in cognitive aging as a modifiable risk factor.

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Eitan Israeli

"When one door of happiness closes, another opens; but often we look so long at the closed door that we do not see the one which has been opened for us"

Helen Keller (1880-1968), American author and political activist and the first deafblind person to earn a Bachelor of Arts degree. The story of how her teacher, Anne Sullivan, broke through the isolation imposed by the complete lack of language, allowing the girl to blossom as she learned to communicate, is told in the film *The Miracle Worker*

Fungal Infections: Blame the TH-17 Cells

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KEY WORDS: TH-17 cells, immunodeficiency, mucocutaneous candidiasis

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Hippocrates, more than 2000 years ago, already described apthus ulcer with oral thrush in debilitated patients. In the mid-19th century it was found to be caused by fungal infection. In 1923 Christine Marie Berkhout coined the term *Candida albicans* for the most common fungus type to cause infection in humans.

While it is almost universal for an infant to suffer from 'oral thrush', a self-limited disease caused by Candida, only infants with immune deficiency will suffer from chronic recurrent oral thrush. Furthermore, adults who are immune compromised may suffer from systemic candidiasis, which can be a life-threatening event [1]. To complete the clinical picture of Candida infection, there are rare cases of individuals with chronic mucocutaneous candidiasis, which can be an isolated phenomenon or may be associated with other abnormal findings [2].

Until recently it was thought that TH1 cells were the main players in the defense against fungal infection [3]; however, current findings twist the interest towards TH17, a newly described T cell subset, and the crucial cell involved in the immunity toward fungal infection [4].

In this issue of *IMAJ* Hamoud et al. [5] describe a healthy woman with recurrent fungal infections. Although no immunological defect was found, this editorial will try to show that most probably an undefined immunological defect does exist. We will present the current knowledge regarding the immune pathway leading to killing Candida, and discuss the pathogenesis of the various rare conditions associated with CMC.

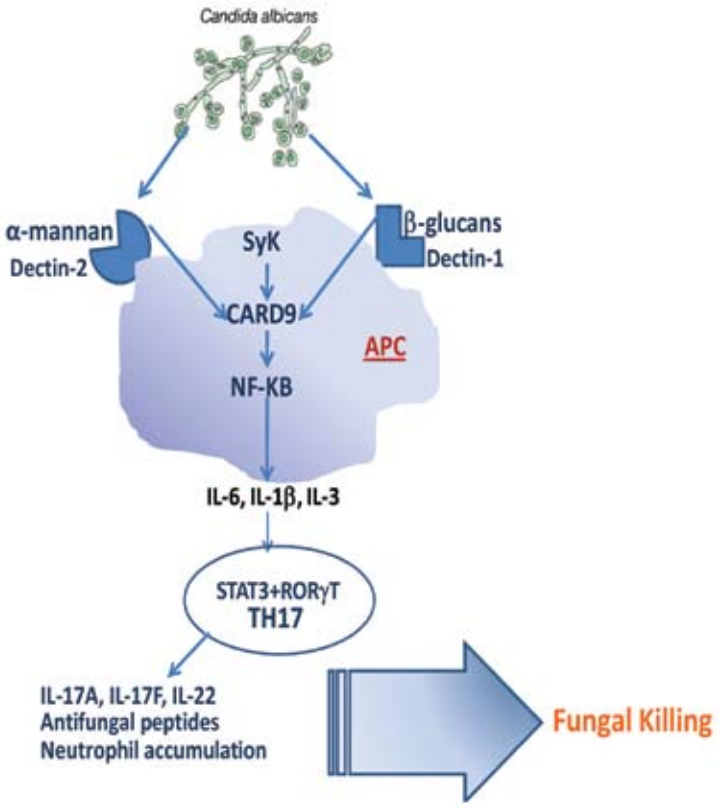
IMMUNE DEFENSE AGAINST FUNGAL INFECTIONS [Figure 1]

Traditionally, CD4 Th1 cells were thought to be involved in the immune response against Candida, mainly through its major cytokine, interferon-gamma. Later, it was found in the INFγ knockout mouse that there was no increased susceptibility to Candida infections and therefore another cell type must be involved [6].

The first step in the recognition of fungal pathogens is by cell-surface receptors that are generally called pattern recognition receptors. Toll-like receptors are the best characterized pattern recognition receptors, but several other families, such as the C-type lectins, have also been described. Indeed, 2 C-type lectins, dectin-1 and 2, have been demonstrated to be pivoted in the immune response towards Candida [7]. Both recognize different specific fungal cell wall components.

CMC = chronic mucocutaneous candidiasis
INFγ = interferon-gamma

The various components involved in the immunity against fungus



Dectin-1 recognizes β-glucan while dectin-2 will bind to α-mannan and seems to be the major pattern recognition receptor in the immune response towards fungus [8]. Binding of fungal components to the dectins will trigger the phosphorylation of the SyK tyrosine kinase, which will then activate downstream an adaptor protein known as CARD9, causing the activation of the transcription factor NF-κB. The dectin-SyK-CARD9-NF-κB signaling pathway triggers the production of cytokines, such as interleukin-1β, IL-6 and IL-23, which are essential for the generation of TH17 cells [9].

Naive CD4+Th precursor cells will develop into TH17 in the presence of these cytokines. They act in a signal transducer and activator of transcription 3 (STAT 3)-dependent manner to induce the expression of the retinoic acid-related orphan receptor (ROR)γt to induce Th17 cells. Differentiated Th17 cells secrete IL-17A, IL-17F and IL-22 cytokines, which are known to promote antifungal immunity by inducing the release of a wide range of pro-inflammatory danger signals, the expansion of antimicrobial factors, chemokine production at sites of infections, and recruitment of neutrophils [10].

Recently, it was shown that T regulatory cells, which normally suppress immune response, can promote TH17 cells to increase production of IL-17A, IL-17F and IL-22 and thus enhance host resistance to Candida infections [11].

GENETIC DEFECTS LEADING TO CMC

Until recently, the genetic etiologies of various disorders associated with CMC were unknown, although a clear autosomal recessive or dominant inheritance was observed. The hyper-immunoglobulin E syndrome has both immunological and connective tissue findings. Severe eczema, CMC, cold abscess and hyper-IgE levels are the prominent immunological parameters [12]. Several years ago, the genetic defect in most cases was found to be due to a dominant mutation in STAT3. As STAT3 is essential for the induction of TH17, it was indeed found that patients with the dominant form of HIES do not have any TH17 cells and thus do not produce any IL-17A, IL-17F or IL-22, leading to the increased susceptibility to mucocutaneous candidiasis [13].

The autoimmune polyendocrinopathy and celebral dystrophy is a rare autosomal recessive syndrome due to mutation in the autoimmune regulator gene (*AIRE*) which is essential for presenting autoantigens to T cells in the thymus, leading to clonal deletion of these T cells. As a consequence, patients with APECED suffer from multiorgan autoimmunity, mainly hyperparathyroidism and adrenal failure.

The association with CMC in this syndrome was an enigma until recently, when it was found that aside from autoantibodies against the various organs, these patients also develop neutralizing autoantibodies against IL-17A, IL-17F and IL-22 [14], which are needed for fungal killing.

Although in most cases of isolated CMC the genetic defect is unknown, several defects were recently discovered. A family with homozygous point mutation in CARD9 with loss of function has been described [15]. The CARD9-deficient patients also displayed a significantly smaller proportion of IL-17-expressing T cells and severe defect in the generation of a TH-17 response [15]. Another family with dectin-1 deficiency was also reported [16]. Still, since this family suffered from only a mild form of CMC, the role of dectin-1 deficiency in humans remains controversial.

Puel et al. [17] recently described two new genetic defects in isolated CMC. One family had a homozygous nonsense mutation in the IL-17 receptor A (IL-17RA). This mutation abrogated IL-17RA receptor expression in mononuclear cells and thus these cells become unresponsive to IL-17A or F. The second family had a missense mutation in IL-17F with autosomal dominant inheritance. The mutation was located in the cavity of the cytokine, a region implicated in receptor binding [17].

Very recently the genetic cause of most cases of the autosomal dominant form of CMC was identified. These patients were found to have mutations in the CC domain of STAT1 [18]. Although mutations in STAT1 were noted in the past to cause increased susceptibility to Mycobacteria due to a defect in the IFNγ pathway, these new CC domain mutations are gain of function mutations with increased IFNγ production and thus impaired IL-17 immunity [19].

It seems logical to assume that additional genetic etiologies related to the TH17 lineage will be found in other subjects suffering from CMC and may pave the way for developing new therapeutic strategies to improve TH17 responses.

IL = interleukin

HIES = hyper-immunoglobulin E syndrome
APECD = autoimmune polyendocrinopathy and celebral dystrophy

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Capsule

Broad neutralization coverage of HIV by multiple highly potent antibodies

Broadly neutralizing antibodies against highly variable viral pathogens are much sought after to treat or protect against global circulating viruses. Walker et al. probed the neutralizing antibody repertoires of four human immunodeficiency virus (HIV)-infected donors with remarkably broad and potent neutralizing responses and rescued 17 new monoclonal antibodies that neutralize broadly across clades. Many of the new monoclonal antibodies are almost tenfold more potent than the recently described PG9, PG16 and VRC01 broadly neutralizing monoclonal antibodies and 100-fold more potent than the original prototype HIV broadly neutralizing monoclonal antibodies. The monoclonal antibodies largely recapitulate the neutralization breadth found in the corresponding donor serum and many recognize novel epitopes on envelope (Env) glycoprotein gp120, illuminating new targets for vaccine design. Analysis of neutralization by the full complement of anti-HIV broadly neutralizing monoclonal antibodies now available reveals that certain combinations of antibodies should offer markedly more favorable coverage of the enormous diversity of global circulating viruses than others, and these combinations might be sought in active or passive immunization regimes. Overall, the isolation of multiple HIV broadly neutralizing monoclonal antibodies from several donors that, in aggregate, provide broad coverage at low concentrations is a highly positive indicator for the eventual design of an effective antibody-based HIV vaccine.

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Eitan Israeli

Capsule

Direct generation of functional dopaminergic neurons from mouse and human fibroblasts

Transplantation of dopaminergic neurons can potentially improve the clinical outcome of Parkinson's disease, a neurological disorder resulting from degeneration of mesencephalic dopaminergic neurons. In particular, transplantation of embryonic-stem-cell-derived dopaminergic neurons has been shown to be efficient in restoring motor symptoms in conditions of dopamine deficiency. However, the use of pluripotent-derived cells might lead to the development of tumors if not properly controlled. Caiazzo et al. identified a minimal set of three transcription factors – *Mash1* (also known as *Ascl1*), *Nurr*1 (also known as *Nr4a2*) and *Lmx1a* – that are able to generate directly functional dopaminergic neurons from mouse and human fibroblasts without reverting to a progenitor cell stage. Induced dopaminergic (iDA) cells release dopamine and show spontaneous electrical activity organized in regular spikes consistent with the pacemaker activity featured by brain dopaminergic neurons. The three factors were able to elicit dopaminergic neuronal conversion in prenatal and adult fibroblasts from healthy donors and Parkinson's disease patients. Direct generation of iDA cells from somatic cells might have significant implications for understanding critical processes for neuronal development, *in vitro* disease modeling and cell replacement therapies.

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Eitan Israeli

"Bigotry tries to keep truth safe in its hand with a grip that kills it"

Rabindranath Tagore (1861-1941), Indian philosopher, author, songwriter, painter, educator and composer. Tagore was viewed as spiritual, and this together with his mesmerizing persona gave him a prophet-like aura in the west. He won the Nobel Prize for literature in 1913

Coronary Computed Tomography with Lower Radiation Dose

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KEY WORDS: computed tomography, coronary artery, Step and Shoot, low dose radiation, angiography

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Imaging of the heart structures, including the coronary arteries, using computed tomography is technically challenging. In order to obtain accurate diagnostic images of a constantly moving structure consisting of chambers that do not contract simultaneously and may change in position because of respiration movements, "freezing" of the heart in the same contraction phase and location for repeat scans is mandatory. Due to improvements in the temporal and spatial resolution of CT, especially after the introduction of the 64-row multidetector, CT has emerged as a non-invasive diagnostic tool for evaluation of the coronary arteries. Scan times are in the order of several seconds (usually 5–12 seconds), thus even patients with severe pulmonary disease or congestive heart failure can hold their breath for the required length of scan time.

The use of coronary CT angiography is constantly increasing, with well-established data confirming its accuracy in various clinical indications in the cardiac vasculature [1]. The indications include diagnosis or exclusion of various coronary pathologies [2], and newer indications such as open heart reoperations [3] and the "triple rule-out" CT angiography protocol in the evaluation of acute chest pain [4]. Additional benefits of CCTA are extracoronary findings, which are frequently detected and sometimes even more important than the coronary disease itself [5].

However, these improvements in spatial and temporal resolution significantly increased the radiation dose. Consequently, concern about exposure to ionizing radiation and its potential risk of cancer is limiting its use by health care providers [6,7]. The radiation levels are derived from the need to scan small structures, to overlap the four to five slices needed to cover the entire heart with the 64-MDCT, to use high kilo voltage for penetrating the surrounding structures in order to differentiate between the small coronaries and their surroundings, and to assess the atheromatous plaque structure. The effective radiation dose for CCTA has been estimated at 6.4–27.8 mSv in several reports [8]. The international Prospective Multicenter Study On RadiaTion Dose Estimates Of Cardiac CT AngIOgraphy I (PROTECTION I) study, the largest observational study on radiation dose estimates of cardiac CT so far, determined the radiation dose of CCTA, as well as the effect of different strategies to reduce the dose in clinical practice. The median dose-length-product of 1965 CCTA examinations was 885 mGy x cm, which corresponds to a median estimated effective radiation dose of 12 mSv. However, a large variation in dose between study sites was observed, indicating a large potential to reduce the dose for individual sites [9].

The conventional CCTA protocols are retrospective gating algorithms that cover the entire cardiac cycle during the scan. The continuous scan, using a low helical pitch, enables selective reconstruction of the data at any time point (phase) in the cardiac cycle and produces cine images of the cardiac movement. Every possible strategy should be used to reduce radiation exposure associated with CCTA. CT radiation protection and dose reduction have become an important focus of attention and new dose-saving algorithms have been developed [10-18].

Body mass index-based kV and tube current should be used to reduce radiation dose whenever possible [10]. Additional reduction can be achieved by other means such as tube voltage, with a reduction from 120 to 100 and even 80 kVp, and tube current modulation, i.e., lower radiation by 40% to 80% during 60%–80% of the cardiac cycle, where the heart movement is higher and the image quality inferior. Lower kV and tube current (e.g., 100 kV and 450 mA) are often sufficient to obtain diagnostic image quality in slim patients (BMI less than 25 kg/m^2). Scan length to the minimum necessary and dual energy scanning further reduce the radiation [11]. Recent MDCT scanners are equipped with prospective gating capabilities. New prospective electrocardiograph triggering algorithms, like Step and Shoot (S&S) mode, are based on the ability to scan only at predefined times during the cardiac phase when the heart is moving minimally (phase 75–80 mid-diastole). With this protocol, only during one-seventh of the cardiac cycle is the X-ray turned on and the heart scanned; in the remaining cycle the X-ray current is off. The partial radiation enables a radiation dose reduction by

CCTA = coronary CT angiography

MDCT = multidetector CT

BMI = body mass index

70% from 10–14 mSv to 2–4 mSv on the 64-slice MDCT [15]. The new MDCT with 256 and 320 detector rows offers a scan of the entire heart in one rotation during one beat, which means less exposure time (one second), no need for slices overlapping, and less contrast media. Durmus et al. [16] reported radiation exposure of 2.0–3.3 mSv with the 320 MDCT, which contains all the phases. New combinations of various protocols based on the patient's BMI, heart rate and MDCT protocols resulted in radiation reduction to even less than 1 mSv on CCTA [17,18].

Acute chest pain suggestive of acute coronary syndrome is a frequent complaint in the emergency department. If the clinical examination and initial cardiac workup suggest that a patient is having myocardial ischemia, the patient will usually be urgently referred for invasive coronary angiography and revascularization. In stable patients without evidence of ST elevation and ongoing myocardial ischemia, an initially conservative approach is sometimes considered. Cardiac risk stratification of this subgroup of patients who are at low and intermediate risk for coronary artery disease is recommended before discharge, and imaging is necessary to exclude ischemia as an etiology. Non-cardiac etiologies of chest pain include aortic dissection, aortic aneurysm, pulmonary embolism, pericardial disease, and lung parenchymal disease. Non-invasive cardiac imaging in patients who are at low and intermediate risk for coronary artery disease may increase confidence regarding the safety of discharge from the emergency department. In addition to risk stratification, non-coronary etiologies for chest pain can be established with CT imaging.

"Triple rule-out" CT angiography is a protocol tailored for such patients; it simultaneously evaluates coronary artery disease, pulmonary embolism, and aortic dissection in a single imaging examination. The average radiation dose of "triple rule-out" using prospective gating on a 64-slice MDCT was 9.2 ± 2.2 mSv, and in another study the radiation dose of dedicated CCTA using prospective gating was less than 3.0 mSv (1.1–3.0 mSv) in patients with lower BMI [19].

In the previous issue of *IMAJ*, Goitein et al. [20] presented their image quality results for accurate diagnosis utilizing prospective gated CCTA in acute chest pain evaluation compared to retrospective gated images. They reported a reduction of the mean effective dose from 17.2 mSv in the retrospective 64-slice CCTA to 3.8 mSv with prospective 64-slice CCTA algorithm without impairment of the overall diagnostic quality.

CCTA is expected to be used more widely for patients with non-specific acute chest pain because it can be performed with lower radiation exposure. Use of the recently released 128,256 and 320 detector row MDCT and further advances in temporal resolution of MDCT scanners may increase the number of patients who can undergo radiation-sparing prospectively gated CCTA examinations and achieve a sufficient imaging quality.

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Ultrasound in the Surgical Intensive Care Unit

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ABSTRACT: Ultrasonography in the intensive care unit (ICU) has become a valuable tool for expeditiously, safely and effectively diagnosing and treating a myriad of conditions commonly encountered in this setting. Most surgeons are familiar with FAST (**F**ocused **A**ssessment with **S**onography in **T**rauma) and can readily grasp the fundamentals of a limited or directed ultrasonographic exam. Thus, with appropriate training and practice, surgeons can utilize this tool in visualizing, characterizing and treating life-threatening conditions in their role as intensivists in the surgical ICU (SICU). In this review we will discuss the role of ultrasonography in evaluating the acute cardiac status of a patient in the SICU as well as its use in general critical care for assessing the thoracic, abdominal and vascular systems.

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KEY WORDS: ultrasound, intensive care unit, echocardiography, limited exam, critical care

Ultrasonography as a tool for exploring the body has a rich history, as described by Krishnamoorthy et al. [1] and Kendall et al. [2]. It has become a valuable tool in the perioperative evaluation of the cardiothoracic patient and by extension all intensive care unit patients. Simultaneously, surgeons have become familiar with ultrasonography's fundamental characteristics through its use as an examination of the traumatically injured patient, first described as a focused abdominal sonogram for trauma (FAST) by Rozycki and Shackford [3]. Thus, it was only a small leap of imagination to envisage the advantages and benefits of this modality for critically ill and injured patients in the surgical intensive care unit. In this review, we will focus on ultrasonographic applications in the SICU. Applying recent definitions provided by the American College of Chest Physicians and La Société de Réanimation de Langue Française Statement on Competence in Critical Care Ultrasonography [4], we will discuss basic and advanced echocardiography as well as general critical care ultrasonography which can be subdivided into thoracic (pleural and lung), abdominal (to include assessment for intraperitoneal fluid, assessment of the urinary tract, and assessment of the aorta), and vascular ultrasonography (for guidance of vascular access and diagnosis of venous thrombosis).

SICU = surgical intensive care unit

CARDIAC APPLICATIONS

The use of bedside cardiac ultrasonography in the SICU is known to be of benefit in the guidance of care for critically ill and injured patients [5]. Transesophageal echocardiography was considered to be superior in critical care settings in providing optimal sonographic windows and excellent image acquisition. However, with the advent of higher quality portable devices, transthoracic echocardiography has become common practice and is considered to be the primary imaging technique in the ICU setting [6]. Reasons for this shift towards transthoracic ultrasonography include its portability, safety, technologically improved imaging, the brevity of image acquisition, its improved diagnostic accuracy over older technology, and the abridged training required to competently perform bedside studies. Another motivating factor is the ability to continually repeat an ultrasonographic study in the midst of dynamic clinical situations [7]. Thus, TTE has become a superior alternative to TEE, although there is still a role for the latter in distinct clinical situations in the SICU [8]. TTE has an immediate diagnostic impact equivalent to TEE [7] and its therapeutic import is such that the surgical intensivist can use real-time information to cyclically guide management and treatment decisions [9-11].

The intensivist-performed echocardiogram has the advantage of being non-invasive and repeatable and, notably, has immediate bedside application

The aim of a TTE study in the SICU patient is to provide a quick, non-invasive means of determining cardiac function and intraventricular filling and, by inference, intravascular volume. The ideal ICU hemodynamic monitor provides data on preload, contractility and afterload in a dynamic, minimally or non-invasive fashion. Monitoring with central venous or pulmonary artery catheters is known to have no correlation between pressure values obtained via these monitors and intravascular volume or ventricular filling status [12-14]. Moreover, four studies have demonstrated no ben-

TTE = transthoracic echocardiography
TEE = transesophageal echocardiography

efit of pulmonary artery catheters vis-à-vis patient outcomes [15-18]. TEE preload measurements have been shown to be "well validated and more accurate than data obtained from pulmonary artery catheters" [19]. By extension, TTE should reasonably be able to garner the same information. However, mixed results have been noted when using echocardiography to predict fluid responsiveness [12] and to date there are no studies documenting a positive patient-oriented outcome with this technology.

There are multiple resources for training in basic echocardiography, including courses offered by the American College of Surgeons, the Society of Critical Care Medicine, the World Interactive Network Focused on Critical UltraSound (WINFOCUS), and Imaging, a program provided by intensive cardiac care units, which consists of a multimedia curriculum titled FOcused Cardiac Ultrasound Study (FOCUS). Guidelines proposed by the American College of Chest Physicians and the La Société de Réanimation de Langue Française Statement on competence in critical care ultrasonography [4] recommend two levels of competence.

Thoracic ultrasonography may be useful in uncovering the etiology of acute hypoxemia in the critically ill or injured patient

The first level of competence, "basic," is considered a bedside TTE defined in the literature as a "limited ultrasound," "goal-directed ultrasound," "point-of-care focused ultrasound" [20], or intensivist bedside ultrasound (INBU) [21]. The goal at this basic level is threefold: a) to acquire the ability to qualitatively assess left and right ventricular size and function, b) to measure the inferior vena cava diameter while accounting for respiratory variation, and c) to qualitatively assess for severe valvular regurgitation. Competences in image interpretation as well as recognition of clinical syndromes are detailed but a minimum number of studies necessary to achieve competency is not defined in this position paper. Variations upon the "basic" study include extension of the examination to visualize pleura on both sides, as in a Focus Assessed Transthoracic Echocardiogram (FATE) [22] or stroke volume measurement using the fractional shortening technique to compute the cardiac index as in the Bedside Echocardiographic Assessment in Trauma/Critical Care (BEAT) [23]. These "basic" studies are not meant to be comprehensive cardiac evaluations but are weighted towards specificity over sensitivity [24] and qualitative over quantitative information in ascertaining whether certain clinical conditions are present.

The second level of competence, "advanced," is a "comprehensive hemodynamic evaluation and monitoring" [4] that addresses specific clinical entities such as infectious endocarditis, right-to-left shunts, pulmonary embolus and complications of acute myocardial infarction that might require more subtle and complex cardiac chamber and valvular pattern and flow recognition. To achieve this level, an individual must also be facile in the use of TEE as many of these disease processes are best imaged in this mode.

Table 1. Bedside echocardiographic assessment: the BEAT exam

Meaning of BEAT acronym	Goal	View	Task
Beat (cardiac index)	Cardiac function	Parasternal long	Stroke volume
Effusion	Pericardial effusion	Parasternal long	Subjective assessment
Area (ventricular size and function)	Right and left ventricle	Parasternal short Apical 4 chamber	Subjective assessment
Tank (preload)	Volume status	M mode subcostal	Inferior vena cava measurement

Can "basic" TTE be learned and performed by surgeon-intensivists with good quality image acquisition? Several studies have demonstrated that after a brief educational intervention non-cardiologists are able to perform limited transthoracic examinations and correctly interpret studies most of the time [25,26]. In answering the question whether quality clinical images can be obtained by surgeon-intensivists, one can look at the study by Gunst and colleagues [23] in which FAST-trained surgeons received a 2 day "Focused Cardiac Ultrasound at Bedside Seminar" and then went on to prove their competence on normal volunteers. Utilizing the framework of a BEAT examination [Table 1], 59% of the cardiac exams were rated as being of good quality.

Do bedside ultrasonographic studies make any difference to patient care? In a study by Orme and associates [10], there was a change in patient management in 48.6% of all TTEs (187 studies). A study by Stanko and colleagues [11] found a change in diagnosis in 29% and a change in management in 41% of the studies performed (135 TTEs done in 126 patients). Although a change in diagnosis or management can frequently be anticipated using this modality, no study has demonstrated a difference in patient outcomes.

THORACIC APPLICATIONS

Due to the physics of ultrasound, air in the inflated lung normally prevents visualization of its detailed structure. Nevertheless, several pathological processes in the thoracic cavity can be identified easily by bedside ultrasound.

Pneumothorax and pleural effusion (hemothorax) are common pulmonary pathologies seen in the ICU setting. A chest radiograph in critically ill patients may have insufficient sensitivity to detect both of these etiologies of respiratory failure in the SICU [27]. Though a computed tomographic scan should offer a more accurate diagnosis, it is often not possible for critically ill patients to travel to the radiology suite. A pneumothorax can be life threatening in SICU patients. Although a detailed physical

FAST = focused assessment with sonography in trauma
BEAT = bedside echocardiographic assessment in trauma/critical care

examination is the first step to establish the diagnosis, thoracic ultrasound demonstrates fairly high sensitivity and specificity compared with chest radiography [27,28]. The ultrasound findings of a pneumothorax can be characterized by loss of artifacts seen in normal lung, namely lung sliding and the presence of B-lines (comet-tail sign). Lung sliding is the movement across the parietal and visceral pleura surfaces seen in the intercostal spaces. B-lines (comet tails) are vertical hyperechoic artifact lines originating from the horizontal pleural line under sonography. Both artifacts are detected with low and high frequency transducer probes.

Pleural effusions and hemothoraces are seen as hypo- or anechoic areas in the posterior and inferior thoracic cavity of a supine patient. Although computed tomography scan is more sensitive for detecting hemothoraces and pleural effusions, pleural ultrasonography can be helpful in detecting these abnormalities in the pleural space. In the setting of trauma, Sisley and co-workers [29] first described transthoracic ultrasonography as an extension of the sonographic evaluation of the trauma patient (FAST). In their examination of both the right and left supradiaphragmatic regions for evidence of a hemothorax, they noted a 97.5% sensitivity and 99.7% specificity, similar to the sensitivity and specificity of a chest X-ray. Rozycki and colleagues [30] reported on the efficacy of bedside ultrasound for detecting pleural effusions in the surgical ICU. Their sensitivity for fluid in the thoracic cavity was 83.6% and specificity was 100%. Once a patient is found to have a pleural effusion, ultrasound-guided thoracentesis is regarded as another utility for the bedside ultrasound [31].

Ultrasound-guided central venous access is the standard of care in all settings, including the SICU, and has been proven to increase the chances for successful placement and reduce the risk of complications

Finally, lung ultrasonography can be used to detect pulmonary edema, pulmonary embolism, pneumonia, chronic obstructive pulmonary disease or asthma, or pneumothoraces utilizing the Bedside Lung Ultrasound in Emergency (BLUE) protocol with 90.5% accuracy in disease identification [32].

ABDOMINAL APPLICATIONS

Deterioration of a patient's condition can often be attributed to intraabdominal pathology in the SICU. Ultrasound can identify the abdominal organ-related etiologies in a timely manner at the bedside without the need for transport to the radiology suite. However, abdominal ultrasound in the ICU setting has several limitations. Tissue edema or obesity may prevent acquisition of a clear view of abdominal organs. Surgical wounds, tubes or drains also make the ultrasound examination more difficult. Patients with an open abdomen are technically not amenable for ultrasound examination. Other limiting factors include rib shadowing, bowel gas, and uncooperativeness of patients (positioning, breathing).

Table 2. Problem-focused abdominal ultrasound in surgical intensive care unit

Goal	Task
Identify fluid	Amount, location, loculation
Characterize mass lesion	Locate fascia
Leukocytosis, abdominal pain	View gallbladder, appendix, bowel, aorta
Jaundice	View gallbladder, common bile duct, intrahepatic biliary ducts, presence of stone
Decreased urine output	View bladder, presence of hydronephrosis
Transplant evaluation	Arterial/venous blood flow, organ size, tenderness

Therefore, the ultrasound technique for critical ill patients should be different from a routine screening examination. A problem-oriented approach is key to the efficient utilization of abdominal ultrasound in the ICU setting [Table 2].

Application of the FAST examination for detecting free fluid within the abdomen dramatically changed the approach to the trauma patient [33]. This technique surveys four points (epigastrium, right upper quadrant, left upper quadrant, and pelvic space) for pericardial and peritoneal fluid and in a trauma cohort was able to identify as little as 100 ml of fluid with 88% sensitivity, 99% specificity and 97% accuracy [34].

Pneumoperitoneum can signal a ruptured hollow viscus. Unreliable physical examinations in sedated patients on mechanical ventilation can often delay the diagnosis and appropriate intervention. Even portable radiography, easily performed at bedside, is not always accurate [35]. Although CT scanning is more sensitive to detect pneumoperitoneum, SICU patients are not always transportable to the scanner. A recent article by Moriwaki et al. [36] demonstrated that surgeon-performed ultrasound achieved 85.7% sensitivity for intraperitoneal free air in blunt abdominal trauma and 85.0% in acute abdominal pain. The ultrasound technique for pneumoperitoneum uses the same principle as that for diagnosing a pneumothorax. In a supine patient, free air can be detected on the surface of the liver. A low frequency transducer is placed in the right upper quadrant and high echoic reverberation is seen as a positive finding of pneumoperitoneum.

Liver abscess, acute cholecystitis and acute cholangitis should be kept in mind as an origin of fever in the ICU setting. Bedside ultrasound is considered a first-choice modality for the workup of jaundice. Factors of interest when performing liver ultrasound include abscesses, mass lesions, dilatation of intrahepatic duct, or portal venous gas. A liver abscess can be drained at bedside by ultrasound guidance. Biliary tract ultrasound in the ICU should focus on searching for cholelithiasis/

sludge, features of cholecystitis, choledocholithiasis and dilatation of the common bile duct. Although wall thickness of the gallbladder (> 3 mm) is a finding suggestive of acute cholecystitis, a variety of other conditions may also manifest this finding. Percutaneous cholecystostomy may be required to definitively establish the diagnosis and treatment of acute cholecystitis in high risk patients. Again, bedside ultrasound-guided drainage can be safely performed by the intensivist [37].

Acute kidney injury is a serious complication often encountered in critically ill patients. Ruling out post-renal etiology is the first step in its workup. The level of obstruction can be estimated based on the findings in the bladder, ureter and kidney. A distended bladder implies an obstructive process in the urethra or urethral catheter. Hydronephrosis without bladder distension suggests an obstructive lesion in the ureter (stone, tumor, fibrosis).

VASCULAR APPLICATIONS

Vascular ultrasonography for central venous line placement has been shown to significantly increase the overall chances for successful placement on the first attempt and to reduce the rate of complications [38]. The data were most compelling for internal jugular vein central venous line placement over subclavian vein cannulations. Thus, this technique has been recommended in the United States by the Agency for Healthcare Research and Quality (2001) [39] for all central venous line insertions and in the United Kingdom by the National Institute for Clinical Excellence (NICE) [40] for internal jugular venous cannulations. Because of demonstrable clinical success and the aforementioned evidence-based reports, ultrasonography for obtaining vascular access in the axillary, brachial, femoral and other peripheral veins (as well as for obtaining arterial access) has become the norm. Vascular ultrasonography has also had a long history of use for the identification of venous thrombosis within the upper and lower extremity veins.

The expansion of ultrasonography in the ICU is due to improved training, improved technology and improved imagination. Now that it is ubiquitous in trauma bays and becoming so in the intensive care units internationally, we as critical care specialists and surgeons need to continue to expand upon its uses and truly utilize ultrasonography as an extension of our physical examination.

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Capsule

DNA released from dying host cells mediates aluminum adjuvant activity

Aluminum-based adjuvants (aluminum salts or alum) are widely used in human vaccination, although their mechanisms of action are poorly understood. Marichal and co-workers report that, in mice, alum causes cell death and the subsequent release of host cell DNA, which acts as a potent endogenous immunostimulatory signal-mediating alum adjuvant activity. Furthermore, the authors propose that host DNA signaling differentially regulates immunoglobulin E (IgE) and IgG1 production after alum-adjuvanted immunization. They suggest that, on the one hand, host DNA induces primary B cell responses, including IgG1 production, through interferon response factor 3 (Irf3)-independent mechanisms. On the other hand, host DNA also stimulates 'canonical' T helper type 2 (T_H2) responses, associated with IgE isotype switching and peripheral effector responses, through Irf3-dependent mechanisms. The finding that host DNA released from dying cells acts as a damage-associated molecular pattern that mediates alum adjuvant activity may increase our understanding of the mechanisms of action of current vaccines and help in the design of new adjuvants.

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Eitan Israeli

Capsule

Alzheimer's therapy by transport of the therapeutic antibody across the blood-brain barrier

With the continued increase in human lifespan, the incidence of Alzheimer's disease is rising, prompting a need for innovative therapies that can slow or stop the progression of this devastating condition. Since the discovery of the β-amyloid precursor protein site cleaving enzyme (BACE), which initiates the production of the Alzheimer's associated peptide Aβ, it has been one of the most intensely investigated Alzheimer's disease targets. Watts et al. have used a bi-specific antibody approach to target this enzyme, which allows transport of the therapeutic antibody across the blood-brain barrier (BBB). The bi-specific antibody reduced the levels of brain Aβ more effectively than a monospecific antibody to BACE1, and this targeting approach could potentially even be applied to treat other neurological diseases.

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Eitan Israeli

"The willow which bends to the tempest, often escapes better than the oak which resists it; and so in great calamities, it sometimes happens that light and frivolous spirits recover their elasticity and presence of mind sooner than those of a loftier character"

Walter Scott (1771-1832), British novelist and poet

Diagnosis of Attention Deficit Hyperactivity Disorder: Much Ado about Something

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ABSTRACT: Attention deficit hyperactivity disorder (ADHD) is among the most prevalent chronic health disorders affecting school-age children. The disorder is the subject of much debate for several reasons, the major one being the diagnostic process, which in some aspects is unstructured and can be relatively easily biased. The impact of undiagnosed or misdiagnosed ADHD on the lives of many children can be severe. Therefore, it is important to understand the complexities of the diagnostic procedure in ADHD, including the cultural bias effect, the limitations of the DSM-IV-TR definitions, the effect of comorbid conditions on the diagnostic process, the gene-environment interaction, and the need to compose an objective, more accurate, and generally accepted diagnostic battery of tests. This review addresses the diagnostic difficulties of ADHD and considers some steps that would make ADHD a more easily identifiable disorder.

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KEY WORDS: attention deficit hyperactivity disorder, diagnosis, bias

Attention deficit hyperactivity disorder is a childhood-onset disorder that has a relatively high prevalence worldwide, ranging from 2.2% to 17.8% [1]. ADHD is considered one of the most common neurobehavioral disorders of childhood and among the most prevalent chronic health conditions affecting school-age children [2]. However, the disorder is the subject of much controversy, both in the medical literature and the public media [3].

One of the main reasons for this controversy is the diagnostic process, which is unstructured in some aspects so that ADHD does not have a conclusive definition, being defined differently in the Diagnostic and Statistical Manual of Mental Disorders-IV-TR and in the International Statistical Classification of Diseases [4]. So severe is the disputation that there are voices suggesting that ADHD is "not a neurobehavioral disorder but rather a constellation of symptoms" [5].

Are the complexities of the clinical phenomena and diagnostic difficulties enough to refute the existence of ADHD? What can be done to increase the utility of the ADHD diagnostic process? This review discusses the diagnostic difficulties regarding ADHD and considers some steps that would make ADHD a more easily identifiable disorder.

ADHD = attention deficit hyperactivity disorder

ADHD DIAGNOSTIC CRITERIA: POSSIBLE BIAS EFFECTS

ADHD is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity, which is maladaptive and inconsistent with a comparable level of developmental age [6]. The DSM-IV-TR criteria classify the disorder into three general subtypes [6,7]:

I. Predominantly hyperactive-impulsive: a child who is excessively fidgety and restless, seems to always be "on the go," and has difficulty waiting and remaining seated, acts immaturely, may not set physical boundaries, and may exhibit destructive behaviors
II. Predominantly inattentive: a child who is easily distracted, forgetful, manifests daydreaming, disorganization, poor concentration, and difficulty completing tasks
III. Combined type.

Children who exhibit the behavioral symptoms of ADHD but demonstrate no functional impairment do not meet the diagnostic criteria [6].

One of the major difficulties in diagnosis is that decisions about the inappropriateness of behavior in children are based on subjective judgments of the observers. Despite efforts of standardization, there are no data to offer a precise estimate of when diagnostic behavior becomes inappropriate [2,7]. So, the behavioral characteristics remain subjective and may be interpreted differently by different observers and in different cultures [2,8,9]. Significant variations in the prevalence rates around the world, based on variations in diagnostic methods, support the hypothesis of the role of diagnostic criteria bias [8].

COMORBIDITIES

Another source of possible bias in the assessment of ADHD is the fact that ADHD often coexists with other conditions – psychiatric, psychological and developmental disorders – that

sometimes overlap with ADHD symptoms [4,7]. Learning disabilities, oppositional defiant disorder, conduct disorder, anxiety and depressive disorders are the most common comorbidities among ADHD children [2,7]. As many as one-third of children with ADHD have one or more coexisting conditions [2]. Most of these disorders have a commonality, such as similarity in symptoms, the role of genetic factors, age at onset, and even some aspects of the clinical course. Since the DSM-IV-TR definitions do not take into account gender, cultural or developmental variations in behavior in their list of diagnosis criteria and do not specify which diagnostic tools should be used, it is even more difficult to separate ADHD symptoms from comorbid conditions.

BIOLOGICAL MARKERS: GENES AND ENVIRONMENT

Scientific research over the past 30 years has helped characterize biological and genetic components involved in ADHD [4,9,10]. Strong evidence based on various types of genetic investigations of adoption, twins, and family studies demonstrates that ADHD has a genetic component [10,11]. The new possibilities that emerged from the human genome project led to the discovery of specific genes for attention, and the heritability of ADHD was estimated to be about 77% [4,11]. Furthermore, a number of susceptibility gene variant findings for ADHD have been independently validated and meta-analyses have yielded significant evidence of association [4,10,11].

There is a need to verify the DSM diagnostic criteria of attention deficit hyperactivity disorder in a more specific way which will take into account gender, cultural bias, and developmental variations

It was expected that with the advanced genetic knowledge, a biological marker for the diagnosis of ADHD would be available [11,12]. However, even the researchers who discovered attention genes are aware of the fact that the course of this disorder cannot be explained solely by genes. A number of environmental factors appear to be significantly associated with ADHD [4,10,13]. Family environment and psychometric studies have suggested separate etiologies and pathophysiological mechanisms for ADHD [14].

The relationship between nature and nurture and genes and environment is still not well understood. This led to the introduction of the endophenotype concept, which divides behavioral symptoms into more stable phenotypes with a clear genetic connection [10,12]. The endophenotypes are heritable quantitative traits that index an individual's potential to develop or manifest a given disease. In ADHD research the endophenotype concept "lags somewhat behind" [12]. Again, one of the difficulties is related to the bias in clinical diagnosis since "the current use of multiple variations of tests for the same cognitive domains prevents thorough generalization of the research findings" [12].

Geneticists and neuroscientists are "well aware that genes do not control behavior directly, that almost all behavioral traits emerge from complex interactions between multiple genes and environments, and that the brain bases of both personality and psychopathology are distributed across complex neural networks and are usually not caused by single loci" [15]. We assume that genetic and environmental interactions may be the reason for the phenotypic complexity of ADHD [11]. The disorder might have its origins in genes, but the course of the disorder is probably influenced by the way these genetic factors interact with and affect an individual's response to the environment [11].

Currently there is no available biological marker for the diagnosis of ADHD that can be used in clinical practice [4]. It is notable that many of the environmental risk factors for ADHD occur early in development, which is consistent with the idea that ADHD is a neurodevelopmental condition [1,16].

It is destined for future studies to discover the interactions between environmental and genetic factors, and to determine whether early recognition of these interactions might provide more effective management [16]. At the same time genetic research in ADHD must be intensified. The literature suggests that multiple replications are necessary before a true association can be made between a given marker or candidate gene and ADHD [4,10]. Thus, more individuals with ADHD and their families need to be recruited for these studies [4,12]. Meanwhile, even though genetic tests are reliable and/or environmental factors indisputable, the clinician cannot rely on them to diagnose ADHD on a routine basis.

CLINICAL DIAGNOSIS

There is a discrepancy between the clinical based procedure of ADHD diagnosis and the expanding scientific, biological, genetic and imaging knowledge. In the absence of available biological markers that would support diagnostic tests, clinicians are asked to continue to use a structured interview based on DSM-IV-TR clinical criteria, together with behavior rating scales [2,6,17]. As mentioned above, this process is subjective and might be easily biased. Given the absence of methods to confirm ADHD diagnosis by other means, it is important to recognize the limitations of the DSM-IV-TR definitions by adding more objective means of assessment to the diagnostic process [2].

• QUESTIONNAIRES

Several questionnaires and rating scales were developed to differentiate between ADHD and comorbid disorders, and to detect coexisting conditions in ADHD children [2,7]. The

use of general clinical impressions or descriptions within the domains of attention and activity is insufficient to diagnose ADHD or to differentiate between ADHD and non-ADHD children [2,7]. Therefore, these tools are not recommended for the diagnostic process [2].

The ADHD-specific questionnaires and rating scales have been shown to have sensitivity and specificity greater than 94% under ideal conditions, but much less in primary care settings even when based on self-report [2,7,18]. The use of questionnaires and rating scales as a developmental screening tool has demonstrated that the sensitivity and positive predictive values were much too low to allow a routine screening procedure for ADHD with these items among children [18]. Like other measures of clinical criteria assessment, questionnaires and rating scales are subjective and subject to bias, so their results may convey a false sense of validity and cannot always be relied upon [2,18]. Therefore, ADHD questionnaires and rating scales add important data to the clinical diagnostic process but cannot serve as a single reliable diagnostic tool.

- **CONTINUOUS PERFORMANCE TESTS**

There has long been interest in developing laboratory-based measures that could support ADHD diagnosis. The interest derives from the potential advantages that objective laboratory-based measures might have over more traditional measures [19].

Computerized continuous performance tests were intended to serve as an objective measure that would aid in the clinical assessment of ADHD. CPT are generally characterized by the rapid presentation of continuously changing stimuli among which there is a designated "target" stimulus or "target" pattern. Most CPT measure the number of correctly detected stimuli as well as response time [2,20]. CPT have several advantages: they are cost effective, are relatively free from bias, provide immediate information, are easy to administer, rely only on the individual being evaluated, and can be administered in a variety of settings [19]. Thus, although not recommended by the American Academy of Pediatrics, CPT are reported to be the most popular clinic-based measure of ADHD [20,21]. The clinical utility of CPT in the diagnosis of ADHD is the subject of much controversy due to the relatively high number of false negative errors and low overall utility [2,20,21].

CPT were found to distinguish between ADHD and non-ADHD children but have been inconsistent in differentiating ADHD from other clinical groups [19,22]. Although some studies indicate that CPT are potentially clinically useful tools in ADHD evaluation, others did not provide support for the validity of the available CPT as an attention measure and failed to demonstrate the discriminant validity of any score regardless of the behavior rating scales used [2,19-21,23]. Most researchers concluded that the data supporting the validity of the CPT are limited and stress the need for further validity studies [2,19,21]. The American Academy of Pediatrics concluded that the current data do not support the use of any CPT in the diagnosis of ADHD [2]. Other tests might be available, but a detailed description of these is beyond the scope of this review.

There is a need to compose an objective, more accurate, and generally accepted diagnostic battery of tests for ADHD including a broad range of tasks in order to add better tools for clinical diagnosis

CONCLUSIONS

It is important to recognize the complexities of the diagnostic procedure in ADHD. The first significant step is the understanding that ADHD is the extreme end of a continuum and not an isolated disorder [4]. Concluding that "ADHD is unlikely to exist as an identifiable disease" [5] is probably short-sighted since it might leave many children neglected, undiagnosed and suffering. The impact of undiagnosed ADHD on the lives of so many could be severe and a better attitude is warranted.

Several recent studies demonstrate this point [7,18]. Elkins et al. [24], who explored whether there is a prospective relationship between ADHD and initiation of substance abuse disorder, concluded that ADHD predicts later substance abuse problems, even when only a single symptom exists. They also claimed that the failure in previous research to consistently observe relationships between ADHD and substance abuse outcomes could be due to reliance on less-sensitive categorical diagnoses [24].

Langley and co-researchers [25] recently suggested that individuals with ADHD represent a high risk group for serious antisocial behavior and impose a significant cost to society as well as to the individual. They recommend that any long-term clinical treatment of individuals with ADHD include monitoring and interventions even at diagnostic subthreshold levels.

Clearly, the diagnostic process of ADHD requires the development of more definitive measures [2]. The solution lies in more research that will guide us towards better diagnostic tools. In conclusion:

- It is important to recognize the limitations of the DSM-IV-TR definitions. Since current criteria do not take into account gender, cultural bias, or developmental variations in behavior, there is a need to verify the DSM criteria in a more specific way that takes all these issues into account [2].

CPT = continuous performance tests

- Coexisting and comorbid conditions are common among children with ADHD [2,7]. Additional research is required, particularly regarding the neural substrates and biomarkers of comorbid conditions. Until research results become available there is a need to carefully assess the occurrence of comorbid conditions among ADHD children by using specific diagnostic tools validated for these conditions.
- The etiology of ADHD is a combination of genetic and environmental factors [11,12]. The early recognition, prevention and treatment of environmental causes may provide more effective management and reduce the reliance on symptom modification with medications [16,26]. Future research needs to determine whether modifying environmental risk factors can lead to preventive interventions [11,16].
- Genetic research must be enhanced by new technologies, combined with imaging, neurophysiologic and neuropsychological measures [12].
- There is a need to compile a mandatory, more accurate, and generally accepted diagnostic battery of tests for all clinicians who assess ADHD children.
- Composing a set of objective diagnostic tests based on computerized (objective) tests including a broad range of tasks that have been examined for validity and reliability will let clinicians use the same battery of tests at the primary care setting and will add better tools for clinical diagnosis [2,12].

These and other improvements of the diagnostic process can be implemented. Such improvements will allow us to develop better measurements of assessment and treatment of ADHD that can be applied even in the primary care setting [2,26] and might make ADHD a more easily identifiable disorder. In view of the high prevalence of ADHD, such improvements will likely have a significant effect on public health.

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"The Golden Rule: whoever has the gold makes the rules"

Anonymous

Recurrent *Saccharomyces Cerevisiae* Fungemia in an Otherwise Healthy Patient

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KEY WORDS: *Saccharomyces cerevisiae*, fungal disease, yeast

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For Editorial see page 561

Fungal diseases are relatively uncommon and occur mostly in immune-compromised patients. *Saccharomyces cerevisiae* is one of the less common fungal pathogens and rarely causes disease in humans. We report a case of recurrent fungemia caused by the yeast in an otherwise healthy patient.

PATIENT DESCRIPTION

A 35 year old woman was admitted in March 2004 with sudden onset of high grade fever, chills, headache, nausea and abdominal pain. Her past medical history was relevant for recurrent vaginal bleeding 3 years earlier, related to arteriovenous malformations located in the uterus, uterine cervix and proximal part of the vagina. Hemostatic sutures for bleeding lesions, angiographic embolizations of the uterine arteries and local radiotherapy to the pelvis failed to stop the bleeding, necessitating transabdominal hysterectomy and upper vaginectomy. During one of the bleeding episodes, an intrauterine device was sought but not found. Explorative laparotomy was performed but failed to reveal the device.

On admission, the patient looked severely ill, pale and drowsy. Her temperature was 40°C, blood pressure 90/60 mmHg and heart rate 110 beats per minute. Neck rigidity and diffuse abdominal tenderness were noted, together with mild hepatosplenomegaly. Laboratory tests revealed leukopenia of 2200 cells/μl with a left shift and 87% neutrophils. The hemoglobin was 12.9 g/dl and mean corpuscular volume 77 fl. Erythrocyte sedimentation rate was 28 mm. Mild elevation was found in aspartate aminotransferase (57 U/L) and alanine aminotransferase (48 U/L). Lumbar puncture revealed normal cerebrospinal fluid, glucose and protein, without cells. CSF culture was sterile. Chest X-ray was normal. Urinalysis showed 3–4 leukocytes and 6–9 erythrocytes in high power field. Multiple blood cultures and a urine culture were obtained, as were viral and bacterial serologic tests.

Intravenous fluids with metoclopramide and papaverine were administered. Her temperature dropped to 38°C and she reported marked relief from her headache and abdominal pain. Leukocyte count increased up to 5500 cells/μl, and ALT and AST values normalized. On the fourth day, urine culture revealed growth of *Escherichia coli* and Enterobacter, both sensitive to quinolones. Ofloxacin was given orally, 400 mg a day. The next day, we were informed about the growth of yeasts in five of nine blood cultures taken earlier. Intravenous fluconazole was started, 400 mg a day. Abdominal ultrasonography and computed tomography demonstrated hepatosplenomegaly with a small effusion surrounding the gallbladder and a moderate amount of pelvic fluid.

CSF = cerebrospinal fluid
ALT = alanine aminotransferase
AST = aspatate aminotransferase

Serology tests revealed the carrier state of hepatitis B virus. Serology tests for cytomegalovirus, Ebstein-Barr virus, parvovirus, Mycoplasma, Q-fever, Brucella and human immunodeficiency virus were all negative. Antinuclear antibody and rheumatoid factor were also negative.

Immunophenotyping performed on peripheral white blood cells, protein electrophoresis and complement factors were normal. Vaginal discharge culture was negative for fungi. The yeast was identified as *Saccharomyces cerivisiae*. Echocardiography (both transthoracic and transesophageal) revealed no vegetations and no valvular pathology. Gastroscopy showed normal upper gastrointestinal tract. Five days later the patient became symptom free, with normal body temperature and laboratory profile. She was discharged with oral fluconazole, 400 mg a day.

Four days later the patient presented again with sudden onset of chills, headache, abdominal pain, nausea and vomiting. On physical examination she looked very ill, pale and drowsy and her temperature was 39.7°C. The abdomen was diffusely tender with mild hepatosplenomegaly. Laboratory tests revealed leukopenia of 4200 cells/μl with left shift and 94% neutrophils. Blood chemistry was normal, and urine examination found 5–8 white blood cells in high power field. Erythrocyte sedimentation rate was 60 mm. Multiple blood cultures were drawn and intravenous amphotericin B (0.8 mg/kg/day) was started. Abdominal ultrasound and CT were performed again and showed mild hepatosplenomegaly and a small amount of pelvic fluid. A small elongated metallic particle (0.8–1 cm long) was demonstrated in the lower pel-

vis. FDG-positron emission tomography scan showed the same findings with no pathological uptake.

On the fifth day the patient became afebrile and had only mild abdominal pain and nausea. Blood cultures grew *Saccharomyces cerivisiae*, which was sensitive for AMB. The patient received amphotericin for 14 days and was discharged with no fever or abdominal pain. Colonoscopy was performed 2 weeks later and showed normal colonic mucosa. All of the blood cultures taken after starting amphotericin were negative.

Six weeks later the patient was again admitted with the same symptoms. Blood tests revealed similar values, especially leukopenia with a left shift, and blood cultures again revealed *Saccharomyces cerevisiae***.** On admission amphotericin 1 mg/kg/day was started. The patient became afebrile within 2 days and remained so for 2 weeks when recurrence of the symptoms was observed, and repeated blood cultures again showed the growth of *Saccharomyces cerevisiae*. Bone marrow aspiration and biopsy showed normal hematopoeitic system. In bone marrow cultures *Saccharomyces cerevisiae* was found.

Gallium scan showed no pathological uptake. Flucytosine was added, 1.5 g four times a day, for 4 additional weeks. The patient became afebrile and repeated cultures were negative. She was free of symptoms for 4 months, before being admitted for the fourth time with the same symptoms and signs and growth of the same pathogen in blood cultures. On the fourth admission she was treated with oral voriconazole, with which she was discharged.

After 2 months of voriconazole treatment the patient was admitted for the fifth time, again with the same symptoms and signs and with the growth in blood cultures of the same pathogen. She was treated with amphotericin and flucytosine, became afebrile 5 days later and was discharged with oral fluconazole therapy. She was free of symptoms for 9 months, when she was admitted again in November 2005. She had four admissions during 2006, one in 2007, seven times in 2008, three times in 2009 and two in 2010. Reevaluation was performed several times but failed to locate a possible endogenous etiology for the fungemia.

COMMENT

S. cerevisiae, the brewer's or baker's yeast, is an ascomyceteous yeast and a plant saprophyte. It is useful in food industries and important in the brewing of beverages and preparation of bread and cakes. A probiotic dietary supplement was used commonly for treating or preventing diarrhea caused by *Clostridium difficile*, infections or associated with inflammatory bowel disease [1-4], mostly in severely ill patients or those hospitalized in intensive care units. Almost all the reports described fungemias in severely ill patients, most of whom had long hospitalizations, mainly in ICUs. Almost all the patients had exposure to the yeast (as a dietary supplement, used to treat diarrhea, or patients in the vicinity of other patients treated with the supplement). Most patients were immunocompromised, had malignant diseases, were receiving chemotherapeutic treatments or had complicated abdominal surgery. Possible mechanisms for the infections were contamination of indwelling catheters, migration of the yeast across damaged mucosal gastrointestinal barriers, or pulmonary infections [1,2]. Treatment is based on discontinuation of the probiotic preparation and the use of anti fungal agents.

Munoz et al. [5] described three patients hospitalized in an ICU in April 2005 who had *S. cerevisiae* fungemia and reviewed all the 57 known cases reported in the English literature of *Saccharomyces cerevisiae*. The only common risk factor for *S. cerevisiae* fungemia was the use of a probiotic containing the yeast, generally for treating or preventing diarrhea. Sixty percent of the patients had an ICU stay while infected and 70% had enteral or parenteral nutrition. Twenty-six patients (48%) had used the probiotic and 17 (30%) died.

Our patient is the first otherwise healthy patient described to have a recurrent, community-acquired infection and no exposure to the yeast. She did not receive any dietary supplementation or probiotic preparations.

ICU = intensive care unit

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"It is not what we do, but also what we do not do, for which we are accountable"

Moliere (1622-1673), French actor and playwright considered one of the greatest masters of comedy in Western literature

"The most dangerous of all falsehoods is a slightly distorted truth"

Georg Christoph Lichtenberg (1742-1799), German scientist and philosopher

Yellow Nail Syndrome

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KEY WORDS: yellow nail syndrome, vascular malformation, D2-40, CD31, vascular endothelial growth factor receptor-3 (VEGFR-3), von Willebrand factor

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Yellow nail syndrome is a rare syndrome characterized by slow-growing, over-curved yellow nails, bilateral leg lymphedema and lung abnormalities including pleural effusion and bronchiectasis. Other manifestations may include recurrent sinusitis, recurrent respiratory tract infections, pericardial effusion and ocular abnormalities. Since its first description in 1964 [1], the pathogenesis and genetic basis of this syndrome have not been established. We present a case of yellow nail syndrome in which the abnormal dilated vessels in the lymphedematous skin stained positively for D2-40 antibody and vascular endothelial growth factor receptor-3, considered to be markers for lymphatic endothelial cells [2,3], and for CD31 and von Willebrand factor, considered to be markers of vascular endothelial cells [4].

PATIENT DESCRIPTION

A 40 year old man, the son of non-consanguineous healthy parents of Arab extraction, was hospitalized in our department because of left leg cellulitis. His medical history included bronchiectasis complicated by recurrent respiratory tract infections that necessitated lobectomy at age 20. Since adolescence he had suffered from swollen feet with recurrent leg cellulitis. The patient also displayed recurrent sinusitis. He had never smoked and there was no history of tuberculosis. Similar abnormalities were not reported in his family.

Physical examination revealed bilateral lymphedema of both legs and toes, which were covered by thick verrucous skin. The toenails were yellow, over-curved, dystrophic, thick and without a cuticle [Figure A]. Chest auscultation demonstrated bilateral, scattered, coarse crackles in the lower lobes.

The routine laboratory studies demonstrated normal liver and renal function tests, normal albumin levels and no proteinuria. Repeated mycological cultures obtained from the involved nails were negative. Pulmonary spirometry revealed moderate limitation of the airflow.

High-resolution computed tomography scan of the chest showed postoperative changes in the left lower lobe, and mild cylindrical bronchiectasis, mainly in the right lower lobe with sub-segmental atelectasis in the right middle lobe and lingula. Small amounts of pericardial effusion were also seen.

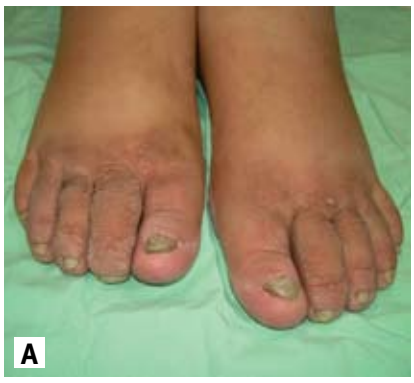
HISTOPATHOLOGY AND IMMUNOHISTOCHEMISTRY

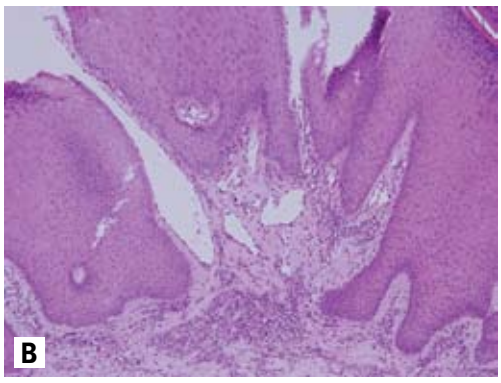
The histological examination of the skin biopsy obtained from the lymphedematous leg showed marked acanthosis and papillomatosis of the epidermis [Figure B]. Multiple dilated vessels lined by thin

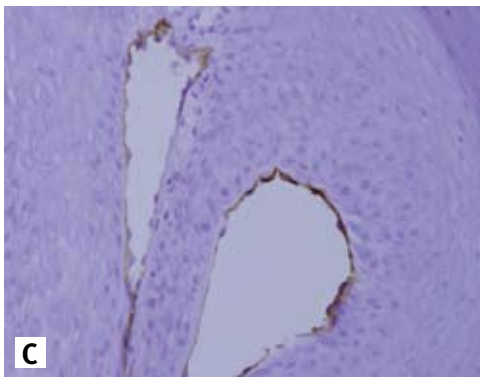
[A] Bilateral leg edema with verrucous thickening of the toes. The nails show dystrophy, thickening, yellow discoloration and overcurvature.

[B] A biopsy from edematous skin showing marked papillomatosis and acanthosis. There are dilated thin-walled vessels in the dermal papilla and upper dermis.

[C] The endothelial cells lining dilated vessels in a dermal papillae stain positively with D2-40 antibody.







endothelial cells were seen in the upper dermis along with mild perivascular mononuclear infiltrates [Figure B]. Some of the dilated vessels were partially encircled by the hyperplastic epidermis in the dermal papillae. Immunohistochemically, the endothelial cells stained positively with D2-40 antibody (Cell Marque, USA) [Figure C], and for VEGFR-3 (Millipore, Canada-USA), CD31 (Neomarkers, USA) and von Willebrand factor (Dako, Denmark).

COMMENT

Yellow nail syndrome (YNS, OMIM 153300) was first described in 1964 by Samman and White [1]. This rare syndrome is characterized by dystrophic, over-curved and slow-growing yellow nails, bilateral lymphedema of the legs, and lung abnormalities including pleural effusion and bronchiectasis. Other variable manifestations are recurrent sinusitis, recurrent respiratory tract infections, pericardial effusion and, rarely, ocular abnormalities. Yellow nail syndrome has been associated with autoimmune disorders such as thyroiditis, systemic lupus erythematosus and rheumatoid arthritis [5]. There are also isolated case reports of yellow nail syndrome associated with malignancy [5]. Familial cases have also been reported [5].

The pathogenesis of this syndrome has not been established. Some authors have proposed anatomic structural abnormalities of lymphatic vessels [1]. Abnormal lymphangiography has been demonstrated in patients with yellow nail syndrome [1], while others have demonstrated abnormally functioning lymphatic vessels on lymphoscintigraphy analysis [1].

D2-40 is a novel monoclonal antibody that reacts with an epitope in lymphatic endothelium [2]. It is considered to be a sensitive and specific marker of lymphatic endothelium, since normal lymphatic endothelial cells stain positively for D2-40 while capillaries and small vascular vessels do not [2,4]. Pusztaszeri et al. [4] found that D2-40 stains small lymphatic vessels around bronchioles in the lungs. In addition, mesothelial cells from the pleura and bronchial wall chondrocytes are also occasionally positive. This was not found in other parenchymal organs [4].

Another novel marker for lymphatic endothelium that may be helpful in identifying endothelial cells of lymphatic malformation is VEGFR-3 [3]. CD31 is one of the best known markers for vascular endothelium [4]. In the skin, CD31 stains small arteries, arterioles, venules and capillaries [4]. Small parts of lymphatic vessels may express CD31 but only weakly and irregularly [4]. In our case, the dilated vessels stained strongly and uniformly for CD31. Similarly, von Willebrand factor, which is stored in endothelial cell-specific organelles known as Weibel-Palade bodies, is also considered a marker for vascular endothelium [4]. In the present case, the histopathological examination of skin from the edematous leg demonstrated dilated thin-walled vessels in the upper dermis. These vessels were stained positively with D2-40 antibody and with antibodies to VEGFR-3, CD31 and von Willebrand factor. A similarly combined vascular and lymphatic immunoreactivity was described previously in lymphangioma, Kaposi's sarcoma, angiosarcoma and Dabska tumor [3]. Lymphatic anomalies occur concurrently with vascular malformation in both Klippel-Trenaunay syndrome and Parkes Weber syndrome [2]. The dual vascular and lymphatic endothelial differentiation, which is manifested in these tumors and malformations, may indicate abnormal vascular spaces that derive from a common immature precursor endothelial cell. This is consistent with previous reports suggesting that early development of lymphatic vessels is from veins and that both lymphatic and venous elements coexist in vascular malformations [2]. Therefore, the dual immunostaining pattern of the lymphedematous skin in our patient may reflect an underlying aberrant vascular development from a common precursor endothelial cell.

VEGFR-3 = vascular endothelial growth factor receptor-3

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Religious freedom should work two ways: we should be free to practice the religion of our choice, but we must also be free from having someone else's religion practiced on us"

John Irving (born 1942), American novelist and Academy Award-winning screenwriter

"There comes a point when a man must refuse to answer to his leader if he is also to answer to his own conscience"

Hartley Shawcross (1902-2003), British barrister, politician, and prosecutor at the Nuremberg War Crimes tribunal

BTK Gene Mutation in Two Non-Identical Twins with X-Linked Agammaglobulinemia Associated with Polyarticular Juvenile Idiopathic Arthritis

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KEY WORDS: juvenile idiopathic arthritis, X-linked agammaglobulinemia, Bruton disease, *BTK* mutation

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X-linked agammaglobulinemia is a genetic disorder of B cell maturation caused by a variety of mutations in the gene encoding Bruton tyrosine kinase (*BTK*). XLA affects only males and results in profound humoral immunodeficiency. The incidence of XLA is around 1:200,000 in newborns. XLA is characterized by recurrent bacterial infections due to low levels or absence of serum immunoglobulin isotypes [1,2]. The early administration of high dose intravenous immunoglobulin may prevent these infections [3].

Among patients with XLA 20% may have arthritis, primarily septic arthritis, and association with rheumatoid arthritis or juvenile idiopathic arthritis may also occur [1,2,4,5]. We present here a pair of non-identical twins who each had a mutation in the *BTK* gene. Both siblings presented with polyarticular juvenile idiopathic arthritis.

PATIENT DESCRIPTIONS

We report two 27 year old non-identical twin boys with XLA associated with seronegative, polyarticular JIA. The twins were born in 1981 and the diagnosis of XLA was established according to standard criteria in 1986 [2]. Their treatment consisted of monthly 400 mg/kg hIVIG.

The first boy originally presented to our rheumatology clinic with recurrent bilateral knee synovitis. He had a medical history of recurrent sinopulmonary infections, and pulmonary segmentectomy was performed due to pulmonary abscess. Serum IgA and IgM levels were below the detection limit (IgG 5.73 g/L, IgA < 0.06 g/L, IgM < 0.05 g/L) and a profound deficiency in circulating $CD19^+$ B cells (0.02%, normal range 5-15%) was observed.

At first presentation, joint radiography could not demonstrate joint erosions. Synovial fluid cultures were negative, excluding septic arthritis. Synovial crystals could not be identified. Serological tests for several viruses and bacteria were also negative. The patients were negative for antinuclear antibody, rheumatoid factor, anti-cyclic citrullinated peptide and HLA-B27. hIVIG substitution did not affect the synovitis: articular symptoms worsened involving both wrists, metacarpophalangeal and proxymal interphalangeal joints. The patient also developed subcutaneous nodules. Radiological progression was observed after one year in the metacarpophalangeal joints. Erythrocyte sedimentation rate was 1 mm/hr due to the lack of B cell products, while C-reactive protein was elevated (9.4 mg/L, normal range < 5 mg/L). Thus, the patient had seronegative, polyarticular JIA associated with humoral immunodeficiency. Considering severe profound polyarthritis in this patient adequately substituted with hIVIG, naproxen, then sulfasalazine therapy was initiated at a dose of 30 mg/kg, which soon resulted in clinical improvement and remission.

In the second boy, XLA was also diagnosed in 1986 after recurrent sinopulmonary infections and pneumonia. hIVIG therapy was administered at a monthly dose of 400 mg/kg.

In June 2000 the patient presented to our rheumatology clinic with recurrent bilateral knee and right hip synovitis. Rheumatoid factor, anti-CCP, antinuclear antibody and HLA-B27 were negative. Radiography showed no erosions. We observed significant $CD19^+$ B cell deficiency (0.02%) with very low serum IgG (5.63 g/L), IgA (< 0.06 g/L) and IgM (< 0.05 g/L).

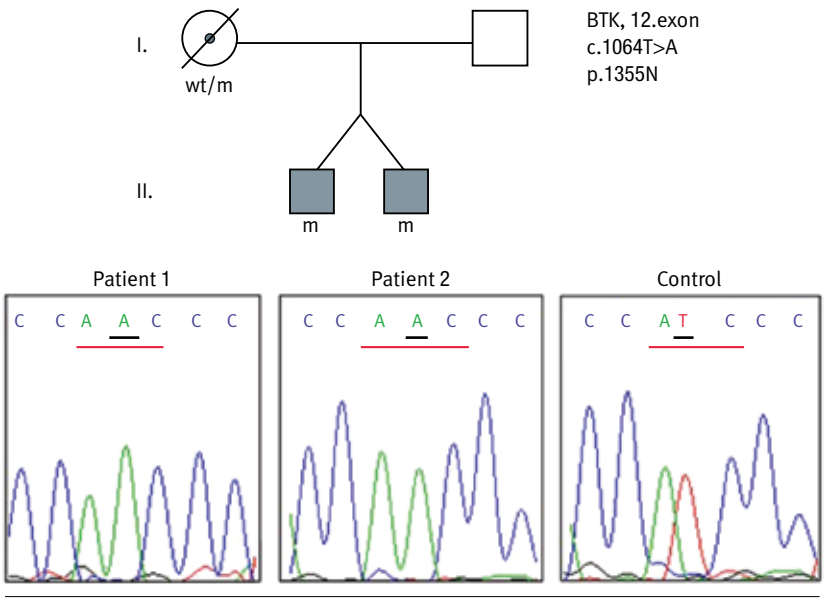
Upon naproxen therapy, synovitis progressed and a classical rheumatoid nodule developed over the elbow. In March 2005, leukocytoclastic vasculitis confirmed by histology developed on the forearm skin. Vasculitis subsided upon corticosteroid therapy. The patient was diagnosed with seronegative polyarticular JIA and 30 mg/kg sulfasalazine was introduced. Peripheral magnetic resonance imaging revealed small erosions in the os capitatum.

In 2006, we wished to confirm XLA by genetic analysis in the twins. Therefore, genomic DNA was extracted from blood leukocytes (GenElute Blood Genomic DNA Kit, Sigma, USA). Exons 1 to 19 and the flanking intron regions of the *BTK* gene were amplified from gDNA by polymerase chain reaction. Amplicons were

XLA = X-linked agammaglobulinemia
JIA = juvenile idiopathic arthritis
hIVIG = high dose intravenous immunoglobulin
anti-CCP = anti-cyclic citrullinated peptide

sequenced using the Big Dye Terminator sequencing kit (Applied Biosystems, USA). Capillary sequence analysis was performed in a blinded fashion with respect to the clinical diagnosis. Sequence variations are described in relation to reference sequences, GenBank accession no. NM_000061 for *BTK* cDNA, where the c.1 position represents A of the ATG translation initiation start site. A mutation (T→A) in exon 12 at position 1064 was identified resulting in an Ile→Asn amino acid change at position 355 in the BTK protein identified by PCR. All the other exons were found to be intact. A normal control was also genotyped. Thus, XLA could be genetically confirmed in these siblings based on the mutation in exon 12 of the *BTK* gene [Figure].

Pedigree and automated sequencing profiles of genomic DNA. Missense mutation (c.1064T>A; p.I355S) in *BTK* was found in both patients



COMMENT

We describe two cases of XLA associated with polyarticular JIA and nodules in non-identical twins. The definitive diagnosis of JIA was established in both cases by clinical and laboratory assessments. XLA was confirmed by recurrent infections, very low B cell numbers and later by the mutation in the *BTK* gene [1,2].

We present for the first time the association of XLA confirmed by molecular genetic analysis with polyarticular JIA in twins. In addition, although the reported XLA-associated cases were relatively mild and responded well to treatment with non-steroidal anti-inflammatory drugs, our twins needed disease-modifying anti-rheumatic drug therapy despite XLA.

PCR = polymerase chain reaction

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"At least one way of measuring the freedom of any society is the amount of comedy that is permitted, and clearly a healthy society permits more satirical comment than a repressive one, so that if comedy is to function in some way as a safety release then it must obviously deal with these taboo areas. This is part of the responsibility we accord our licensed jesters, that nothing be excused the searching light of comedy. If anything can survive the probe of humor it is clearly of value, and conversely all groups who claim immunity from laughter are claiming special privileges which should not be granted"

Eric Idle (b. 1943), English comedian, actor, author, singer, writer, and comedic composer who wrote and performed as a member of the popular British comedy group *Monty Python*

"I have never met a man so ignorant that I couldn't learn something from him"

Galileo Galilei (1564-1642), Italian physicist and astronomer

Idiopathic Pulmonary Artery Aneurysm Detected with Multidetector Computed Tomography: a Rare but Potentially Lethal Vascular Abnormality

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KEY WORDS: multidetector computed tomography (MDCT), pulmonary artery aneurysm, aneurysms, pseudoaneurysms, pulmonary trunk

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A 39 year old woman presented with upper respiratory infection symptoms that did not respond to conventional treatment. Physical examination was unremarkable and there was no history of any systemic disease. A chest radiograph was obtained and revealed a left hilar enlargement and normal lungs [Figure 1A]. The patient then underwent transthoracic echocardiography to rule out structural cardiac abnormalities or pulmonary hypertension. The TTE was normal except for mild mitral regurgitation. For further evaluation, she was referred by her physician to our department for chest computed tomography examination. Pulmonary CT angiography was performed using 64-row multidetector computed tomography and revealed saccular aneurysmal dilatation of the left inferior lobar pulmonary artery, associated with small mural thrombus [Figure 1 B and C]. The maximum diameter of the aneurysm was 35 mm. No cardiac or pulmonary cause was found for the pulmonary artery aneurysm.

PAA is a vascular abnormality morphologically characterized by focal dilatation of the vessel involving all three layers of the vessel wall, with or without mural thrombi or wall calcifications. A pseudoaneurysm does not involve all layers of the arterial wall. Pulmonary aneurysms may occur in association with congenital cardiac defects, particularly patent ductus arteriosus. More common causes include vasculitides and alterations in connective tissue (e.g., Behcet disease, Takayasu disease, Marfan syndrome), and pulmonary hypertension [1]. Pulmonary pseudoaneurysms are usually caused by trauma (especially iatrogenic: during placement of a catheter, chest tube insertion, surgical procedures). A less common cause is penetrating chest trauma. Infection with tuberculosis, pyogenic bacteria, and fungi can also cause pulmonary pseudoaneurysm. Malignant lung tumors can cause erosion into the pulmonary arteries and result in pseudoaneurysm formation. Idiopathic PAA without any

TTE = transthoracic echocardiography
PAA = pulmonary artery aneurysm

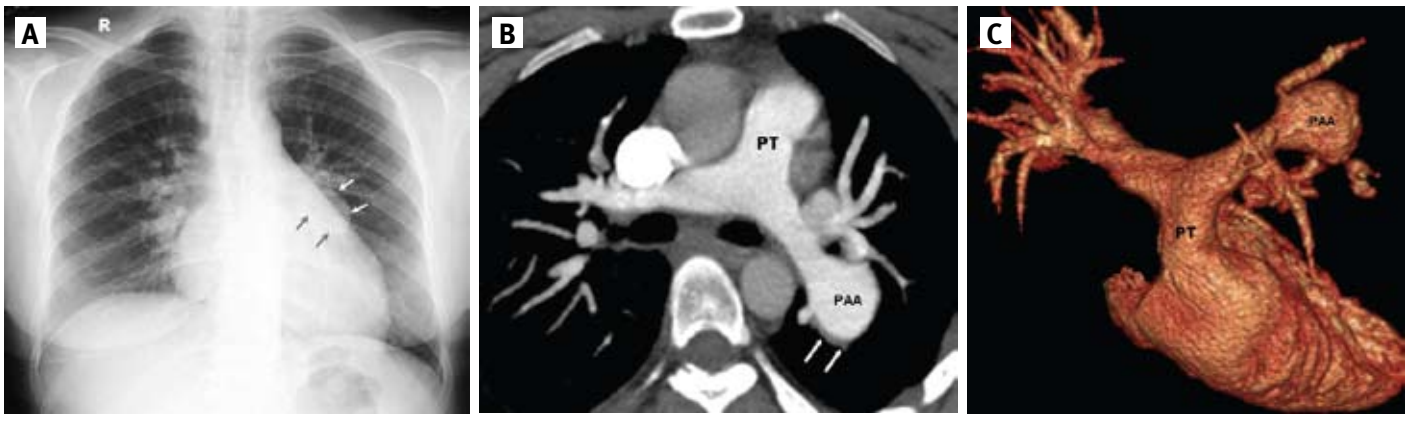

Figure 1. Pulmonary artery aneurysm in a 39 year old asymptomatic woman. **[A]** Chest radiograph show left hilar enlargement (arrows) and normal lungs. Contrast-enhanced axial **[B]** and 3D volume rendering **[C]** CT images show saccular aneurysmal dilatation of the left inferior lobar pulmonary artery with small mural thrombi (arrows). PAA = pulmonary artery aneurysm, PT = pulmonary trunk.

associated diseases is a rare lesion and has infrequently been reported. Most patients with PAA are asymptomatic or have non-specific symptoms. Patients with PAA may present with hemoptysis. The mortality rate for patients with a ruptured PAA is very high; thus early and accurate diagnosis of PAA is essential. Owing to its high spatial resolution, contrast-enhanced MDCT is considered the primary technique for diagnosing PAA since it offers a unique opportunity to evaluate the presence, size, shape and exact location of the aneurysm, and concomitant cardiovascular abnormalities [2]. The aneurysms appear as saccular or fusiform areas of dilatation of various sizes, with homogeneous contrast material filling that occurs simultaneously with that in the pulmonary artery. Based on the imaging findings only, the differentiation between pulmonary aneurysms and pseudoaneurysms is very difficult.

In patients with idiopathic PAA, surgical treatment may be considered when the aneurysm is large and when it is associated with pulmonary regurgitation. However, the role of surgery in main pulmonary artery aneurysms is still undetermined. Pulmonary CT angiography could emerge as an ideal non-invasive technique for percutaneous intervention (embolization) or surgical treatment planning. Magnetic resonance imaging can also be used for establishing the diagnosis; furthermore, it may show the arterial wall thickening in connective tissue disease, and provide information regarding blood flow direction in cases of post-stenotic dilatation due to disease involving the pulmonary valve.

MDCT = multidetector CT

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Erratum

In the article "Treatment of Crohn's Disease with Cannabis: An Observation Study" that appeared in the August issue [*IMAJ* 2011; 13 (8): 455-8], a mistake occurred in the spelling of the third author's name. The correct spelling is D. Yablecovitch and not D. Yablekovitz as printed.

Capsule

Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis

Multiple sclerosis is a common disease of the central nervous system in which the interplay between inflammatory and neurodegenerative processes typically results in intermittent neurological disturbance followed by progressive accumulation of disability. Epidemiological studies have shown that genetic factors are primarily responsible for the substantially increased frequency of the disease seen in the relatives of affected individuals, and systematic attempts to identify linkage in multiplex families have confirmed that variation within the major histocompatibility complex (MHC) exerts the greatest individual effect on risk. Modestly powered genome-wide association studies (GWAS) have enabled more than 20 additional risk loci to be identified and have shown that multiple variants exerting modest individual effects have a key role in disease susceptibility. Most of the genetic architecture underlying susceptibility to the disease remains to be defined and is anticipated to require the analysis of sample sizes that are beyond the numbers currently available to individual research groups. In a collaborative GWAS involving 9772 cases of European descent collected by 23 research groups working in 15 different countries, The International Multiple Sclerosis Genetics Consortium & The Wellcome Trust Case Control Consortium 2 have replicated almost all of the previously suggested associations and identified at least a further 29 novel susceptibility loci. Within the MHC they have refined the identity of the *HLA-DRB*1 risk alleles and confirmed that variation in the *HLA-A* gene underlies the independent protective effect attributable to the class I region. Immunologically relevant genes are significantly overrepresented among those mapping close to the identified loci and particularly implicate T helper cell differentiation in the pathogenesis of multiple sclerosis.

Nature 2011; 476: 214

Eitan Israeli

"Where is the life we have lost in living? Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?"

T.S. Eliot (1888-1965), American-born British playwright, literary critic and Nobel Prize laureate

"Everybody wants to save the earth; nobody wants to help mom do the dishes"

P.J. O' Rourke (born 1947), American writer and satirist