Omalizumab Therapy for Chronic Spontaneous Urticaria: The Israeli Experience

Menachem Rottem MD[1], Ramit Segal MD[2], Shmuel Kivity MD[3], Laliv Shamshines MD[3], Yael Graif MD[4], Meir Shalit MD[5], Aharon Kessel MD[6], Josef Panasoff MD[7], Shai Cohen MD[7,8], Elias Toubi MD[6] and Nancy Agmon-Levin MD[2]

[1]Allergy, Asthma and Immunology Unit, Emek Medical Center, Afula, affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
[2]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Allergy and Clinical Immunology Unit, Tel Aviv Sourasky Medical Center, Tel Aviv, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[4]Allergy and Clinical Immunology Unit, Lung Institute, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel
[5]Allergy and Clinical Immunology Unit, Department of Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
[6]Allergy and Clinical Immunology Division, Bnai Zion Medical Center, Haifa, affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
[7]Allergy Department, Lin Medical Center, Haifa, Israel
[8]Department of Internal Medicine B, Carmel Medical Center, Haifa, affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

ABSTRACT: **Background:** Chronic spontaneous urticaria (CSU) is a common, debilitating disease that is frequently resistant to standard therapy. Omalizumab, anti-immunoglobulin-E humanized monclonal antibody, was recently shown to be effective in treating resistant CSU.

Objectives: To investigated the treatment of CSU with omalizumab in Israel.

Methods: We conducted a multicenter retrospective analysis of patients with refractory CSU treated with omalizuamb in Israel during 2012–2013. Complete improvement was defined as resolution of symptoms with no need for other medications, or satisfactory when patients' condition improved but required regular or intermittent doses of antihistamines.

Results: Forty-three patients received omalizumab off-label for refractory CSU. Their mean age was 45 ± 12 years and CSU duration was 4.3 ± 4 years. In this cohort, 98% were unsuccessfully treated with high dose H(1)-antihistamines, 88% with systemic glucocorticoids and 30% with cyclosporine and/or other immune-modulators. Fourteen patients received only one injection of omalizumab, while the other 29 received on average of 4.3 ± 3.2 injections; 30 patients received 150 mg/month and 13 received 300 mg/month. Following omalizumab therapy, disease remitted within weeks in 86% of patients, of whom half achieved complete remission. The latter was associated with usage of high dose omalizumab, 300 mg/month vs. 150 mg/month ($P = 0.02$) and repeated therapy (i.e., multiple injections vs. a single injection) ($P = 0.0005$).

Conclusions: Omalizumab is an effective and safe treatment for refractory CSU with rapid onset of action for inducing and maintaining remission. Treating CSU patients mandates an individual approach, because while low dose omalizumab will suffice for some patients others might need higher doses and prolonged therapy.

IMAJ 2014; 16: 487–490

KEY WORDS: omalizumab, urticaria, autoimmune, allergy, anti-histamine

Chronic spontaneous urticaria is a common disease, affecting 1%–1.3% of the population, and is characterized by a typical and severe itching rash lasting for more than 6 weeks [1,2]. This disease may be associated with comorbidities. It may persist for years and adversely affects quality of life, sleep, daily activities, school and work life, as well as social interactions.

The current revised and unified guidelines of the European Academy of Allergy and Clinical Immunology and Global Allergy and Asthma European Network, as well as the World Allergy Association committees (EAACI/GALEN/EDF/WAO) suggest a step-wise approach to the management of CSU [3,4]. This approach aims to achieve complete symptom control, using a three-step process. The first step is the use of a standard-dose non-sedating H1 antihistamine [4]. These drugs are efficacious but increasing the dose fourfold (step 2), above the licensed doses, is frequently required and still leaves a substantial proportion of patients symptomatic. Hence, short-term corticosteroid therapy (3–7 days) may be required. Unfortunately, for most unresponsive CSU patients longer periods of corticosteroid therapy are needed and are associated with numerous undesired side effects [1-4]. Refractory disease requires further interventions (step 3), using cyclosporine A, omalizumab, or montelukast. Low dose cyclosporine A is efficacious in 70% of patients with glucocorticoid-dependent CSU; however, this response generally lasts in only 50% of responders [5]. Furthermore, toxicity associated with cyclosporine A therapy, although less common following the use of low doses as required for CSU, still raises concern. Hence this therapy may not be suitable for all CSU patients.

Omalizumab, an anti-immunoglobulin E humanized monoclonal antibody, is becoming increasingly recognized as an effective therapy for difficult-to-treat CSU. Before 2013 its use was off-label for this condition. Omalizumab is an anti-IgE antibody that binds only circulating free IgE and not cell-bound IgE. It

CSU = chronic spontaneous urticaria
IgE = immunoglobulin

was originally designed to treat allergic asthma and rhinitis [6]. In these conditions the postulated mechanisms by which omalizumab exerts its effects are decreased free IgE and down-regulation of IgE receptors (FcεRI) on mast and other cells, occurring within 12–16 weeks [6-9]. In the last few years, several clinical studies reported that omalizumab therapy was highly effective for resistant CSU as well. Notably, in some studies even a single injection of omalizumab was beneficial, while in others the response was dose-dependent [7-11]. Since omalizumab was used worldwide as off-label therapy for refractory CSU, there is currently a lack of data regarding the length of therapy required, tapering-down protocols, as well as concomitant therapy use. The present study investigated the efficacy and tolerability of omalizumab for CSU in a 'real-life' scenario in Israel.

PATIENTS AND METHODS

We conducted a multicenter retrospective review of all patients with CSU who were treated with omalizuamb from January 2012 to December 2013. CSU was defined as episodes of hives with or without angioedema and occurring either intermittently or continuously for 6 weeks or longer. Patients were excluded if they had drug-related urticaria or angioedema exclusively. Demographic data were recorded, including age, gender, and prior and concurrent therapy. Omalizumab was administered off-label, when available, and in the amount available (i.e., once or more in doses of either 150 mg or 300 mg monthly). Due to the retrospective nature of this study, response was recorded as a categorical result (complete, partial, none) based on the patients' subjective evaluation and on their need for additional treatment with H1-antihistamines. Complete response was defined as complete resolution of symptoms and no need for further medications (other than omalizumab). A satisfactory (partial) response was defined as an improvement in the patient's condition, with the patient still requiring regular or intermittent doses of antihistamines.

STATISTICAL ANALYSIS

Microsoft Excel version 2003 (Microsoft Corp., Seattle, WA) and the statistical program SPSS 13.0 (SPSS, Chicago, IL, USA) were used for statistical analysis. Results are presented as means and standard deviations. Findings were compared between the groups using the Student *t*-test or Fisher's exact test as appropriate. *P* values < 0.05 were considered statistically significant

RESULTS

The study group consisted of 43 CSU patients treated with omalizumab [Figure 1]. In this cohort 30 (70%) were females, their mean age was 45 ± 12 years (range 20–64), and the duration of CSU prior to omalizumab therapy was 4.3 ± 4 years [Table 1]. While all patients were treated with antihistamines, at initiation of omalizumab therapy 42 patients (98%) received high dose (fourfold) H(1)-antihistamines. In addition, 38 (88%) received systemic glucocorticoids, and 13 (30%) were treated with other immune modulating agents: namely, cyclosporine A (26%), montelukast (9%), and others, such as methotrexate (14%). All were unresponsive. Since at the time of the study omlizumab was prescribed off-label for the indication of CSU, 14 patients received only one injection while the other 29 received an average of 4.3 ± 3.2 injections (range 2–12). Of those receiving multiple injections, 7 were given more than one injection but only once every 2–12 months, and the other 22

Figure 1. Response of chronic spontaneous urticaria to therapy with omalizumab

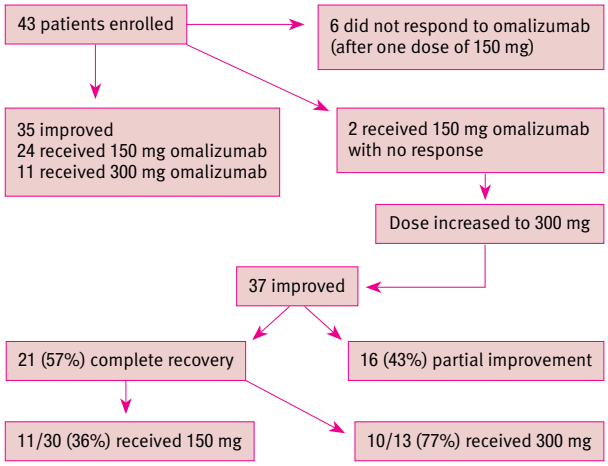


Table 1. Clinical parameters of 43 urticaria patients treated with omalizumab for CSU

	Patients (n=43)
Gender (female %)	30 (70%)
Age (yr)	45 ± 12
Duration of disease (yr)	4.3 ± 4
IgE mean levels (IU/ml)	151 ± 255
Other diseases	
Allergic rhinitis	4 (9%)
Asthma	6 (14%)
Other therapies	
High dose anti-H1-histamines	42 (98%)
High dose corticosteroids	38 (88%)
No. of corticosteroids courses (in the previous year)	2.3 ± 2
Cyclosporine	11 (26%)
Monetelukast	4 (9%)
Other immunosupressants (methotrexate, mycophenolate mofetil, azatioprine, etc.)	6 (14%)
Treatment with omalizumab	
150 mg/month	30 (70%)
300 mg/month	13 (30%)
Responded	37 (86%)
Adverse events (within 2 hours)	1 (2%)

patients were treated regularly each month. In this cohort 13 patients received 300 mg omalizumab/month while 30 patients received 150 mg once or more.

Following treatment with omalizumab CSU subsided in 37 patients (86%) of whom 21 (57%) showed complete response and 16 (43%) a satisfactory improvement. In 35 of the 37 responders to omalizumab, the effect was documented within the first few weeks after the first injection, while in the other 2 patients a dose increment to 300 mg was required to achieve response. It is noteworthy that complete recovery occurred in 11 of 30 patients (36%) treated with 150 mg omalizumab as compared to 10 of 13 (77%) who were finally treated with 300 mg ($P = 0.02$).

Treatment failure was observed in six patients, all of whom received only one dose of 150 mg. In other words, treatment failure was diagnosed in 6 of 14 patients (43%) who received one dose vs. none of 29 who received multiple doses ($P = 0.0005$). One patient experienced palpitations and weakness during the first 2 hours of the first course of omalizumab therapy; further courses were uneventful.

DISCUSSION

We found omalizumab to be efficacious in the vast majority of patients with severe and resistant CSU, following failure of high dose H1-antihistamines and other immune modulating agents. The overall response rate to omalizumab in our cohort was impressively high: 86%, with 57% of responders showing complete response and 43% a partial remission. Only 14% of patients showed no response, most of whom received low dose and/or a single injection of omalizumab, mainly due to the low availability of the drug.

This biologic drug recently emerged as an effective and safe alternative for treating CSU patients [7,13-16]. However, unlike omalizumab dosing for moderate-severe asthma, which is based on IgE levels and body weight, the effect of omalizumab on CSU seems to be unrelated to these parameters [7-12]. Moreover, even a single injection was found to be beneficial in some of our patients, as noted also in other observational and small clinical studies [8,12]. In contrast, in phase III studies of omalizumab for CSU a fixed dose of 300 mg/month was the most efficacious [7,10]. In the study by Maurer et al. [7], the proportion of patients completely free of hives was 10%, 23% and 53%, in those receiving placebo, 150 mg omalizumab, and 300 mg omalizumab, respectively. In another study, even higher doses of 450 mg/month were needed for some patients [8]. In our cohort the doses were limited by the availability of omalizumab, thus the initial dose was either 150 or 300 mg thereafter if plausible therapy was continued. For non-responders who received the 150 mg dose, a higher dose of 300 mg/month was used. We observed that omalizumab was most effective for CSU when higher doses were used and for a prolonged period. Therefore, it seems that a higher dose of omalizumab is more efficacious, although lower doses may suffice for some patients. These findings support the need for tailored use of omalizumab for CSU.

Our cohort of CSU patients included patients diagnosed with autoimmune chronic urticaria as well as patients with no autoimmune features. Few studies have investigated the response of various CSU phenotypes to the available medications, especially omalizumab. In a selective cohort of 12 patients who were designated as having an autoimmune basis for their urticaria, improvement was noted in 11 of 12 patients [14]. Similarly, efficacy was shown in a cohort of patients with IgE autoantibodies to thyroperoxidase [2]. On the other hand, a case series of eight CSU patients with no autoimmune features also showed improvement following omalizumab therapy [17]. A more recent study of a mixed cohort of CSU patients examined whether any specific autoimmune marker or clinical characteristics would serve as predictor(s) of responsiveness to omalizumab. The results showed that indeed all phenotypes of CSU are responsive to omalizumab therapy [18]. Finally, a retrospective study of patients with both spontaneous and inducible urticaria documented a high rate of response in both groups [8]. Therefore, it appears that omalizumab may benefit patients with chronic urticaria, regardless of the immune process underlying this condition.

CSU is a disease of spontaneous remission and exacerbation; thus, the length of therapy with omablizumab or other immune modulators is yet to be determined. In the randomized clinical studies published so far, recurrence of symptoms following termination of 3–6 months therapy was common [7,11]. However, in the current study some patients achieved a long-standing remission (months or a year) after treatment with omalizumab, with no need for further medication. On the other hand, prolonged therapy of up to 12 months in our study and 37 months in other studies was both beneficial and safe [8,19,20].

Consequently, although omalizumab is remarkably effective for patients with different CSU phenotypes (and probably for other types of chronic urticaria), the dose and length of therapy with this drug has yet to be determined and will probably be individually based. Omalizumab is an expensive drug that may have adverse events (e.g., anaphylaxis). Thus, it remains prudent to consider this therapy only after a full assessment by a specialist who is experienced both in treating moderate-severe CSU and in using omalizumab.

The mechanisms whereby omalizumab ameliorates CSU symptoms are currently uncertain and are under investigation. Previous studies have shown that omalizumab decreases free IgE levels and down-regulates receptor ($Fc\varepsilon R1$) expression on mast cells and basophils within 12–16 weeks after initiation of therapy [21,22]. These mechanisms of action, while also playing a role in CSU, cannot be the sole explana-

tion for the effect of omalizumab in this condition since most patients, in this study and others, experienced rapid improvement (within 1–3 weeks) [12,14]. Recent studies showed that omalizumab may intervene in immune mediated processes through direct basophil stabilization [12], effects on pathogenic IgE antibodies [23], or a decrease in IgE synthesis by targeting membrane IgE-positive B cells [24].

There are some limitations to our study, such as its retrospective design, small study population, and the lack of a standard protocol for the assessment and management of CSU.

CONCLUSIONS

We found omalizumab to be an effective and safe treatment for moderate to severe CSU, with a rapid onset of action for inducing and maintaining remission. A tailored regimen of omalizumab, considering dose and length of therapy, is required, as are step-down protocols regarding concomitant medications.

Correspondence
Dr. M. Rottem
Head, Allergy Asthma and Immunology Unit, Emek Medical Center, Afula 18101, Israel
Fax: (972-4) 814-1556
email: menachem@rottem.net

References

1. Greeves MW. Chronic urticaria. *N Engl J Med* 1995; 332: 1767-72.
2. Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria: a GA2LEN task force report. *Allergy* 2011; 66: 317-30.
3. Zuberbier T, Asero R, Bindslev-Jensen C, et al., Dermatology Section of the European Academy of Allergology and Clinical Immunology; Global Allergy and Asthma European Network; European Dermatology Forum; World Allergy Organization. EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. *Allergy* 2009; 64 (10): 1427-43.
4. Zuberbier T. A summary of the new international EAACI/GA2LEN/EDF/WAO Guidelines in Urticaria. *World Allergy Organ J* 2012; 5 (Suppl 1): S1-5.
5. Toubi E, Kessel A, Avshovich N, et al. Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. *Allergy* 2004; 59 :869-73.
6. Novartis G. Xolair (omalizumab). January 2010 (package insert) (http://www.gene.com/patients/medicines/xolair).
7. Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013; 368: 924-35.
8. Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. *J Dermatol Sci* 2014; 73 (1): 57-62.
9. Sussman G, Hébert J, Barron C, et al. Real-life experiences with omalizumab for the treatment of chronic urticaria. *Ann Allergy Asthma Immunol* 2014; 112 (2): 170-4.
10. Viswanathan RK, Moss MH, Mathur SK. Retrospective analysis of the efficacy of omalizumab in chronic refractory urticaria. *Allergy Asthma Proc* 2013; 34 (5): 446-52.
11. Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol* 2013; 132 (1): 101-9.
12. Saini S, Rosen KE, Hsieh HJ, et al. A randomized, placebo controlled, dose-ranging study of single-dose omalizumab inpatients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol* 2011; 128: 567-73.e1.
13. Buyukozturk S, Gelincik A, Demirturk M, et al. Omalizumab markedly improves urticaria activity scores and quality of life scores in chronic spontaneous urticaria patients: a real life survey. *J Dermatol* 2012; 39: 439-42.
14. Kaplan AP, Joseph K, Maykut RJ, et al. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol* 2008 ;122: 569-73.
15. Nam YH, Kim JH, Jin HJ, et al. Effects of omalizumab treatment in patients with refractory chronic urticaria. *Allergy Asthma Immunol Res* 2012; 4: 357-61.
16. Maurer M, Altrichter S, Bieber T, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol* 2011; 128: 202-9e5.
17. Ferrer M, Gamboa P, Sanz ML, et al. Omalizumab is effective in non-autoimmune urticaria. *J Allergy Clin Immunol* 2011; 127: 1300-2.
18. Ravi K. Viswanathan RK, Moss MH, Mathur SK. Retrospective analysis of the efficacy of omalizumab in chronic refractory urticaria. *Allergy Asthma Proc* 2013; 34: 446-52.
19. Lefévre AC, Deleuran M, Vestergaard C. A long term case series study of the effect of omalizumab on chronic spontaneous urticaria. *Ann Dermatol* 2013; 25 (2): 242-5.
20. Song CH, Stern S, Giruparajah M, Berlin N, Sussman GL. Long-term efficacy of fixed-dose omalizumab for patients with severe chronic spontaneous urticaria. *Ann Allergy Asthma Immunol* 2013; 110 (2): 113-17.
21. Eckman JA, Sterba PM, Kelly D, et al. Effects of omalizumab on basophil and mast cell responses using an intranasal cat allergen challenge. *J Allergy Clin Immunol* 2010; 125: 889-95.e7.
22. Beck LA, Marcotte GV, MacGlashan D, et al. Omalizumab induced reductions in mast cell Fc epsilon RI expression and function. *J Allergy Clin Immunol* 2004; 114: 527-30.
23. Metz M, Maurer M. Omalizumab in chronic urticaria. *Curr Opin Allergy Clin Immunol* 2012; 12: 406-11.
24. Chan MA, Gigliotti NM, Dotson AL, Rosenwasser LJ. Omalizumab may decrease IgE synthesis by targeting membrane IgE+ human B cells. *Clin Transl Allergy* 2013; 3 (1): 29.

Capsule

Ex vivo culture of circulating breast tumor cells for individualized testing of drug susceptibility

Circulating tumor cells (CTCs) are present at low concentrations in the peripheral blood of patients with solid tumors. It has been proposed that the isolation, ex vivo culture, and characterization of CTCs may provide an opportunity to non-invasively monitor the changing patterns of drug susceptibility in individual patients as their tumors acquire new mutations. In a proof-of-concept study, Yu et al. established CTC cultures from six patients with estrogen receptor-positive breast cancer. Three of five CTC lines tested were tumorigenic in mice. Genome sequencing of the CTC lines revealed preexisting mutations in the *PIK3CA*gene and newly acquired mutations in the estrogen receptor gene (*ESR1*), *PIK3CA* gene, and fibroblast growth factor receptor gene (*FGFR2*), among others. Drug sensitivity testing of CTC lines with multiple mutations revealed potential new therapeutic targets. With optimization of CTC culture conditions, this strategy may help identify the best therapies for individual cancer patients over the course of their disease.

Science 2014; 345: 216

Eitan Israeli

Blys Levels in Sera of Patients with Systemic Lupus Erythematosus: Clinical and Serological Correlation

Daniel Elbirt MD[1]*, Ilan Asher MD[1]*, Keren Mahlab-Guri MD[1], Shira Bezalel-Rosenberg MD[1], Victor Edelstein MD[2] and Zev Sthoeger MD[1,2]

[1]Department of Clinical Immunology, Allergy and Neve-Or AIDS Center and [2]Department of Internal Medicine B, Kaplan Medical Center, Rehovot, affiliated with Hebrew University-Hadassah Medical School, Jerusalem, Israel

ABSTRACT: **Background:** Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by disturbance of the innate and adaptive immune systems with the production of autoantibodies by stimulated B lymphocytes. The BLyS protein (B lymphocyte stimulator) is secreted mainly by monocytes and activated T cells and is responsible for the proliferation, maturation and survival of B cells.

Objectivs: To study sera BLyS level and its clinical significance in Israeli lupus patients over time.

Methods: The study population included 41 lupus patients (8 males, 33 females; mean age 35.56 ± 15.35 years) and 50 healthy controls. The patients were followed for 5.02 ± 1.95 years. We tested 221 lupus sera (mean 5.4 samples/patient) and 50 normal sera for BLyS levels by a capture ELISA. Disease activity was determined by the SLEDAI score.

Results: Sera BLyS levels were significantly higher in SLE patients than in controls (3.37 ± 3.73 vs. 0.32 ± 0.96 ng/ml, $P < 0.05$). BLyS levels were high in at least one sera sample in 80.5% of the patients but were normal in all sera in the control group. There was no correlation between sera BLyS and anti-ds-DNA autoantibody levels. BLyS levels fluctuated over time in sera of lupus patients with no significant correlation to disease activity.

Conclusions: Most of our lupus patients had high sera BLyS levels, suggesting a role for BLyS in the pathogenesis and course of SLE. Our results support the current novel approach of targeting BLyS (neutralization by antibodies or soluble receptors) in the treatment of active lupus patients.

IMAJ 2014; 16: 491–496

KEY WORDS: BLyS, BAFF, systemic lupus erythematosus (SLE), lupus pathogenesis, anti-ds-DNA autoantibodies

Systemic lupus erythematosus is an autoimmune disease affecting almost any organ in the body including the nervous system, kidneys, lungs, cardiovascular system, skin, eyes, digestive system and the hematological system. The disease appears at any age in both genders but is more common in females of reproductive age [1]. Although the precise etiology of SLE has not yet been determined, it has been shown that genetic, environmental and hormonal factors play a role in its pathogenesis. SLE is characterized by disturbances of both the innate and the adaptive immune systems with dysregulation of T and B cells, cytokines and the complement system, as well as in the production of autoantibodies [1].

The basis for the development of autoimmune diseases, like SLE, is the loss of self tolerance by the immune system. The latter involves dysregulation of CD4 and CD8 cells with upregulation of soluble and intracellular pro-inflammatory cytokines (e.g., interleukins-6 and 18 and interferon-gamma), and downregulation of suppressive cytokines (e.g., transforming growth factor-beta) [2,3]. Recently, reports from several groups demonstrated a low prevalence of $CD4^+$ $CD25^+$ $FoxP3^+$ regulatory T cells in mice and humans with SLE [3]. In addition to the dysregulation of T cells, SLE is characterized by the production of autoantibodies by "autoreactive" B cells [2]. Thus, antinuclear antibodies can be detected in the sera of almost all SLE patients though these autoantibodies are not highly specific for lupus [4]. More specific autoantibodies such as anti-ds-DNA and anti-Sm autoantibodies were demonstrated in the sera of 80–85% and 20–30% of SLE patients, respectively [1].

B lymphocyte stimulator (BLyS), also designated B cell-activating factor (BAFF), is a 250 amino acid protein that belongs to the tumor necrosis factor ligand superfamily [5]. It is produced and secreted mainly by monocytes and activated T cells. The three BLyS receptors – BLyS receptor 3 (BR3, also known as BAFF-R), transmembrane activator-1 and calcium modulator and cyclophilin ligand interactor (TACI), and B cell maturation antigen (BCMA) – are expressed by B cells [6]. BLyS plays a major role in the stimulation, proliferation and maturation of B cells to plasma cells which produce immunoglobulins [5,6]. Mice with overexpression of BLyS demonstrated high immunoglobulin levels, including high levels of autoantibodies and SLE-like disease with immune

*The first two authors contributed equally to this study

SLE = systemic lupus erythematosus
BLyS = B lymphocyte stimulator

complex glomerulonephritis [7]. Furthermore, NZB/NZW F1 mice (murine model for spontaneous SLE) revealed high BLyS levels in their sera, while neutralization of BLyS in those mice by soluble TACI receptor led to amelioration of the disease and a reduced mortality rate [8].

Similar to the mice studies, high BLyS levels were reported in sera obtained from 40–50% of SLE patients [9,10]. The correlation between BLyS levels in the sera of lupus patients and disease activity has not yet been defined. It was suggested that high mRNA BLyS levels in monocytes of SLE patients correlate with disease activity better than BLyS sera levels do [11].

The present study was aimed at determining BLyS levels in the sera of a cohort of SLE patients as compared to healthy matched controls over 5 years of clinical and serological follow-up and to define the correlation of sera BLyS levels, disease activity and levels of anti-ds-DNA autoantibodies.

PATIENTS AND METHODS

The participants in this study were 41 SLE patients and 50 healthy volunteers matched for age, gender and ethnic background. All 41 lupus patients were diagnosed with SLE according to at least four diagnostic criteria of the American College of Rheumatology [12]. Disease activity score was determined according to the Systemic Lupus Erythematosus Disease Activity Index [13]. The mean follow-up was 5.02 ± 1.95 years (range 2–10 years). All patients (and healthy volunteers) signed an informed consent form before entering the study. The study was approved by the Kaplan Medical Center ethics committee and was performed according to all GCP guidelines.

BLOOD SAMPLES

Sera obtained from SLE patients or healthy controls were frozen and stored at -70°C prior to BLyS measurement. At every time point that we obtained a blood sample, once every 3–6 months, disease activity was evaluated by SLEDAI, and ANA and ds-DNA autoantibodies were also measured. For every patient we obtained at least two different samples at two different time points during the follow-up. Overall we obtained 221 sera samples from our 41 SLE patients during the study: the mean number of samples per patient was 5.4 ± 2.18 (range 2–10).

BLYS DETERMINATION

The sera levels of BLyS were determined by a capture enzyme-linked immunosorbent assay [14]. Briefly, plates (96 wells, Nunc, Waltham, MA, USA) were covered overnight (at least 6 hours) with 50 µl of mice monoclonal antibodies at a concentration of 10 µg/ml directed against human BLyS. After washing (phosphate-buffered saline Tween 0.001%), blocking with fetal calf serum) (10%) (200 µl per well) at room temperature for 3 hours, plates were washed again and sera samples were added in triplicate at 1:10 to 1:1000 dilutions for one hour at room temperature. Following another wash (x 3), polyclonal anti-human BLyS rabbit antibodies were added (1 hour, room temperature) [14,15]. Known concentrations of recombinant BLyS were used as positive controls (standard curve). The lower limit for BLyS detection of our capture ELISA was 0.32 ng/ml. Normal upper level (3.2 ng/ml) was defined as mean BLyS levels in the sera of 50 healthy volunteers plus 3 standard deviations (mean + 3SD). BLyS levels higher than 10 ng/ml, about three times the normal level, were (arbitrarily) considered "very high."

STATISTICAL ANALYSIS

Data are presented as means ± SD. Mann-Whitney, unpaired Student's *t*-test and chi-square tests were used for statistical analysis. Correlation between variables was assessed by the Pearson's coefficient correlation test. A value of $P \leq 0.05$ was considered statistically significant.

RESULTS

The study group comprised 41 SLE patients, 33 (80.5%) females and 8 (19.5%) males. Their mean age at study entry was 35.56 ± 15.35 years (range 9–79). Fifty healthy volunteers matched for age, gender and ethnic background served as a control group. The mean time of follow-up was 5.02 ± 1.95 years (range 2–10 years).

CLINICAL AND SEROLOGICAL CHARACTERISTICS

The 41 lupus patients in our study demonstrated typical SLE-related serological and clinical disease manifestations [Table 1]. Arthritis was present in 78% of the patients, photosensitivity was observed in 29%, lupus-related skin involvement (either malar rash or discoid lupus erythematosus) in 20%, mucosal ulcers in 22%, serositis (pleuritis and/or pericarditis) in 24%, and kidney disease (proteinuria > 0.5 g/24 hr or nephritis) in 48% of the patients. Hematological disease (hemolytic anemia and/or leukopenia and/or lymphopenia and/or thrombocytopenia) was observed in 42% of our SLE patients and central nervous system involvement (psychosis and/or epilepsy) in 12%. In all 41 lupus patients, significant (≥ 1:320) titers of ANA were detected whereas anti-ds-DNA autoantibodies were observed in the sera of 33 (85%) (at least at one time point during the follow-up period) [Table 1]. SLE disease activity (SLEDAI) was determined at every study visit with a mean score of 6.95 ± 5.94 (range 0–28).

TACI = transmembrane activator-1 and calcium modulator and cyclophilin ligand interactor
SLEDAI = Systemic Lupus Erythematosus Disease Activity Index
ANA = antinuclear antibody

ELISA = enzyme-linked immunosorbent assay

Table 1. Major clinical and serological manifestations in 41 SLE patients

Clinical manifestation	No. of patients (%)*
Arthritis	32 (78%)
Renal involvement (proteinuria > 0.5 g/day or cellular casts)	20 (48%)
Photosensitivity	12 (29%)
Serositis (Pleuritis or pericarditis documented by ECG, rub, or evidence of effusion)	10 (24%)
Vasculitis	8 (20%)
Mucosal ulcers	9 (22%)
Malar rash	5 (15%)
Central nervous system (seizures or psychosis without other cause)	5 (12%)
Reynaud's phenomenon	4 (10%)
Discoid lupus erythematosus	2 (5%)
Thrombocytopenia (< 100,000/L in the absence of an offending drug)	13 (32%)
Hemolytic anemia	7 (17%)
Antinuclear antibodies	41 (100%)
ds-DNA autoantibodies	33 (85%)
Anticardiolipin antibodies	15 (36%)

*Clinical and serological involvement at any time since SLE diagnosis. A patient can have more than one major organ involvement

The patients in our cohort were treated with one or more of the following modalities at the time of the study and since SLE diagnosis:

- corticosteroids (68% of the patients at the time of the study and 85% since SLE diagnosis)
- non-steroidal anti-inflammatory drugs) (17% and 46%, respectively)
- antimalarials (e.g., plaquenil) (66% and 88%, respectively)
- cytotoxic agents (e.g., cyclophosphamide or methotexate) (39% and 54%, respectively).

BLYS LEVELS IN THE SERA OF SLE PATIENTS

The mean BLyS level in the sera of the 50 healthy volunteers was 0.32 ± 0.96 ng/ml. Thus, we defined 3.2 ng/ml (mean of normals + 3SD) as the upper normal limit for BLyS sera levels. The mean BLyS level in all 221 lupus sera samples (3.37 ± 3.73, range 0.3–22.6 ng/ml) was significantly higher ($P < 0.05$) than levels in the normal control group (0.32 ± 0.96 ng/ml). BLyS levels were high (above the upper limit of normal, 3.2 ng/ml) in about a third (71/221) of the sera from the SLE patients, and within the normal range in the healthy control group. At the time of study entry (first blood sample), 20 of the 41 SLE patients (49%) had high (> 3.2 ng/ml) BLyS sera levels. During the follow-up period an additional 13 patients demonstrated high levels (at least in one sera sample). Thus, 33 (80.5%) of our SLE patients revealed high BLyS levels at least once during a mean follow-up period of 5.02 years. In the sera of the other eight patients BLyS levels were within the normal range (similar to levels observed in the healthy controls) during the entire follow-up period. There was no difference in the number of sera samples (tested for BLyS levels) between the "positive" and "negative" SLE patients.

The determination of BLyS levels during the follow-up period revealed fluctuations in sera BLyS levels with different patterns (e.g., high-normal-high, high-high-normal, normal-high-high, etc.). In none of our SLE patients were high BLyS levels consistently demonstrated during the follow-up period.

CORRELATION BETWEEN BLYS SERA LEVELS AND SLE-RELATED CLINICAL MANIFESTATIONS

All lupus males in our study had high BLyS sera levels as compared to 76% of the female patients. However, this difference was not statistically significant ($P = 0.14$). The 33 patients who had elevated sera BLyS levels during the course of the study (as compared to the 8 SLE patients who had never had elevated BLyS levels) had a higher rate of arthritis ($P = 0.04$). In addition, an insignificant higher rate of renal ($P = 0.40$) and hematological ($P = 0.29$) involvement was observed in patients with high BLyS levels. On the other hand, the rate of CNS involvement was non-significantly higher (25% vs. 9%, $P = 0.26$) in the 8 patients with normal sera BLyS levels. There was no significant difference regarding treatment modality (e.g. corticosteroids) between patients with elevated BLyS levels and those with normal sera BLyS levels.

Nine of our lupus patients (27% of patients with elevated BLyS levels) demonstrated very high (≥ 10 ng/ml) BLyS levels in their sera at least at one time point during the study. There were no significant differences in the demographic, clinical or serological manifestations between the 9 patients with very high sera BLyS levels and the 24 patients with moderately high (3.2-10 ng/ml) levels or the 8 patients with normal levels.

CORRELATION BETWEEN ANTI-DS-DNA AUTOANTIBODIES AND BLYS LEVELS

We also looked for a possible correlation between BLyS and anti-ds-DNA autoantibody levels in the same sera samples of our lupus patients. The anti-ds-DNA autoantibody levels were determined by the *Crithia luciliae* assay. The ds-DNA reactivity was set as 0 (negative reaction) to +1, +2, +3, +4 (semiquantitative estimation of fluorescence intensity). There was no correlation ($R = 0.06$) between BLyS and anti-ds-DNA autoantibody levels. Thus, some sera samples demonstrated high BLyS levels and low ds-DNA reactivity and vice versa. The correlation between BLyS and other ANAs (e.g., anti-SM) was not assessed due to the small number of patients in our cohort with such autoantibodies.

Figure 1. Correlation between BLyS sera levels and erythrocyte sedimentation rate (ESR). **[A]** ($R = 0.26$) or SLE disease activity index (SLEDAI). **[B]** ($R = 0.127$) in 41 SLE patients (221 samples)

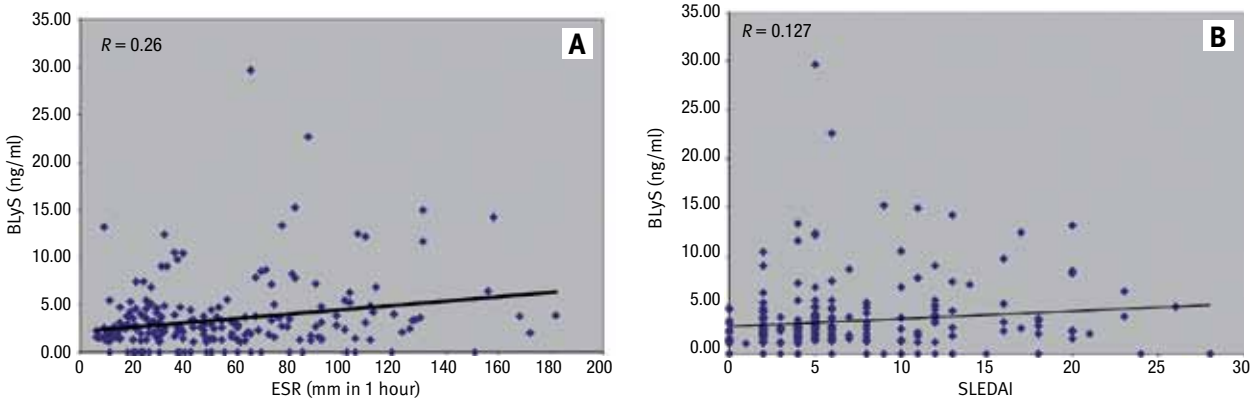
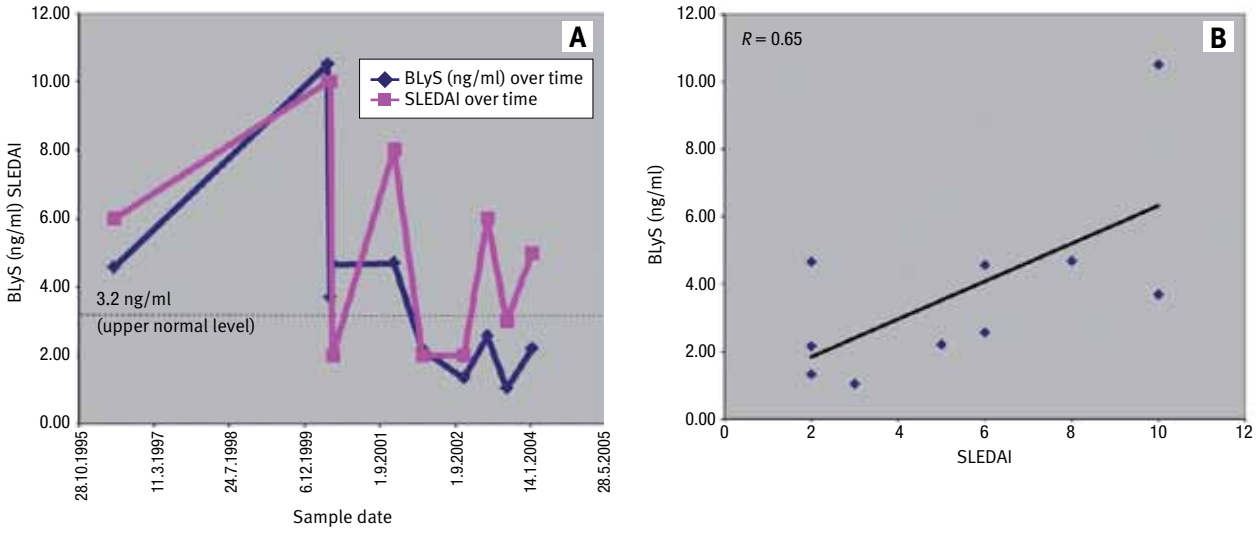


Figure 2. Correlation between sera BLyS levels and SLE disease activity (in a 20 year old female lupus patient) determined by SLEDAI during a follow-up period of 10 years **[A].** The correlation is statistically significant ($R = 0.65$) **[B]**



CORRELATION BETWEEN SERA BLYS LEVELS AND SLEDAI

For the evaluation of SLE activity we used the SLEDAI score [13] and erythrocyte sedimentation rate. Overall, there was no significant correlation between sera BLyS levels and ESR ($R = 0.127$) or SLEDAI scores ($R = 0.26$) (at the same visit) [Figure 1A & B]. Nevertheless, in some patients (4 of 33), close follow-up revealed a significant correlation between sera BLyS levels and disease activity (SLEDAI). Thus, a female SLE patient aged 20 whose major clinical problem was vasculitis demonstrated a close correlation ($R = 0.65$) between sera BLyS levels and lupus-related disease exacerbations (presented as high SLEDAI scores) during 10 years of follow-up [Figure 2A & B].

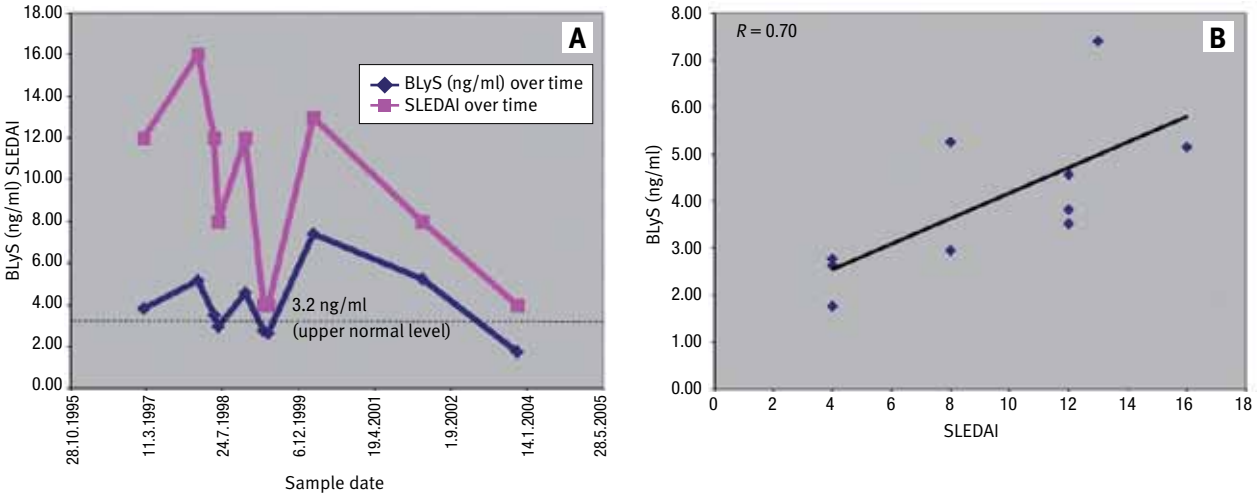
ESR = erythrocyte sedimentation rate

In another SLE male patient whose major SLE-related manifestation was renal disease, we observed a similar significant ($R = 0.70$) correlation between sera BLyS levels and disease activity (SLEDAI) during 9.5 years of follow-up [Figure 3A & B].

DISCUSSION

The main finding of this study was the high prevalence of elevated serum BLyS levels in the SLE patients (80.5%). BLyS levels fluctuated over time in the patient sera without significant correlation to lupus disease activity. The SLE cohort in our study is typical in terms of age, organ involvement, moderate disease activity (SLEDAI 0–28, mean 6.95 ± 5.94) and serological markers (ANA, anti-ds-DNA) [Table 1]. Similarly,

Figure 3. Correlation between sera BLyS levels and SLE disease activity (in an 11 year old male lupus patient) determined by SLEDAI during a follow-up period of 9.5 years **[A].** The correlation is statistically significant ($R = 0.70$) **[B]**



the treatment modalities – which included NSAIDs, steroids, plaquenil and cytotoxic agents (especially cyclophosphamide) – used during both the study period and the entire course of the disease were not different from those in other SLE cohorts [14,16]. Our cohort, however, included a relatively high proportion of males (19.5%) as compared to others (about 10%) [1].

The upper normal limit of BLyS sera levels in the present study (3.2 ng/ml) was relatively high (3SD above the mean in 50 healthy matched controls). If a lower normal limit for BLyS was determined (e.g., mean +2SD) the proportion of SLE patients with sera BLyS levels above the normal range would be even higher. It is important to note that in all samples from the healthy matched control volunteers, BLyS levels were within the normal range. Thus, the mean sera BLyS levels in our SLE cohort (3.37 ± 3.73 ng/ml) were significantly higher ($P < 0.05$) than those in the control group (0.32 ± 0.96 ng/ml). At the time of study entry, high BLyS sera levels were noted in only 49% of our SLE patients, but this rose to 80.5% by the end of the follow-up period (mean 5.02 years). Only 8 patients (19.5%) demonstrated normal BLyS sera levels during the entire follow-up period. Since fluctuations (negative-positive levels) occurred in all our lupus patients with high BLyS levels during the follow up period, it is essential to test BLyS levels periodically in order to define the prevalence of lupus patients with high sera BLyS levels (currently without any clinical significance).

The prevalence of SLE patients with elevated BLyS levels was higher in our study than in previous studies (80.5% vs. 40–50% respectively) [9,17,18]. The relatively long follow-up period (5 years) as compared to previous reports [14-16] and the repeated measurements performed in our study may explain this difference. In addition, the high prevalence of males in our study, all with elevated BLyS levels, may also have contributed to the high rate of patients with high BLyS levels. It is also possible that SLE patients in Israel are genetically different and/or have different environmental exposure (e.g., to the sun) which would result in higher BLyS levels. More studies with a larger number of SLE patients (including males) with longer follow-up periods are needed in Israel and in other parts of the world to define the exact prevalence of lupus patients with elevated BLyS levels.

Similar to previous studies [15,16,18], we did not find a significant correlation between the high sera BLyS levels and disease manifestations or disease activity. Recently, Vincent et al. [9] reported the presence of high BLyS levels in 44% of their lupus cohort. Similar to our results, there was no significant correlation between lupus-related disease activity and BLyS levels. Nevertheless, we observed several patients (4 of 33) [Figures 2 & 3] whose high sera BLyS levels correlated significantly with disease activity (flares and remissions). It should be noted that the reduction in BLyS levels, which was correlated with clinical improvement, may be due to the treatment (corticosteroids or cytotoxic agents) given to the patients at the time of lupus flares. Some studies suggested a better clinical correlation for BLyS mRNA levels (rather than the sera protein levels) [19], but this was not confirmed by other studies, mainly in pediatric lupus [20]. Interestingly, anti-BLyS treatments were shown to be effective in lupus patients with moderate disease activity regardless of sera BLyS levels. Thus, there is no clinical need to measure BLyS levels in the sera of lupus patients prior to the initiation of anti-BLyS treatment [21].

Previous studies [14] reported a significant correlation between BLyS levels and anti-ds-DNA autoantibodies in the

NSAIDs = non-steroidal anti-inflammatory drugs

sera of lupus patients. Although the prevalence of anti-ds-DNA autoantibodies in patient sera in our study (85%) was similar to other reports [4,22], we did not observe any correlation between these autoantibodies and BLyS levels. Different methods for detection of anti-ds-DNA autoantibodies (ELISA vs. *Crithidia luciliae*) may explain the different observations.

To conclude, we were able to demonstrate that a high proportion of Israeli lupus patients have elevated BLyS levels in their sera. BLyS levels fluctuated during the follow-up period without significant correlation to disease activity. Our results support the rationale for the current novel therapeutic approach aimed at neutralizing BLyS in lupus patients (either by monoclonal antibodies or by specific soluble receptor) [21,23-25].

Correspondence
Dr. Z. Sthoeger
Head, Dept. of Internal Medicine B and Clinical Immunology, Allergy and Neve-Or AIDS Center, Kaplan Medical Center, Rehovot 76100, Israel
Phone: (972-8) 944-1917/403
Fax: (972-8) 941-0461
email: Zev_S@clalit.org.il

References

1. Rahman A, Isenberg DA. Systemic lupus erythematosus. *N Engl J Med*. 2008; 358: 929-39.
2. Mok CC, Lau CS. Pathogenesis of systemic lupus erythematosus. *J Clin Pathol* 2003; 56: 481-90.
3. Osnes LT, Nakken B, Bodolay E, Szodoray P. Assessment of intracellular cytokines and regulatory cells in patients with autoimmune diseases and primary immunodeficiencies – novel tool for diagnostics and patient follow-up. *Autoimmun Rev* 2013; 12 (10): 967-71.
4. Lauwerys BR, Houssiau FA. Cytokines: clues to the pathogenesis of SLE. *Lupus* 1998; 7: 211-13.
5. Moore PA, Belvedere O, Orr A, et al. BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. *Science* 1999; 285: 260-3.
6. Marsters SA, Yan M, Pitti RM, Haas PE, Dixit VM, Ashkenazi A. Interaction of the TNF homologues BLyS and APRIL with the TNF receptor homologues BCMA and TACI. *Curr Biol* 2000; 10: 785-8.
7. Khare SD, Sarosi I, Xia X-Z, et al. Severe B cell hyperplasia and autoimmune disease in TALL-1 transgenic mice. *Proc Natl Acad Sci USA* 2000; 97: 3370–5.
8. Stohl W, Xu D, Kim KS, et al. BAFF overexpression and accelerated glomerular disease in mice with an incomplete genetic predisposition to systemic lupus erythematosus. *Arthritis Rheum* 2005; 52: 2080-91.
9. Vincent FB, Northcott M, Hoi A, Mackay F, Morand EF. Association of serum B cell activating factor from the tumour necrosis factor family (BAFF) and a proliferation-inducing ligand (APRIL) with central nervous system and renal disease in systemic lupus erythematosus. *Lupus* 2013; 22 (9): 873-84.
10. Cheema GS, Roschke V, Hilbert DM, Stohl W. Elevated serum B lymphocyte stimulator levels in patients with systemic immune-based rheumatic diseases. *Arthritis Rheum* 2001; 44: 1313-19.
11. Collins CE, Gavin AL, Migone TS, Hilbert DM, Nemazee D, Stohl W. B lymphocyte stimulator (BLyS) isoforms in systemic lupus erythematosus: disease activity correlates better with blood leukocyte BLyS mRNA levels than with plasma BLyS protein levels. *Arthritis Res Ther* 2006; 8: R6.
12. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-7.
13. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang DH, and the Committee on Prognosis Studies in SLE. Derivation of the SLEDAI: a disease activity index for lupus patients. *Arthritis Rheum* 1992; 35: 630-40.
14. Petri M, Stohl W, Chatham W, et al. Association of plasma B lymphocyte stimulator levels and disease activity in systemic lupus erythematosus. *Arthritis Rheum* 2008; 58: 2453-9.
15. Stohl W. B lymphocyte stimulator protein levels in systemic lupus erythematosus and other diseases. *Curr Rheumatol Rep* 2002; 4: 345-50.
16. Stohl W, Metyas S, Tan SM, et al. B lymphocyte stimulator overexpression in patients with systemic lupus erythematosus: longitudinal observations. *Arthritis Rheum* 2003; 48: 3475-86.
17. Cancro MP, D'Cruz DP, Khamashta MA. The role of B lymphocyte stimulator (BLyS) in systemic lupus erythematosus. *J Clin Invest* 2009; 119: 1066-73.
18. Stohl W. Systemic lupus erythematosus and its ABCs (APRIL/BLyS complexes). *Arthritis Res Ther* 2010; 12: 111.
19. Ju S, Zhang D, Wang Y, Ni H, Kong X, Zhong R. Correlation of the expression levels of BLyS and its receptors mRNA in patients with systemic lupus erythematosus. *Clin Biochem* 2006; 39: 1131-7.
20. Hong SD, Reiff A, Yang HT, et al. B lymphocyte stimulator expression in pediatric systemic lupus erythematosus and juvenile idiopathic arthritis patients. *Arthritis Rheum* 2009; 60: 3400-9.
21. Bezalel S, Asher I, Elbirt D, Sthoeger ZM. Novel biological treatments for systemic lupus erythematosus: current and future modalities. *IMAJ* 2012; 14 (8): 508-14.
22. Sthoeger ZM, Chiorazzi N, Lahita RG. Regulation of immune response by sex hormones. I. In vivo effects of estradiol and testosterone on pokeweed mitogen-induced human B cell differentiation. *J Immunol* 1988; 141: 91-8.
23. Toubi E, Kessel A, Rosner I, Rozenbaum M, Paran D, Shoenfeld Y. The reduction of serum B-lymphocyte activating factor levels following quinacrine add-on therapy in systemic lupus erythematosus. *Scand J Immunol* 2006; 63: 299-303.
24. Hahn BH. Belimumab for systemic lupus erythematosus. *N Engl J Med* 2013; 368: 1528-35.
25. Toubi E, Shoenfeld Y. BLyS/BAFF: a potential target in the treatment of active systemic lupus erythematosus. *IMAJ* 2004; 6: 99-102.

Capsule

HIV needs to be fit to transmit

Although you might not think it, it's hard to catch HIV. Less than 1% of unprotected sexual exposures result in infection. What then leads to transmission? Carlson et al. determined the amino acid sequence of viruses infecting 137 Zambian heterosexual couples in which one partner infected the other. The authors then used statistical modeling and found that transmitted viruses are typically the most evolutionarily fit. That is, compared to other viral variants in the infected person, the transmitted virus most closely matches the most common viral sequence found in the Zambian population.

Science 2014; 345: 10.1126/science.1254031

Eitan Israeli

"The best way to be more free is to grant more freedom to others"

Carlo Dossi (1849-1910), Italian writer, politician and diplomat

History-Taking and the Usefulness Index in the Diagnosis of Functional Dyspepsia

Matti Eskelinen MD PhD[1], Tuomas Selander MSc[2], Pertti Lipponen MD PhD[1] and Petri Juvonen MD PhD[1]

[1]Department of Surgery and [2]Science Service Center, Kuopio University Hospital and School of Medicine, University of Eastern Finland, Kuopio, Finland

ABSTRACT: **Background:** The primary diagnosis of functional dyspepsia (FD) is made on the basis of typical symptoms and by excluding organic gastrointestinal diseases that cause dyspeptic symptoms. However, there is difficulty reaching a diagnosis in FD.

Objectives: To assess the efficiency of the Usefulness Index (UI) test and history-taking in diagnosing FD.

Methods: A study on acute abdominal pain conducted by the World Organization of Gastroenterology Research Committee (OMGE) included 1333 patients presenting with acute abdominal pain. The clinical history-taking variables (n=23) for each patient were recorded in detail using a predefined structured data collection sheet, and the collected data were compared with the final diagnoses.

Results: The most significant clinical history-taking variables of FD in univariate analysis were risk ratio (RR): location of pain at diagnosis (RR = 5.7), location of initial pain (RR = 6.5), previous similar pain (RR = 4.0), duration of pain (RR = 2.9), previous abdominal surgery (RR = 4.1), previous abdominal diseases (RR = 4.0), and previous indigestion (RR = 3.1). The sensitivity of the physicians' initial decision in detecting FD was 0.44, specificity 0.99 and efficiency 0.98; UI was 0.19 and RR 195.3. In the stepwise multivariate logistic regression analysis, the independent predictors of FD were the physicians' initial decision (RR = 266.4), location of initial pain (RR = 3.4), duration of pain (RR = 3.1), previous abdominal surgery (RR = 3.7), previous indigestion (RR = 2.2) and vomiting (RR = 2.0).

Conclusions: The patients with upper abdominal pain initially and a previous history of abdominal surgery and indigestion tended to be at risk for FD. In these patients the UI test could help the clinician differentiate FD from other diagnoses of acute abdominal pain.

IMAJ 2014; 16: 497–501

KEY WORDS: acute abdominal pain, functional dyspepsia (FD), Usefulness Index (UI), diagnostic accuracy

Functional gastrointestinal disorders are the most common conditions encountered in gastroenterology practice and constitute a significant proportion of primary care visits [1-3]. National surveys in Western countries have estimated that the prevalence of one or more functional gastrointestinal disorders, including functional dyspepsia and irritable bowel syndrome, is about 62%–69% [4,5]. Functional dyspepsia, previously called non-ulcer dyspepsia [6], is "a collection of symptoms" without evidence of an organic disease that could explain the symptoms [7]. FD is estimated to affect about 15–40% of the general population in Western countries [6,8]. It may be accompanied by bloating, belching, nausea, or heartburn [1]. According to American and British national guidelines, the clinical examination is an essential part of the evaluation of patients with FD [9,10].

In 1990, Lavelle and Kanagaratnam [11] introduced the Usefulness Index test to assess the effectiveness of clinical observations. We have previously described the accuracy of the UI test in the clinical diagnosis of acute appendicitis, acute small bowel obstruction, acute renal colic, and non-specific abdominal pain [12-16]. Since the diagnostic accuracy of the UI test has rarely been considered in functional dyspepsia, the aim of the present study was to investigate the contribution of this test to correctly diagnose functional dyspepsia in the clinical situation.

PATIENTS AND METHODS

Criteria for inclusion in this study and the diagnostic criteria were established by the World Organization of Gastroenterology Research Committee (OMGE) [17]. The study group included 636 males (47.7%) and 697 females (52.3%), mean age (± SD) 38.0 ± 22.1 years, with acute abdominal pain of less than 7 days duration. Also included were patients who had been examined clinically by general practitioners and were transferred to the study hospitals. Informed consent was obtained from the patients and study was approved by the Institutional Review Board. The clinical findings in each patient were recorded in detail using a predefined structured data collection sheet [17]. In practice, the structured data sheets were collected by the surgeon in charge, although the same surgeon was responsible for the study and data collection. The selection of patients is described in the OMGE acute abdominal pain survey report [17]. Examinations of the clinical symptoms were conducted using the structured data collection sheets [17] and the clinical symptoms were graded positive (+ = dyspepsia) or negative (- = other diagnosis).

FD = functional dyspepsia
UI = usefulness index

The final diagnosis of acute abdominal pain and FD was reached by considering all symptoms, signs and the results of laboratory tests; the diagnostic criteria are defined elsewhere (OMGE) [17]. The sensitivity, specificity, efficiency, likelihood ratios and predictive values, and the Usefulness Index of the diagnostic methods were calculated [11,18,19]. The UI is defined as d x (d-r), where d is the incidence of the finding in the disease (= sensitivity) and r is the incidence of the finding in a reference population (1 = specificity). It ranges continuously from -1 to 1, and tests where the UI is > 0.35 are regarded as useful [11]. The UI is explained further by Lavelle and Kanagaratnam [11].

The likelihood ratio of a positive test result (LR+) indicates how many times greater the probability of a positive test result is among patients with FD than in subjects without FD. LR+ should always be larger than 1 and LR+ of a good test (diagnostic method) is 10 or more. The likelihood ratio of a negative test result (LR-) is the probability of a negative test result among patients with FD divided by the corresponding probability for subjects without FD. LR- should be less than 1 and the LR- ratio of a good test is less than 0.1.

Efficiency is a measure of the potential discriminating effect of a test before the results of the test are known. Because the efficiency is dependent on the prevalence of disease, the estimated efficiency of the test can only be extrapolated to other populations with a similar prevalence of disease.

When the test result is positive the positive predictive value (PV+) of the test is the probability that a patient has the disease (FD). Likewise, when negative, the negative predictive value (PV-) of the test is the probability that a patient does not have the disease (FD).

A logistic stepwise multivariate regression analysis of the SPSS (Scientific Package for Social Sciences, SPSS, USA) program package was used for calculating the risk ratios of a patient with a given symptom to have FD. The coefficient of the multivariate analysis shows the relative risk of a patient with a given symptom or sign to have FD. All the variables presented in Table 2 were included in the analysis as binary data, e.g., functional dyspepsia (1) and no FD (0).

RESULTS

The present study is based on the clinical presentation of 1333 patients with acute abdominal pain [Table 1]. Of the 27 patients initially considered (in the hospital outpatient unit) to have FD, the final diagnosis of FD was correct in 22 (81.5%). In addition, 28 patients later found to have FD were missed at the initial diagnosis. Thus, the total number of patients with FD was 50 (18 females and 32 males). Sensitivity, specificity, efficiency, LR+, LR-, PV+ and PV- values of the various clinical symptoms and doctors' initial decision in detecting FD are summarized in Table 2. It is of interest to compare the relative "usefulness" of the doctor's initial decision and clinical symptoms; Table 3 shows the variables with a UI greater than 0.10.

In FD the location of the initial pain is usually in the upper abdomen, and in our study the diagnostic efficiency of "the location of initial pain" variable was 0.65 with the UI showing 0.33 and the RR 6.5 [Table 3]. The location of pain at diagnosis was also classified to be in the upper abdomen. In our study the diagnostic efficiency of "the location of pain at diagnosis" variable was 0.67 with a UI of 0.30 and RR of 5.7. About 40% of patients with the diagnosis of FD had nausea and about 60% had vomiting. The vomiting variable had a UI of 0.11 and RR of 2.0. The duration of acute abdominal pain was documented as more than 12 hours in most of the patients with FD (42/50, 84%). The diagnostic efficiency of the duration of pain variable was 0.37 with a UI of 0.19 and RR of 2.9 [Table 3]. The intensity of the pain is usually classified as subjectively weak or moderate in most patients with FD, and in our study 84% of patients (42/50) had subjectively weak or moderate pain. Although the diagnostic sensitivity of the variable for intensity of pain was high, the diagnostic efficiency was only 0.19 with a UI of 0.002 and RR of 1.02.

Previous abdominal disease was recorded in 22/50 patients (44%) with FD, with a diagnostic efficiency of 0.82, UI of 0.12

RR = relative risk

Table 1. Distribution of diagnoses in patients with acute abdominal pain according to physicians' diagnosis, initial diagnosis and final diagnosis

	Diagnosis		
Disease category*	**GP N (%)**	**Initial N (%)**	**Final N (%)**
NSAP (1)	360 (41.1)	552 (41.4)	614 (46.1)
Acute appendicitis (2)	379 (43.3)	402 (30.2)	270 (20.3)
Acute cholecystitis (3)	67 (7.6)	135 (10.1)	125 (9.4)
Small bowel obstruction (4)	15 (1.7)	57 (4.3)	54 (4.1)
Functional dyspepsia (5)	1 (0.1)	27 (2.0)	50 (3.8)
Renal colic (6)	24 (2.7)	59 (4.4)	59 (4.4)
Diverticular disease (7)	0 (0.0)	13 (1.0)	19 (1.4)
Mesenteric lymphadenitis (8)	0 (0.0)	9 (0.7)	11 (0.8)
Acute pancreatitis (9)	18 (2.1)	29 (2.2)	22 (1.7)
Perf peptic ulcer (10)	6 (0.7)	6 (0.5)	9 (0.7)
Urinary tract infection (11)	0 (0.0)	10 (0.8)	22 (1.7)
Acute gyn disease (12)	4 (0.5)	12 (0.9)	15 (1.1)
Miscellaneous (13)	2 (0.2)	22 (1.7)	63 (4.7)
Total	876 (100.0)	1,333 (100.0)	1,333 (100.0)**

*The number in parentheses is the OMGE rank order
** 457 patients with acute abdominal pain presented directly to the hospital for the initial diagnosis

N = no. of patients, GP = general practitioner, NSAP = non-specific abdominal pain, Perf = perforated, gyn = gynecological

LR = likelihood ratio
PV = positive predictive value

Table 2. Clinical symptoms at initial diagnosis of FD: sensitivity, specificity, diagnostic efficiency, LR+, LR-, PV+ and PV-

Symptom	Sens	Spec	Effic	LR+	LR-	PV+	PV-
Location of initial pain (upper vs. other)	0.78	0.65	0.65	2.22	0.34	0.08	0.99
Location of pain at diagnosis (upper vs. other)	0.74	0.67	0.67	2.24	0.39	0.08	0.99
Duration of pain (› 12 hr)	0.84	0.35	0.37	1.30	0.45	0.05	0.98
Intensity of pain (weak/ moderate)	0.84	0.16	0.19	1.002	0.99	0.04	0.96
Progression of pain (same/weaker pain)	0.66	0.29	0.30	0.93	0.48	0.04	0.96
Type of pain (continuous)	0.54	0.45	0.46	0.98	1.02	0.04	0.96
Aggravating factors (yes)	0.28	0.73	0.72	1.04	0.99	0.04	0.96
Relieving factors (none)	0.74	0.33	0.34	1.10	0.79	0.04	0.97
Previous similar pain (yes)	0.66	0.67	0.67	2.00	0.51	0.07	0.98
Vertigo (no)	0.96	0.03	0.06	0.99	1.33	0.04	0.95
Nausea (yes)	0.38	0.57	0.57	0.88	1.09	0.03	0.96
Vomiting (yes)	0.60	0.58	0.58	1.43	0.69	0.52	0.97
Appetite (poor)	0.86	0.27	0.29	1.18	0.52	0.04	0.98
Previous indigestion (yes)	0.44	0.80	0.78	2.20	0.70	0.08	0.97
Jaundice (no)	0.94	0.02	0.06	0.96	2.61	0.04	0.91
Bowel function (abnormal)	0.32	0.74	0.75	1.23	0.92	0.05	0.97
Micturition (normal)	0.96	0.07	0.01	1.03	0.61	0.04	0.98
Drugs for abdominal pain (yes)	0.16	0.96	0.93	4.44	0.87	0.15	0.97
Previous abdominal surgery (yes)	0.56	0.76	0.75	2.33	0.58	0.08	0.98
Previous abdominal diseases (yes)	0.44	0.83	0.82	2.59	0.67	0.09	0.97
Use of alcohol (no)	0.94	0.05	0.08	0.99	1.20	0.04	0.96
Initial diagnosis	0.44	0.99	0.98	110.0	0.56	0.81	0.98

The positive results for FD are in parenthesis

Sens = sensitivity, Spec = specificity, Effic = efficiency, LR = likelihood ratio, PV = predictive value

and RR of 4.0. About two-thirds of the patients with a diagnosis of FD (33/50) had experienced previous similar pain. About one-half of the patients with FD had undergone previous abdominal surgery (UI = 0.18, RR = 4.1).

The sensitivity of the general practitioners' initial decision in detecting FD was 0.44, with a specificity of 0.99 and an efficiency of 0.98 (UI = 0.19, RR = 195.3). The most significant predictors of FD in univariate analysis were: location of pain at diagnosis (upper abdomen vs. other, E = 0.67, UI = 0.30, RR = 5.7), location of initial pain (upper abdomen vs. other, E = 0.65, UI = 0.33, RR = 6.5), previous similar pain (yes, E = 0.67, UI = 0.22, RR = 4.0), duration of pain (> 12 hours, E = 0.37, UI = 0.19, RR = 2.9), previous abdominal surgery (yes, E = 0.75, UI = 0.18, RR = 4.1), previous abdominal diseases (yes, E = 0.82, UI = 0.12, RR = 4.0), and previous indigestion (yes, E = 0.78, UI = 0.11, RR = 3.1). In the stepwise multivariate logistic regression analysis, the independent predictors of FD were the doctor's initial decision (RR = 266.4), location of initial pain (RR = 3.4), duration of pain (RR = 3.1), previous abdominal surgery (RR = 3.7), previous indigestion (RR = 2.2) and vomiting (RR = 2.0) [Table 4].

E = efficiency

Table 3. Initial diagnosis and clinical symptoms in patients with FD: usefulness index (UI) › 0.10, diagnostic efficiency (E), positive likelihood ratios (LR+) and risk ratios (RR)

Symptom	E	LR+	UI	RR (95% CI)
Initial diagnosis	0.98	110.0	0.19	195.3 (66.3–697.0)
Location of initial pain (upper abdomen vs. other)	0.65	2.22	0.33	6.5 (3.2–14.2)
Location of pain at diagnosis (upper abdomen vs. other)	0.67	2.24	0.30	5.7 (2.9–11.9)
Previous similar pain (yes)	0.67	2.02	0.22	4.0 (2.1–7.8)
Duration of pain (› 12 hr)	0.37	1.30	0.19	2.9 (1.3–7.1)
Previous abdominal surgery (yes)	0.75	2.33	0.18	4.1 (2.2–7.6)
Previous abdominal diseases (yes)	0.82	2.59	0.12	4.0 (2.1–7.3)
Previous indigestion (yes)	0.78	2.20	0.11	3.1(1.7–5.8)
Appetite (poor)	0.29	1.18	0.11	2.3 (1.0–6.1)
Vomiting (yes)	0.58	1.43	0.11	2.0 (1.1–3.8)

RR = risk ratio, CI = confidence interval

Table 4. Independent predictors of functional dyspepsia as diagnosis of acute abdominal pain in logistic stepwise multivariate regression analysis

Predictor	B (SE)	RR (95% CI)	*P* value
Doctors' initial diagnosis	5.6 (0.6)	266.4 (83.5–1036.2)	‹ 0.001
Location of initial pain (upper abdomen vs. other)	1.2 (0.4)	3.4 (1.5–8.1)	‹ 0.01
Duration of pain (› 12 hr)	1.1 (0.5)	3.1 (1.3–9.4)	‹ 0.05
Previous abdominal surgery (yes)	1.3 (0.4)	3.7 (1.7–8.3)	‹ 0.01
Previous indigestion (yes)	0.8 (0.4)	2.2 (1.0–4.9)	‹ 0.05
Vomiting (yes)	0.7 (0.4)	2.0 (0.9–4.7)	0.09

B = coefficient of the logistic regression mode standard error, RR = risk ratio, CI = confidence interval

DISCUSSION

Most studies on the value of history-taking in FD have been performed in patients referred for gastroscopy. The diagnostic efficiency of UI has rarely been investigated. One of the most difficult problems in diagnosing FD is the lack of a 'golden standard' [8]. To overcome this problem we calculated the sensitivity, specificity, efficiency, likelihood ratios and predictive values, and the UI of history-taking in FD.

The location of initial pain and at diagnosis is usually in the upper abdomen in FD. Pajala et al. [20] reported that in

77% of patients with FD the location of pain was the upper abdomen. In our study 78% of patients with FD (39/50) had initial pain in the upper abdomen and 70% (35/50) had pain in the upper abdomen at diagnosis.

The duration of acute abdominal pain should be accurately quantified in hours or days. The time of onset of the abdominal pain and whether it has been continuous or intermittent should be noted. If the present episode of acute abdominal pain has lasted for more than one week it may not be an acute abdominal pain episode at all. In our study 84% of patients with a diagnosis of FD had > 12 hours pain duration and a diagnostic efficiency of 0.37 and UI of 0.19.

Acute abdominal pain is usually weak or moderate in FD. In 84% of the patients with FD (42/50) the acute abdominal pain was mild or moderate and only in 16% was the pain severe, i.e., causing the patient to shiver, sweat, roll around, or cry out. The diagnostic efficiency of the "intensity of pain" variable was 0.19. Acute abdominal pain often varies in intensity, but the doctor should note the variation if the pain is clearly the same or decreases/increases over a period of at least an hour or two. Acute abdominal pain was classified to be the same or decreasing in 66% of patients with FD, and the diagnostic efficiency of the symptom progression of pain was 0.30.

In patients with acute abdominal pain the questions on nausea and vomiting should be asked separately although they are usually regarded as well-defined symptoms. In our study only 38% of patients with an FD diagnosis had nausea and the diagnostic efficiency of nausea was only 0.57. Some junior doctors are unaware that a patient can vomit without nausea, and this applies especially to adolescents and children. In our study 60% of patients with an FD diagnosis had vomiting, and the diagnostic efficiency of nausea was only 0.58 with a UI of 0.11.

"Previous similar pain" means similar episodes of acute abdominal pain at some point in the past. The doctor should distinguish between these previous episodes and the present episode of pain and try to determine when the pain occurred and what, if anything, had been done about it. In our study 66% of patients with an FD diagnosis had previous similar pain, with a diagnostic efficiency of 0.67 and UI of 0.22.

If possible, the physician should try to establish where and when any previous abdominal surgery was performed, the reason for the surgery, and whether any problems occurred during or after. In our study 56% of patients with an FD diagnosis had previous abdominal surgery, with a diagnostic efficiency of 0.75 and UI of 0.18.

A history-taking of a patient with acute abdominal pain is not complete without information about medications and previous abdominal diseases. In our study 44% of patients with an FD diagnosis had previous abdominal diseases with a diagnostic efficiency of 0.82 and UI of 0.12.

Some of the terms regarding FD should be considered. Efficiency (E) is the ability to diagnose the disease correctly or incorrectly. Findings with high LRs will achieve that goal. The efficiency is also dependent on the prior probability or prevalence of the disease [16]. Therefore, the most compelling findings of FD are location of initial pain (E = 0.65), previous indigestion (E = 0.78), and previous abdominal surgery (E = 0.75). Each has a positive likelihood ratio > 2.0 with an RR of 3.1–6.5.

In conclusion, the results of this study do not support a strong link between specific clinical symptoms and functional dyspepsia. However, patients with upper abdomen pain initially and a previous history of abdominal surgery and indigestion tended to be at risk for FD. In these patients the Usefulness Index test might be an aid for the clinician to differentiate dyspepsia from other diagnoses.

Acknowledgments

The support from the Academy of Finland and EVO funds from Kuopio University Hospital is gratefully acknowledged. Our special thanks are due to the late Professor Tim (F.T.) de Dombal MA MD FRCS, University of Leeds, England, who was the principal coordinator of the OMGE survey when this study started in Finland. His scientific advice and positive attitude during this study were invaluable.

Correspondence

Dr. M. Eskelinen

Dept. of Surgery, Kuopio University Hospital, P.O. Box 100, FI-70029 KYS, Finland

Phone: (358-17) 172-609

Fax: (358-17) 172-611

email: matti.eskelinen@kuh.fi

References

1. Heikkinen MT, Pikkarainen PH, Takala JK, Räsänen HT, Eskelinen MJ, Julkunen RJK. Diagnostic methods in dyspepsia: the usefulness of upper abdominal ultrasound and gastroscopy. *Scand J Prim Health Care* 1997; 15: 82-6.
2. Heikkinen M, Pikkarainen P, Eskelinen M, Julkunen R. GP's ability to diagnose dyspepsia based only on physical examination and patient history. *Scand J Prim Health Care* 2000; 18: 99-104.
3. Talley NJ, Vakil N. Guidelines for the management of dyspepsia. *Am J Gastroenterol* 2005; 100: 2324-37.
4. Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders: prevalence, sociodemography and health impact. *Dig Dis Sci* 1993; 38: 1569-80.
5. Thompson WG, Irvine EJ, Pare P, Ferazzi S, Rance L. Functional gastrointestinal disorders in Canada: first population-based survey using Rome II criteria with suggestions improving the questionnaire. *Dig Dis Sci* 2002; 47: 225-35.
6. Saad RJ, Chey WD. Current and emerging therapies for functional dyspepsia: review article. *Aliment Pharm Ther* 2006; 24: 475-92.
7. van Kerkhoven LA, van Rossum LG, van Oijen MG, et al. Upper gastrointestinal endoscopy does not reassure patients with functional dyspepsia. *Endoscopy* 2006; 38: 879-85.
8. Moayyedi P, Talley NJ, Fennerty MB, Vakil N. Can the clinical history distiguish between organic and functional dyspepsia? *JAMA* 2006; 295: 1566-76.
9. North of England Dyspepsia Guideline Development Group. Dyspepsia: Managing Dyspepsia in Adult in Primary Care. London, UK: National Institute of Health and Clinical Excellence, 2004.
10. Talley NJ, Vakil N, Moayyedi P. American Gastroenterology Association Technical Review on the evaluation of dyspepsia. *Gastroenterology* 2005; 129: 1756-80.
11. Lavelle SM, Kanagaratnam B. The information value of clinical data. *Int J Biomed Comput* 1990; 26: 203-9.

12. Eskelinen M, Ikonen J, Lipponen P. Sex-specific diagnostic scores for acute appendicitis. *Scand J Gastroenterol* 1994; 29: 59-66.
13. Eskelinen M, Ikonen J, Lipponen P. Contributions of history-taking, physical examination, and computer assisstance to diagnosis acute small-bowel obstruction. A prospective study of 1333 patients with acute abdominal pain. *Scand J Gastroenterol* 1994; 29: 715-21.
14. Eskelinen M, Ikonen J, Lipponen P. The value of history-taking, physical examination, and computer assisstance in the diagnosis acute appendicitis in patients more than 50 years of old. A prospective study of 1333 patients with acute abdominal pain. *Scand J Gastroenterol* 1995; 30: 349-55.
15. Eskelinen M, Ikonen J, Lipponen P. Usefulness of history-taking, physical examination, and diagnostic scoring in acute renal colic. *Eur Urol* 1998; 34: 467-73.
16. Eskelinen M, Lipponen P. Usefulness index in nonspecific abdominal pain-an aid in the diagnosis. *Scand J Gastroenterol* 2012; 47: 1475-9.
17. de Dombal FT. The OMGE acute abdominal pain survey. Progress report 1986. *Scand J Gastroenterol* 1988; 23 (Suppl 144): 35-42.
18. Clarke JR, Hayward CZ. A scientific basis for surgical reasoning. I. Diagnostic accuracy – sensitivity, specificity, prevalence and predictive value. *Theor Surg* 1990; 5: 129-32.
19. Clarke JR. A scientific basis for surgical reasoning. II. Probability revision – odds ratios, likelihood ratios and Bayes' theorem. *Theor Surg* 1990; 5: 206-10.
20. Pajala M, Heikkinen M, Hintikka J. A prospective 1-year follow-up study in patients with functional or organic dyspepsia: changes in gastrointestinal symptoms, mental distress and fear of serious illness. *Aliment Pharmacol Ther* 2006; 24: 1241-6.

Capsule

The NLRP3 inflammasome is released as a particulate danger signal that amplifies the inflammatory response

Assembly of the NLRP3 inflammasome activates caspase-1 and mediates the processing and release of the leaderless cytokine IL-1β and thereby serves a central role in the inflammatory response and in diverse human diseases. Baroja-Mazo et al. found that upon activation of caspase-1, oligomeric NLRP3 inflammasome particles were released from macrophages. Recombinant oligomeric protein particles composed of the adaptor ASC or the p.D303N mutant form of NLRP3 associated with cryopyrin-associated periodic syndromes (CAPS) stimulated further activation of caspase-1 extracellularly, as well as intracellularly after phagocytosis by surrounding macrophages. The authors found oligomeric ASC particles in the serum of patients with active CAPS but not in that of patients with other inherited autoinflammatory diseases. These findings support a model whereby the NLRP3 inflammasome, acting as an extracellular oligomeric complex, amplifies the inflammatory response.

Nature Immunol 2014; 15: 738

Eitan Israeli

Capsule

Citrulline-specific Th1 cells are increased in rheumatoid arthritis and their frequency is influenced by disease duration and therapy

Rheumatoid arthritis (RA) is thought to be a T cell-mediated disease, based on its strong association with HLA class II alleles, clinical responsiveness to T cell-directed therapies, and the presence of CD4+ T cells in rheumatoid joints. The presence of anti-citrullinated protein antibodies (ACPAs) in RA serum and the association of these antibodies with HLA-DR4 alleles implicate citrulline-specific autoreactive T cells in the development and progression of RA. To determine the characteristics and specificity of autoreactive T cell responses in RA. James et al. developed a panel of HLA-DRB1*04:01 tetramers, selecting citrullinated peptides from synovial antigens and verifying their immunogenicity in DRB1*04:01-transgenic mice. Seven tetramers were used to examine the ex vivo frequency and surface phenotype of citrulline-specific (Cit-specific) T cells in patients with RA and healthy subjects with DRB1*04:01 haplotypes, using a magnetic enrichment procedure. Cit-specific T cells were detectable in peripheral blood samples from both healthy subjects and RA patients. Compared to healthy subjects, RA patients had significantly higher frequencies of Cit-specific T cells, and a greater proportion of these cells displayed a Th1 memory phenotype. Among RA patients, the frequency of Cit-specific T cells was highest within the first 5 years after diagnosis of RA and was decreased in patients taking biologic agents, irrespective of disease duration. These findings link the presence of ACPAs in RA with Th1 cells specific for citrullinated epitopes and provide tools for disease-specific immuno-monitoring of autoreactive T cells.

Arthritis Rheum 2014; 66: 1712

Eitan Israeli

"The measure of a country's greatness is its ability to retain compassion in times of crisis"

Thurgood Marshall (1908-1993), U.S. Supreme Court Justice and its first African American judge. As a lawyer Marshall was best known for his high success rate in arguing before the Supreme Court and for the victory in *Brown v. Board of Education*, a decision that desegregated public schools

Retained Placental Tissue as an Emerging Cause for Malpractice Claims

Moshe D. Fejgin MD, Tal Y. Shvit MD, Yael Gershtansky MSc and Tal Biron-Shental MD

Maternal Fetal Unit, Department of Obstetrics and Gynecology, Meir Medical Center, Kfar Saba, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** Removal of retained placental tissue postpartum and retained products of conception (RPOC) abortion is done by uterine curettage or hysteroscopy. Trauma to the endometrium from surgical procedures, primarily curettage, can cause intrauterine adhesions (Asherman's syndrome) and subsequent infertility. The incidence of malpractice claims relating to intrauterine adhesions is rising, justifying reevaluation of the optimal way of handling these complications.

Objectives: To review malpractice claims regarding intrauterine adhesions, and to explore the clinical approach that might reduce those claims or improve their medical and legal outcomes.

Methods: We examined 42 Asherman's syndrome claims handled by MCI, the largest professional liability insurer in Israel. The clinical chart of each case was reviewed and analyzed by the event preceding the adhesion formations, timing and mode of diagnosis, and outcome. We also assessed whether the adverse outcome was caused by substandard care and it it could have been avoided by different clinical practice. The legal outcome was also evaluated.

Results: Forty-seven percent of the cases occurred following vaginal delivery, 19% followed cesarean section, 28% were RPOC following a first-trimester pregnancy termination, and 2% followed a second-trimester pregnancy termination.

Conclusions: It is apparent that due to the lack of an accepted management protocol for cases of RPOC, it is difficult to legally defend those cases when the complication of Asherman syndrome develops.

IMAJ 2014; 16: 502–505

KEY WORDS: retained products of conception (RPOC), Asherman's syndrome, intrauterine adhesions, litigation

Retained placental tissue following birth, and retained products of conception following curettage, are not uncommon complications. In most cases, secondary evacuation of the retained tissue ends without any sequelae. However, in a minority of cases this may lead to the formation of intrauterine adhesions and, consequently, fertility problems.

Amenorrhea due to intrauterine adhesions was first described in 1894; it was defined by Asherman in 1948 and 1950 and thus carries his name, Asherman syndrome [1]. Intrauterine adhesions mostly develop as a result of trauma to the basal layer of the endometrium. Most cases are related to curettage for pregnancy termination, postpartum hemorrhage, or delayed removal of RCPO [2]. The role of intrauterine infection in adhesion formation is controversial. Repeated curettage for pregnancy loss increases the risk of developing adhesions from 8% after the first curettage to > 35% with the third. Intrauterine adhesions can be asymptomatic or can cause hypomenorrhea, amenorrhea, pelvic pains, recurrent pregnancy loss, or infertility [2-4]. Infertility is the most common reason patients present for evaluation: 43% of women with intrauterine adhesions have some degree of infertility [2].

The most reliable way to diagnose intrauterine adhesions is by hysteroscopy, which allows diagnosis and treatment at the same time. Another mode of diagnosis is a hysterosalpingogram or a sonohysterogram [3,4]. No randomized trials have been conducted to guide therapy in these patients. When symptomatic, the common treatment is surgical hysteroscopy for adhesiolysis [4,5]. For reducing the risk of reformation of adhesions, estrogen therapy followed by a withdrawal bleed stimulated by progesterone is recommended [2].

Retained placental tissue is a major cause of immediate postpartum hemorrhage. In such cases evacuation of the uterus is obligatory. In contrast, there are no clear guidelines for optimal treatment in cases of suspected asymptomatic retained products of conception. Historically, immediate curettage using a large curette was the standard of care [7]. However, this procedure may damage the basal layer of the endometrium and subsequently lead to the formation of intrauterine adhesions. Therefore, many authors [8] recommend a more conservative approach: holding off the curettage and awaiting spontaneous expulsion of the placental tissue with the aid of prostaglandins. Hysteroscopy-directed removal of the retained tissue is theoretically less traumatic to the uterus than curettage. However, this may be problematic in the immediate postpartum period due to heavy vaginal bleeding and the large size of the uterus. It has been suggested that hysteroscopic selective resection of the retained products of conception should be considered in patients with secondary (delayed) postpartum bleeding [9].

RPOC = retained products of conception

When fertility problems develop secondary to intrauterine adhesions, legal action may be quick to follow. Lately, we have encountered increasing numbers of claims and litigation activity relating to infertility secondary to Asherman syndrome. For some reason, this risk management issue has been somewhat ignored by the medical literature.

In this study we review all Asherman syndrome cases that were reported to Medical Consultants International over a 20 year period and that involved some legal action.

METHODS

We examined all claims related to retained placental tissue and RPOC that were reported/handled by MCI between 1991 and 2011. MCI is the largest professional liability insurer in Israel, providing malpractice coverage to institutions where more than 50% of the obstetric care in the country is conducted. We did not seek Institutional Review Board approval for this study since all the information was obtained from the insurance company (MCI) database (all women signed a release form).

Both the medical and the legal records were reviewed. Each medical file was analyzed with regard to the event preceding the adhesion formations, timing and mode of diagnosis, primary and secondary management, as well as the final medical outcome. The legal file was analyzed regarding the condemnation of the management, weaknesses due to substandard management, medical outcome, and legal process and outcome.

RESULTS

We identified 42 charts dealing with retained placental and products of conception in the MCI database. Twenty (47%) of the cases of retained placental tissue followed a vaginal delivery [Figure 1] and 8 cases (19%) followed a cesarean section [Figure 2].

Only in 4 of the 20 vaginal delivery cases was there an immediate diagnosis of retained placenta. In the other 16 the placenta was felt to be "intact" upon inspection following the delivery.

Twelve (28%) of the cases of RPOC followed first-trimester curettage for pregnancy terminations or missed abortions, and 2 cases (4%) followed second-trimester pregnancy terminations.

All 42 cases resulted in the formation of intrauterine adhesions (Asherman syndrome) of various degrees. Permanent infertility occurred in 24 patients.

Two patients delivered prematurely and underwent a postpartum hysterectomy due to placenta accrete.

The reason for legal action in 30 (71%) of the claims was fertility problems. Among other reasons were: permanent complete amenorrhea (2 cases, 4.7%), requirement for hysterectomy (2 cases, 4.7%), and psychiatric damage (2 cases, 4.7%).

Figure 1. Retained placental tissue following vaginal delivery

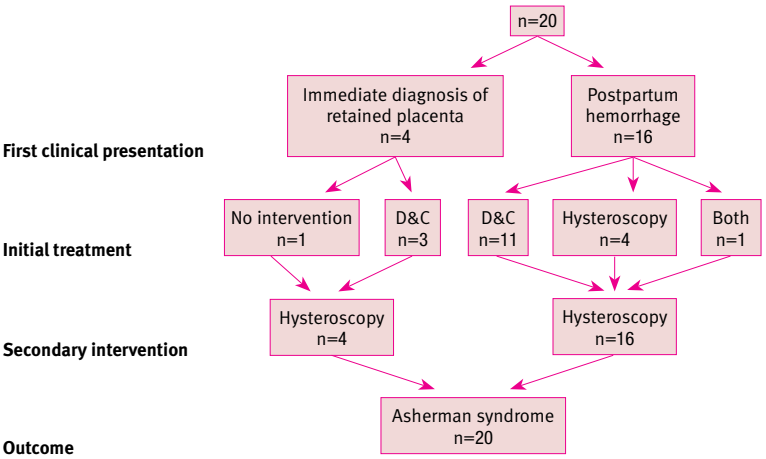
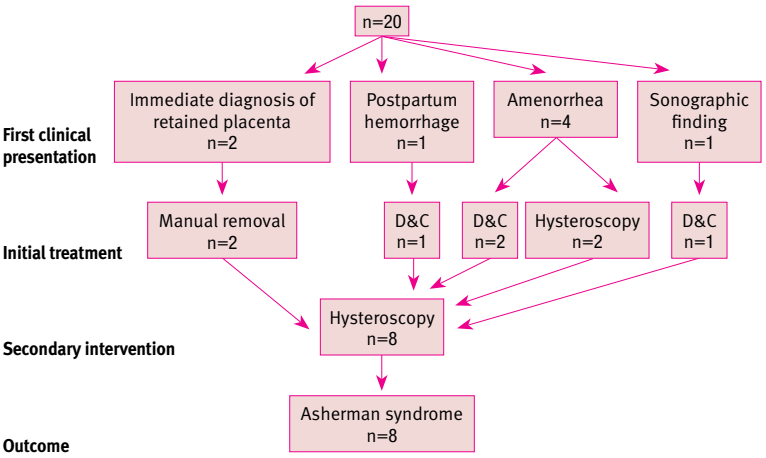


Figure 2. Retained placental tissue following cesarean section



THE LEGAL OUTCOME

The main clinical criticism by the plaintiff's expert witness related to the selection of "aggressive" D+C as the primary procedure for removal of retained tissue and the delay in the diagnosis of retained tissue, which caused a delay in evacuating the uterus. Other criticism related to not prescribing antibiotics and estrogens.

Most cases (n=20) resulted in an out-of-court settlement. Eight cases were handled by the courts; in two of them the decision was in favor of the plaintive and one case was rejected. Five cases are awaiting a court decision but will most likely be settled

MCI = Medical Consultants International

D + C = dilation and curettage

before the court decision. In 14 cases the file was closed due to the lack of legal activity or to statute of limitation. The mean compensation was $56,300.

DISCUSSION

The threat of medical malpractice claims has a huge effect on clinical practice, especially in obstetrics. Malpractice claims regarding intrauterine adhesions and their consequences have become more common in Israel in recent years. This trend is not reflected in the international medical literature. In view of the fact that there are no clear clinical guidelines for reducing the risk of intrauterine adhesion development, as well as the lack of risk management guidelines to reduce the risk of litigation and compensation, we decided to review the experience that has accumulated in the MCI over the last 20 years.

MEDICAL MANAGEMENT ISSUES

It is well known that failure to remove all placental tissue following birth, or incomplete evacuation of the products of conception during D+C, usually cause delayed bleeding with or without fever. In a few cases amenorrhea may occur. Our data show that in most of the cases there was no clinical suspicion of retained placental tissue prior to the onset of symptoms.

Delayed vaginal bleeding was the typical presenting symptom, occurring in all the cases that followed vaginal delivery (in none of the cases was amenorrhea the presenting symptom), while in the first-trimester curettage group amenorrhea was the presenting symptom in 41% of the cases.

While the first step in all bleeding cases was to evaluate the uterine cavity by ultrasound, sometimes it was difficult to distinguish between placental tissue and blood clots. Ultrasound is the best predictor of RPOC in women with a suspicion of incomplete miscarriage after spontaneous first-trimester miscarriage that was evacuated surgically, compared to clinical predictors such as vaginal bleeding and abdominal pains [10]. Shaamash et al. [11] used ultrasound to examine postpartum women to determine if there is a relationship between the findings on routine postpartum ultrasonographic scanning and puerperal uterine complications. According to the study intrauterine echogenic/heterogeneous mass was the most predictive variable for delayed heavy bleeding [11].

Once there is a suspicion of retained placental tissue, the initial approach is controversial: should we proceed directly to surgical intervention or try medical treatment (uterotonics) first. It has been shown that in a majority of cases spontaneous expulsion of the placental tissue occurs within 2–4 weeks [9].

In a retrospective cohort study of 200 patients, Pather and co-authors [7] assessed whether delivery details, clinical features at presentation, and laboratory investigations could accurately predict the presence of RPOC. They found that the sensitivity and specificity of ultrasound in detecting RPOC was 94% and 16%, respectively; the presence of an echogenic focus together with a thickened endometrium of more than 10 mm was the most accurate ultrasound feature of RPOC (positive predictive value 80%). Seventeen patients (8.5%) experienced major morbidity following curettage and 14 (7%) underwent a repeat procedure with further morbidity. Patients presenting with pelvic infection were more likely to experience postoperative morbidity. They concluded that a postpartum curettage has a low diagnostic yield and is associated with a significant complication rate. While the therapeutic benefit of this procedure is unclear, the authors felt that expectant management is appropriate [7].

Another question yet to be determined is the primary surgical intervention: curettage or hysteroscopy. Our data show that in most of the cases with poor outcome an immediate curettage was performed. A conservative approach was taken in only a few of the more recent cases.

Hysteroscopy and surgical hysteroscopy have been the gold standard of diagnosis and treatment of Asherman syndrome. This syndrome occurs mainly as a result of trauma to the gravid uterine cavity, which leads to the formation of intrauterine and/or intracervical adhesions. Despite the advances in hysteroscopic surgery, the treatment of moderate to severe Asherman syndrome still presents a challenge. Furthermore, pregnancy following treatment remains high risk, with complications including spontaneous abortion, preterm delivery, intrauterine growth restriction, placenta accrete or placenta previa, and even uterine rupture [9,11].

In many of our cases the medical record specified that curettage was performed under ultrasonographic guidance. However, this information was available in only a few charts.

Goldenberg et al. [13] reported their experience with 18 patients (16 post-abortion and 2 postpartum) who underwent a hysteroscopy for removal of residual trophoblastic tissue causing continuous bleeding. Complete removal of the residual tissue was achieved in all patients. No short-term complications were reported. The authors concluded that selective curettage of residual trophoblastic tissue performed under hysteroscopy is an easy and rapid procedure and might be preferable to conventional, non-selective, blind curettage [13].

Since the placenta is removed manually during a C-section, the number of cases of retained placentas following a C-section was surprising: 8 of 28 birth-related cases (28%). In 25% of them there was a clinical picture of placenta accrete. In two cases, one following B-Lynch uterine suturing for compression [14], sutures were observed in the uterine cavity on hysteroscopy.

LEGAL ISSUES

Our review of the medical and legal literature failed to reveal even a single study addressing legal experience with Asherman's syndrome. However, we did find several reports on internet sites published by private law firms describing the

legal outcome of single cases managed by those offices. The common ground for the lawsuits was negligence and deviation from the "standard of care" when managing cases with retained products of conception and retained placentas postpartum. These case reports are descriptive in nature and are without recommendations.

The problem when dealing with legal cases of RPOC is that there is no real "standard of care." It is not clear which approach is better: the active (immediate surgical intervention) or the conservative one (await spontaneous expulsion). Also, although recently the most common initial intervention is by hysteroscopy, a D+C is still considered an optional procedure. Due to these difficulties, MCI consultants adopted a "reduction of risk" attitude in these cases and recommended settlement in most cases, especially those with an immediate intervention by D+C. The consultants felt that there was no defense for such an aggressive approach.

RECOMMENDATIONS

Although our study group includes only the poor outcome cases, several repeated issues among our cases generate some management recommendations that might reduce the risk of uterine injury, adhesions formation, infertility, and malpractice claims:

• POST-DELIVERY

- ▹ Every placenta should be inspected after expulsion
- ▹ Manual exploration of the uterus should be performed in doubtful cases, followed by immediate ultrasound
- ▹ Postpartum hemorrhage requires curettage with a large blunt curette under ultrasound guidance
- ▹ In doubtful asymptomatic cases ultrasound should be performed before discharge from the hospital. Unless there is a large amount of residual placental tissue (> 5 cm) that requires surgical intervention, observation alone is recommended. Ultrasound should be repeated after 2 weeks. If the patient becomes symptomatic or if the uterus does not seem to be empty by 6 weeks, intervention is recommended
- ▹ Unless there is major bleeding, hysteroscopy is the procedure of choice
- ▹ Antibiotics should be used in febrile cases
- ▹ The addition of estrogens may be useful.

• POST D+C

- ▹ At the end of the procedure ultrasound should be used to demonstrate an empty uterus
- ▹ When there is a delayed suspicion of retained products of conception, hysteroscopy should be used. Adhesions should be separated during the same procedure
- ▹ Estrogens may be used in all these cases.

In conclusion, retained placental tissue following delivery, as well as retained products of conception, are common clinical complications that may carry a heavy medico-legal burden. Our accumulated experience may assist the clinician in selecting the safest approach.

Correspondence
Dr. T. Biron-Shental
Dept. of Obstetrics and Gynecology, Meir Medical Center, Kfar Saba 44281, Israel
email: shentalt@inter.net.il

References

1. Asherman JG. Amenorrhea traumatica. *J Obstet Gynaec Brit Emp* 1948; 55: 23-30.
2. Schenker JG. Etiology of and therapeutic approach to synechia uteri. *Eur J Obstet Gynecol Reprod Biol* 1996; 65: 109-13.
3. Roma Dalfo A, Ubeda B, Ubeda A. Diagnostic value of hysterosalpingography in the detection of intrauterine abnormalities: a comparison with hysteroscopy. *AJR Am J Roentgenol* 2004; 183: 1405-9.
4. Farhi J, Ben-Haroush A. Distribution of causes of infertility in patients attending primary fertility clinics in Israel. *IMAJ* 2011; 13 (1): 51-4.
5. Silberstein T, Saphier O, van Voorhis BJ, Plosker SM. Endometrial polyps in reproductive-age fertile and infertile women. *IMAJ* 2006; 8 (3): 192-5.
6. Fernandez H, Gervaise A, de Tayrac R. Operative hysteroscopy for infertility using normal saline solution and a coaxial bipolar electrode: a pilot study. *Hum Reprod* 2000; 15: 1773-5.
7. Pather S, Ford M, Reid R, Sykes P. Postpartum curettage: an audit of 200 cases. *Aust N Z J Obstet Gynaecol* 2005; 45 (5): 368-71.
8. Matijevic R, Knezevic M, Grgic O, Zlodi-Hrsak L. Diagnostic accuracy of sonographic and clinical parameters in the prediction of retained products of conception. *J Ultrasound Med* 2009; 28 (3): 295-9.
9. Cohen SB, Kalter-Ferber A, Weisz BS, et al. Hysteroscopy may be the method of choice for management of residual trophoblastic tissue. *J Am Assoc Gynecol Laparosc* 2001; 8 (2): 199-202.
10. Abbasi S, Jamal A, Eslamian L, Marsousi V. Role of clinical and ultrasound findings in the diagnosis of retained products of conception. *Ultrasound Obstet Gynecol* 2008; 32 (5): 704-7.
11. Shaamash AH, Ahmed AG, Abdel Latef MM, Abdullah SA. Routine postpartum ultrasonography in the prediction of puerperal uterine complications. *Int J Gynaecol Obstet* 2007; 98 (2): 93-9.
12. Yu D, Wong YM, Cheong Y, Xia E, Li TC. Asherman syndrome – one century later. *Fertil Steril* 2008; 89 (4): 759-79.
13. Goldenberg M, Schiff E, Achiron R, Lipitz S, Mashiach S. Managing residual trophoblastic tissue. Hysteroscopy for directing curettage. *J Reprod Med* 1997; 42 (1): 26-8.
14. Poujade O, Grosseti A, Mougel L, Ceccaldi PF, Ducarme G, Luton D. Risk of synechiae following uterine compression sutures in the management of major postpartum haemorrhage. *BJOG* 2011; 118 (4): 433-9.

"It's fine to celebrate success but it is more important to heed the lessons of failure"

Bill Gates

"The greatest dangers to liberty lurk in the insidious encroachment by men of zeal, well meaning but without understanding"

Louis D. Brandeis

Early Nephrology Referral for the Chronic Kidney Disease Patient: Seeing the Light or Groping in the Dark?

Linda Shavit MD and Itzchak Slotki MD

Adult Nephrology Unit, Shaare Zedek Medical Center, affiliated with Hebrew University-Hadassah Medical School, Jerusalem, Israel

KEY WORDS: chronic kidney disease (CKD), end-stage renal disease (ESRD), renal replacement therapy (RRT), early referral, late referral, mortality, morbidity

IMAJ 2014; 16: 506–508

Chronic kidney disease and end-stage renal disease are worldwide public health problems associated with high morbidity and a substantial expenditure on health care resources [1]. In Israel, at the end of 2013 the number of patients undergoing chronic dialysis was approximately 6000 and the annual direct cost of dialysis care approximately 5% of the total health budget (estimated 1.25 billion of 26 billion Israeli shekels; 0.26 billion of 7.46 billion U.S. dollars, respectively) [2].

CKD and ESRD patients suffer from low quality of life, and high rates of comorbidities, hospitalization, morbidity and mortality [1]. As reported in the United States Renal Data System summary for 2013, once renal replacement therapy is initiated the expected remaining life span is approximately 8 years (varying with race) for dialysis patients aged 40 to 44, and 4.5 years for those 60 to 64 years of age [1]. In fact, the life expectancy of dialysis patients is only one-third to one-sixth that in the general population and, in older dialysis patients, only slightly better than that in patients with lung cancer. However, recent evidence suggests that mortality rates among incident dialysis patients have decreased over the last few years [1]. For example, between 2003 and 2010, first-year death rates in the U.S. fell by more than 16%, while second-year death rates declined by 21% between 2002 and 2009 [1].

Substantial clinical data indicate that many of the clinical features and outcomes observed among patients with ESRD are already evident in those with earlier stages of CKD, with the risk of hospitalization and cardiovascular events in CKD patients progressively increasing as glomerular filtration rate declines [3,4]. This finding suggests that the comorbidities and complications observed in ESRD manifest themselves well before the onset of ESRD and, therefore, appropriate CKD care might have a significant impact on subsequent morbidity and mortality of patients after initiation of dialysis. In light of this evidence, several important questions come to mind. Is early CKD (eGFR < 60 ml/min/1.73 m^2) care provided by primary care physicians or internists sufficient, or should these patients be referred to a nephrologist for specialist care? What evidence is there in favor of a potential added value of nephrology care over standard care and, if there is a significant benefit, when is the ideal time for the CKD patient to be referred for specialist care? What are the possible causes of late referral worldwide and specifically in Israel? Finally, is there any impact of guideline-driven pre-dialysis nephrology care on survival of CKD patients?

During the last decade, a succession of observational studies that included thousands of CKD patients from France, USA, Australia, Canada, Korea, Holland and many other countries has shown a striking benefit of early nephrology referral on subsequent survival following commencement of dialysis [5-12]. This benefit appears to be time-dependent: those who received nephrology care for more than 3 months have better outcomes than those with less than 3 months follow-up. Even more impressive, nephrology care for longer than one year before dialysis initiation was associated with the greatest survival benefit. A recent meta-analysis summarized currently available data from 27 longitudinal cohort studies, providing information on 17,646 participants, 11,734 of whom were referred early and 5912 (33%) referred late [12]. A highly significant reduction in mortality for patients who were referred early was evident 3 months after dialysis initiation (odds ratio 0.51, 95% confidence interval 0.44–0.59, $P < 0.00001$) and the effect persisted at 5 years (OR 0.45, 95%CI 0.38–0.53). Similarly favorable effects were seen for hospitalization. Differences in mortality and hospitalization data were not explained by differences in prevalence of diabetes mellitus, previous coronary artery disease, blood pressure control, serum phosphate or serum albumin.

It should be emphasized that this evidence comes from large-scale cohort studies. Ideally, randomized controlled trials comparing outcomes of early vs. late referral should be performed to verify the advantage of early referral. However, since enrolment to such studies would be ethically and scientifically challenging given the inevitable biases of participating physicians and the inability to blind patients and

CKD = chronic kidney disease
ESRD = end-stage renal disease

eGFR = estimated glomerular filtration rate

OR = odds ratio
CI = confidence interval

physicians to the treatment arms, we have to accept the current level of evidence as the best possible.

Assuming that early referral is truly advantageous, are there specific underlying factors that could explain the benefit of predialysis nephrology care? Few studies have assessed this question and it appears likely that multiple factors can be invoked. An obvious and perhaps most powerful factor is avoidance of the dangers associated with acute complications of uremia necessitating emergency dialysis and hospital admission, as well as the need for central venous catheters for vascular access in this situation [5,6,13,14]. Additional established benefits of prolonged nephrology care are better blood pressure control, slower progression of CKD, avoidance of potentially nephrotoxic medications, and treatment of CKD-specific complications that are also cardiovascular risk factors. These include anemia (erythropoiesis-stimulating agents and iron), hyperlipidemia (statins), low serum albumin (dietary modification), vitamin D deficiency (supplementation), metabolic acidosis (bicarbonate supplementation), abnormal mineral metabolism (correction of calcium, phosphate, parathyroid hormone), as well as psychosocial disturbances (referral to psychiatrist and social worker). In addition, education regarding the options available for RRT allows for informed patient choice, leading to better uptake of home peritoneal dialysis, earlier placement of an arteriovenous fistula for hemodialysis, and early assessment for preemptive kidney transplantation [1,6,12-14]. Obviously, this list does not imply that all aspects will always be covered adequately by all nephrologists. Rather, nephrologists are challenged to implement these tasks according to the standards of the profession. Indeed, in light of the above mentioned evidence, it is reasonable to believe that nephrologists will perform these tasks more fully and efficiently than non-nephrologists.

Against the background of the above discussion, the article by Berar Yanay et al. in this issue of *IMAJ* [16] is to be welcomed; it is the first Israeli study to assess the impact of the timing of nephrology referral on outcome of CKD patients after initiation of dialysis [15]. The study analyzed 200 incident dialysis patients; 41% were referred late (dialysis required less than 3 months after their first nephrology consultation). The early and late referral groups were similar in mean age, gender distribution, prevalence of diabetes, hemoglobin and albumin levels at dialysis initiation. All patients in the late referral group started dialysis with central venous catheters. The 4 year survival rate was 41.1% in the early and 18.7% in the late referral group ($P < 0.0001$). Multivariate analysis demonstrated a powerful impact of late referral on mortality rate (hazard ratio 1.873, 95% CI 1.133–3.094), with the effect being most prominent in patients < 70 years old, females and diabetics. Unfortunately, apart from the probably greater use of permanent vascular hemodialysis access in the early referral group, the specific factors responsible for the benefit, and the possible reasons for the greater benefit in specific subgroups, cannot be determined based on the data presented in this article. Nevertheless, the findings by Berar Yanay and co-authors that predialysis nephrology care in the Israeli CKD population improves survival after the initiation of RRT support current evidence from other countries. Moreover, the current work demonstrates an unacceptably high prevalence of late nephrology referral in Israel, irrespective of the underlying causes that could not be explored due to insufficient data.

Multiple causes of late referral have been identified worldwide. These include factors that are difficult to correct, such as referral bias of physicians; refusal, noncompliance and socioeconomic status of the patient; and the structure of the health care system within a given country [12,14]. Referral depends upon practice patterns, which are not uniform across health care systems or geographic regions. As a result, there is a variety of recommendations regarding the indications for referral to nephrologists, but none has been universally adopted [16-18]. Obviously, based on the current evidence, patients should be referred at least one year before dialysis is required. However, this time-dependent definition presupposes that the primary care physician, internist or other physician is able to predict when dialysis will be necessary in any given patient – an absolutely unrealistic expectation. Based on the overall data available, we suggest that the eGFR be the primary determinant of referral, and that patients with stage 3 CKD (eGFR 30–59 ml/min per 1.73 m^2) should be seen by a nephrologist, who would then co-manage the patient with the primary care physician. Additional factors that should influence the decision to refer are: resistant hypertension, prominent proteinuria, hematuria, presumed hereditary kidney disease, inability to identify a presumed cause of CKD, eGFR decline of more than 30% in less than 4 months without an obvious explanation, and difficult-to-manage complications of CKD, as described earlier.

Ideally, a collaborative multicenter national study should be performed to address the subject of timely referral of CKD patients to nephrologists in Israel. However, given the challenges in organizing such a trial, we suggest, in the meantime, appropriate training of primary care physicians with regard to guidelines on timing and indications for referral, and understanding of the potential consequences of late referral. These initiatives will help promote better communication among nephrologists, referring physicians and other specialists, thereby paving the way towards improved outcomes following the commencement of RRT.

In summary, based on current evidence, we suggest that timely referral of CKD patients to a nephrologist is a simple strategy that can favorably impact on survival of these patients in Israel as well as globally.

RRT = renal replacement therapy

Correspondence
Dr. I. Slotki
Adult Nephrology Unit, Shaare Zedek Medical Center, P.O. Box 3235, Jerusalem 91031, Israel
email: islotki@szmc.org.il

References

1. United States Renal Data System 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2014.
2. "New research indicates: Israel pays a heavy economic price due to lack of investment in prevention and early diagnosis of kidney disease." Translated and adapted from http://www.klayot.org.il/?CategoryID=148&ArticleID=870. Accessed February 10, 2014.
3. van der Velde M, Matsushita K, Coresh J, et al.; Chronic Kidney Disease Prognosis Consortium. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2011; 79: 1341-52.
4. Chronic Kidney Disease Prognosis Consortium; Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; 375: 2073-81.
5. Kessler M, Frimat L, Panescu V, Briançon S. Impact of nephrology referral on early and midterm outcomes in ESRD (EPIREL): results of a 2-year, prospective, community-based study. *Am J Kidney Dis* 2003; 42: 474-85.
6. Winkelmayer WC, Owen W, Levin R, Avorn J. A propensity analysis of late versus early nephrologist referral and mortality on dialysis. *J Am Soc Nephrol* 2003; 14: 486-92.
7. Stack AG. Impact of timing of nephrology referral and pre-ESRD care on mortality risk among new ESRD patients in the United States. *Am J Kidney Dis* 2003; 41: 310-18.
8. Cass A, Cunningham J, Arnold PC, Snelling P, Wang Z, Hoy W. Delayed referral to a nephrologist: outcomes among patients who survive at least one year on dialysis. *Med J Aust* 2002; 177: 135-8.
9. Kim do H, Kim M, Kim H, et al. Early referral to a nephrologist improved patient survival: prospective cohort study for end-stage renal disease in Korea. *PLoS One* 2013; 8: e55323.
10. Hommel K, Madsen M, Kamper AL. The importance of early referral for the treatment of chronic kidney disease: a Danish nationwide cohort study. *BMC Nephrol* 2012; 13: 1-8.
11. Winkelmayer WC, Liu J, Chertow GM, Kurella Tamura M. Predialysis nephrology care of older patients approaching end-stage renal disease. *Arch Intern Med*. 2011; 171: 1371-8.
12. Smart NA, Titus TT. Outcomes of early versus late nephrology referral in chronic kidney disease: a systematic review. *Am J Med* 2011; 124: 1073-80.
13. Schmidt RJ, Domico JR, Sorkin MI, Hobbs G. Early referral and its impact on emergent first dialyses. Health care costs and outcome. *Am J Kidney Dis* 1998; 32: 278-83.
14. Arora P, Obrador GT, Ruthazer R, et al. Prevalence, predictors and consequences of late nephrology referral at a tertiary care center. *J Am Soc Nephrol* 1999; 10: 1281-6.
15. Berar Yanay N, Scherbakov L, Sachs D, Peleg N, Slovodkin Y, Gershkovich R. Effect of early nephrology referral on the mortality of dialysis patients in Israel. *IMAJ* 2014; 16: 479-82.
16. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004; 43 (Suppl 1): S1-290.
17. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 2002; 39: S1-266.
18. Caring for Australasians with Renal Impairment (CARI). Dialysis Guidelines. Acceptance onto Dialysis. Timing of referral of chronic kidney disease patients to nephrology services (adult). 2010 http://www.cari.org.au/dialysis_accept_published.php Accessed February 10, 2014

Capsule

Changing skin cells in development with TGF-β

Transforming growth factor-β (TGF-β) makes some cells stop dividing, separate from one another, and start migrating. This process, called the epithelial-to-mesenchymal transition, occurs during normal development and can help cancers progress. D'Souza and co-workers cultured skin cells and measured changes in their proteins as they underwent this process. TGF-β caused thousands of protein changes that varied depending on how long cells were exposed to TGF-β. The protein changes correlated with changes in cell behavior. The authors modeled the network of interacting proteins affected by TGF-β, creating a road map that can explain how TGF-β influences cell behavior.

Sci Signal 2014; 7: rs5

Eitan Israeli

Capsule

Targeting transcription regulation in cancer with a covalent CDK7 inhibitor

Tumor oncogenes include transcription factors that co-opt the general transcriptional machinery to sustain the oncogenic state, but direct pharmacological inhibition of transcription factors has so far proven difficult. However, the transcriptional machinery contains various enzymatic cofactors that can be targeted for the development of new therapeutic candidates, including cyclin-dependent kinases (CDKs). Kwiatkowski et al. present the discovery and characterization of a covalent CDK7 inhibitor, THZ1, which has the unprecedented ability to target a remote cysteine residue located outside of the canonical kinase domain, providing an unanticipated means of achieving selectivity for CDK7. Cancer cell-line profiling indicates that a subset of cancer cell lines, including human T cell acute lymphoblastic leukemia (T-ALL), have exceptional sensitivity to THZ1. Genome-wide analysis in Jurkat T-ALL cells shows that THZ1 disproportionally affects transcription of RUNX1 and suggests that sensitivity to THZ1 may be due to vulnerability conferred by the RUNX1 super-enhancer and the key role of RUNX1 in the core transcriptional regulatory circuitry of these tumor cells. Pharmacological modulation of CDK7 kinase activity may thus provide an approach to identify and treat tumor types that are dependent on transcription for maintenance of the oncogenic state.

Nature 2014; 511: 616

Eitan Israeli

Screening for Glaucoma

Dan Gaton MD

Department of Ophthalmology, Rabin Medical Center (Beilinson Campus), Petah Tikva, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

KEY WORDS: glaucoma, optic nerve, intraocular pressure (IOP), visual field, screening,

IMAJ 2014; 16: 509–510

Glaucoma is a chronic progressive degeneration of the optic nerve that may cause irreversible visual field damage and ultimately blindness. Open-angle glaucoma is the most common type of the disease and a leading cause of blindness, affecting more than 60 million people worldwide [1].

The main diagnostic tools for characterizing a glaucoma patient typically include optic nerve evaluation, and detection of visual field loss and elevated intraocular pressure. Modern glaucoma management has shown that a substantial proportion of glaucoma patients have normal-to-low intraocular tension; therefore, high IOP is no longer required for glaucoma diagnosis. Managing glaucoma has also shown us that the optic nerve may be damaged in a glaucomatous optic neuropathy pattern much earlier than the appearance of visual field defects [2]. The diagnosis of GON prior to the appearance of visual field defects has been termed pre-perimetric glaucoma. Thus, visual field damage is also not a requirement for a definite glaucoma diagnosis. However, GON has a pathognomonic pattern that enables the diagnosis of glaucoma based solely on optic nerve evaluation.

Glaucomatous damage to the optic nerve is irreversible. End-stage glaucoma has huge quality-of-life implications, and this is where our intervention may prevent deterioration to advanced debilitating stages. Early treatment has been shown to prevent further nerve fiber loss and atrophy, saving or slowing the optic nerve from ongoing deterioration. Early detection of GON can therefore prevent severe visual loss and blindness. Glaucoma treatment is aimed not only at preventing severe visual impairment but also at maintaining the patient's visual abilities for a better quality of life. Therefore, the prevention of early-stage deterioration may be of great importance.

The literature shows that only about 50% of glaucoma cases are identified, suggesting that about 50% are completely undiagnosed [3]. The main reasons for this include the fact that this disease remains asymptomatic and unnoticed until its advanced stages, when visual disturbances interfere with daily life. Also, there is no single definite test to screen mass populations for glaucoma. Therefore, implementing screening-based programs to detect this disease is not an easy, rapid and efficient undertaking. What's more, the severe cases often seek medical care, while the milder cases remain undiagnosed.

A full eye examination focused on glaucoma includes: best corrected visual acuity, a full slit-lamp and fundus examination, including IOP measurement. Following the results of these tests further examinations include: functional tests: visual field test (the Humphrey Standard Automated Perimetry device in Israel), structural tests, optic nerve imaging (Optic Coherence Tomography imaging device in Israel), and stereo photography of the optic nerve head.

A good glaucoma screening program would involve a process for assessing a population for glaucoma, including those without ocular or visual symptoms and those not at high risk for developing glaucoma. Many health authorities around the world tried to confront this challenge. In the United States a U.S. Preventive Services Task Force recently systematically reviewed data sources and clinical trials mainly of population-based studies, only to conclude: "Diagnosis of glaucoma is usually made on the basis of several tests that, when combined, evaluate the biologic structure and function of the optic nerve and intraocular pressure" [4]. One of the main "take-home" messages is that because a meaningful proportion of glaucoma patients may have normal pressures in the eye, measuring IOP should not be considered the only or even the main screening test for glaucoma detection. It has to be combined with the other tests for a conclusive diagnosis. Most tests that are available in a primary care setting do not have acceptable accuracy to detect glaucoma. These recommendations are based on cost-effectiveness issues and involve the health authorities [5]. In the meantime, the ophthalmic community, especially glaucoma expert circles, continue to search for improved and efficient screening tools. An alternative to non-efficient screening programs is increasing glaucoma awareness among health care professionals, particularly the primary health care providers, combined with proper education for both medical staff and patients.

In 2008 the World Glaucoma Association launched an international annual "World Glaucoma Day" and recently modified it to the "World Glaucoma Week" with the intention of getting the message across with regard to glaucoma awareness in more than 100 countries across the world, including Israel.

I would like to congratulate Dr. Nesher for collecting the data from the various centers that run the glaucoma week screening program, in Israel, as published in this issue

IOP = intraocular pressure
GON = glaucomatous optic neuropathy

of *IMAJ* [6]. This study demonstrates that more than 10% of the screened population had ocular hypertension, pre-perimetric glaucoma, or glaucoma. Not only is this finding important, but this study shows also that the yield of the screening programs increased significantly with age, in cases with diabetes and in those with a family history of glaucoma. The most important conclusion of the long-lasting debate on glaucoma screening was the agreement regarding its objectives and implementation. The major purpose of such programs is not necessarily to diagnose incident new cases, but rather to achieve a comprehensive awareness by the public to seek early and regular checkups with their ophthalmologist. This becomes even more critical when targeting people with risk factors such as a family history of glaucoma. The American Academy of Ophthalmology adopted the recommendation for a complete eye examinatiion every 5 years, including tests for glaucoma, depending also on age and other risk factors for eye diseases [7]. In conclusion, since early detection of glaucoma prevents irreversible damage and visual disability, physicians should urge their patients to visit their ophthalmic health provider regularly.

Correspondence
Dr. D. Gaton
Dept. of Ophthalmology, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel
email: gaton@post.tau.ac.il

References

1. Quigley HA, Browman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol* 2006; 90: 262-7.
2. Kerrigan–Baumrind LA, Quigley HA, Pease ME, et al. Number of ganglion cells in glaucoma eyes compared with threshold visual field tests in the same persons. *Invest Ophthalmol Vis Sci* 2000; 41: 741-8.
3. Quigley HA, Vitale S. Models of open-angle glaucoma prevalence and incidence in the United States. *Invest Ophthalmol Vis Sci* 1997; 38: 83-91.
4. U.S. Preventive Services Task Force. Screening for glaucoma. Clinical summary of U.S. Preventive Services Task Force recommendation. 2013; AHRQ Publication No. 10-05182-EF-5.
5. Stoutenbeek R, de Voogd S, Wolfs RCW, et al. The additional yield of a periodic screening program for open-angle glaucoma: a population-based comparison of incident glaucoma cases detected during screening. *Br J Ophthalmol* 2008; 92: 1222-6.
6. Nesher R. Prevalence of intraocular pressure and optic disk cupping: multicenter glaucoma screening in Israel during the 2009 and 2010 World Glaucoma Weeks. *IMAJ* 2014; 16: 483-6.
7. The American Academy of Ophthalmology Recommendations: Glaucoma Screening 2014. Article Link: http://www.webmed.com/eye-health/tc/glaucoma-screening-topic-overview.

Capsule

In CF, two drugs are no better than one

Cystic fibrosis (CF), a disabling lung disease, is caused by mutations in a protein called CFTR, which acts as a channel to move chloride ions into and out of cells. Ivacaftor, the only targeted drug available, does not work well for the severest, most common form of disease. Cholon et al. and Veit et al. explain why efforts to improve CF treatment by combining ivacaftor with new drugs have failed. Ivacaftor increases mutant CFTR activity, but it only works when CFTR is on the cell surface. The new drugs under development bring mutant CFTR to the surface, but combining the two types of drugs has not been effective because ivacaftor also makes CFTR less stable, so cells remove it quickly from their membranes.

Sci Transl Med 2014; 6: 246ra96, 246ra97

Eitan Israeli

Capsule

Macrophages help food move through

Food needs a complex array of cellular interactions to move through the body. Neurons, muscle cells, and interstitial cells all cooperate to ease it through the gastrointestinal (GI) tract. Now Muller and colleagues report intestinal muscularis macrophages, a type of immune cell that resides in the smooth muscles that surround the GI tract, participate, too. These macrophages secrete a substance called bone morphogenetic protein 2 (BMP2), which binds to enteric neurons and directs them to coordinate the muscle cell contractions that squeeze food through. The neurons, in turn, produce a growth factor required by the macrophages. Macrophage-neuron crosstalk is essential: When mice don't have enough of the growth factor, BMP2, or muscularis macrophages, they have defects in gut muscle contractions.

Cell 2014; 10.1016/j.cell.2014.04.050

Eitan Israeli

"I believe that in the course of the next century the notion that it's a woman's duty to have children will change and make way for the respect and admiration of all women, who bear their burdens without complaint or a lot of pompous words"

Anne Frank (1929-1945), one of the most discussed Jewish victims of the Holocaust. Her wartime *Diary of a Young Girl* has been the basis for several plays and films. She was born in Frankfurt but lived most of her life in Amsterdam. She gained international fame posthumously after her diary was published. It documents her experiences hiding during the German occupation of the Netherlands

Rescue from a Storm

David Luria MD

Cardiac Arrhythmia and Pacing Unit, Heart Institute, Hadassah Medical Center and Hebrew University-Hadassah Medical School, Jerusalem, Israel

KEY WORDS: ventricular tachycardia (VT), ventricular fibrillation (VF), myocardial infarction, radiofrequency ablation, electrical storm

IMAJ 2014; 16: 511–512

Recurrent ventricular tachycardia and ventricular fibrillation episodes have become an increasingly frequent clinical problem with the ever-expanding use of implantable cardioverter defibrillators. Patients, saved from cardiac arrest by an ICD, may suffer multiple ICD shocks and require close medical attention. When ICD therapies (shocks or anti-tachycardia pacing) occurs ≥ 3 times/24 hours, it is referred to as an "electrical storm" and is recognized as a medical emergency. Indeed, recurrent frequent VT events may be symptomatic and, even more importantly, carry a significant risk of cardiac death during the short and mid-term follow-up [1-4].

About 85% of ES cases are caused by sustained monomorphic VT [4,5]. However, an important minority of cases, the remaining 15%, is due to recurrent polymorphic VT/VF. These are challenging and life-threatening cases; they include different cardiac diseases, ranging from normal structure in the case of channelopathy to severe structural disorder of the heart, and require immediate and comprehensive therapy [4-7].

In this issue of *IMAJ*, Sela et al. [8] present the case of a patient with severe ischemic cardiomyopathy (ejection fraction 15%) and ES due to polymorphic VT/VF 7 days after non-Q myocardial infarction. Over 4 days the patient experienced more than 100 (!) ICD shocks, which completely depleted the device battery. After medical therapy failed, the patient underwent successful ablation of monomorphic premature ventricular beats, triggering VT.

Polymorphic VT/VF is usually associated with non-ischemic cardiomyopathy [4]. In stable ischemic heart disease, slow and anisotropic conduction within the myocardial scar may serve as a substrate for the re-entry mechanism, causing sustained monomorphic VT and in severe cases ES.

Acute myocardial infarction or ischemia may complicate with polymorphic VT/VF. Therefore, in cases of ES due to polymorphic VT, it seems reasonable to exclude acute coronary occlusion. Surprisingly, in all reported cases, as in the current case, no evidence of acute ischemia was found and revascularization was not performed [5-7]. In these reports, ES due to polymorphic VT was not a result of temporary conditions, such as ischemia, hypokalemia or QT prolongation due to medical (anti-arrhythmic) therapy. It was caused by recurrent monomorphic premature ventricular beats, initiating VT.

Acute management of severe ES must include deep sedation (usually general anesthesia with mechanical ventilation) to decrease severe anxiety related to recurrent ICD shocks, which induce a hypercatecholaminergic state and provoke arrhythmia recurrence. The drug regimen must include beta-blockers, preferably intravenous. Non-selective beta-1 and beta-2 blockers (propranolol) were shown to have the best effect. The most efficient anti-arrhythmic drug is intravenous amiodarone [1]. Lidocaine can have a temporary effect, but high doses of the drug are usually required, imposing the risk of significant side effects.

In most ES cases, however, as in the case presented by Sela and team [8], conservative management fails and ablation has to be performed to save the patient. Ablation of ES is unequivocally recommended by the recent "Consensus Document on Catheter Ablation of Ventricular Tachycardia" [4]. While the timing of the ablation procedure is not defined in this document, many experts favor early rather than deferred intervention. In the largest series of patients undergoing ES ablation, the procedure was considered an emergency and was performed within 24 hours of hospitalization in most of the cases [6]. This approach is more applicable in large referral centers that have extensive expertise in VT ablation.

Understandably, this complicated ablation procedure in such sick patients may be reserved as a "last resort" intervention by smaller electrophysiologic groups. One needs to keep in mind, however, that early ablation has been proved superior to medical therapy in severe ES, improving immediate and mid-term results of arrhythmia control and survival [4,7].

Mapping and ablation of ES is a technically demanding procedure. Yet, in recent reports, in up to 90% of cases the procedure was successful in terminating an ES and the patients could be discharged. The complication rate was low and did not exceed 1–2% and the mortality rate was about 0.5% [4-6].

Polymorphic VT in the context of ischemic cardiomyopathy is usually triggered by monomorphic VPB arising from the myocardial scar border. Of interest, Purkinje arborization was demonstrated to be an

ICD = implantable cardioverter defibrillators
VT = ventricular tachycardia
ES = electrical storm

VPB = ventricular premature beats

essential part of polymorphic VT initiation and maintenance in many cases. Careful mapping of the scar border during sinus rhythm and during VPB and/or VT often uncovered Purkinje potentials before ventricular electrogram in successful ablation spots [6,9,10].

In the present report, Sela's team [8] did not focus on PP mapping; however, the figure in the article demonstrates endocardial recording of successful ablation points with a small, sharp, fractionated potential compatible with distal PP. Furthermore, this recording is located in the basal anterior wall, the area of the anterior left bundle fascicle. This fascicle was demonstrated to be the potential source of VPB, triggering polymorphic VT in patients after anterior myocardial infarction [6]. Mapping of PP in such a case may assist significantly in mapping and ablation, when used together with activation mapping of VPB (earliest activation spot) and pace-mapping, especially if the amount of VPB is small.

Monomorphic VT ablation, even in a case of ES, may require activation/entrainment mapping of VT and/or substrate mapping of scars and late potentials [4]. The situation is different in cases of polymorphic VT, triggered by monomorphic VPB. In the reported cases, ablation of the VPB focus was effective enough to terminate ES and prevent further VT recurrence [6,7]. It seems that, given the usually complicated clinical situation in such cases, extensive ablation of the scar border in addition to VPB focus, as performed by Sela et al., may not be essential. For the same reason, programmed ventricular stimulation at the end of the procedure, which is crucial to define the success of monomorphic VT ablation, may not be necessary after successful elimination of VPB, triggering polymorphic VT.

In summary, this case report demonstrates that even in an extremely difficult clinical situation of severe ES, ablation can rescue the patient. The procedure should be performed on an emergency basis and should be as short and precise as possible, based on an understanding of the pathophysiology of specific arrhythmia.

Contemporary advances in the ablation technique are generating new methods to improve the results of complicated ablation procedures. Among the most useful features for VT/VPB ablation in addition to three-dimensional mapping systems used by the authors, pent-array multi-polar mapping catheter and ablation systems with control of contact pressure should be mentioned. These tools enhance our capability of quick and precise mapping as well as safe and effective application of radiofrequency energy.

PP = Purkinje potentials

Correspondence
Dr. D. Luria
Director, Cardiac Arrhythmia and Pacing Unit, Heart Institute, Hadassah Medical Center, P.O. Box 12000, Jerusalem 9112001, Israel
Fax: (972-2) 677-7373
email: dluria@hadassah.org.il

References

1. Gao D, Sapp JL. Electrical storm: definitions, clinical importance and treatment. *Curr Opin Cardiol* 2013; 28: 72-9.
2. Nayyar S, Ganesan AN, Brooks AG, Sullivan T, Roberts-Thomson KC, Sanders P. Venturing into ventricular arrhythmia storm: a systematic review and meta-analysis. *Eur Heart J* 2013; 34: 560-9.
3. Eifling M, Razavi M, Massumi A. The evaluation and management of electrical storm. *Tex Heart Inst J* 2011; 38 (2): 111-21.
4. Aliot EM, Stevenson WG, Almendral-Garrote, JM, et al., EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias. *Heart Rhythm* 2009; 6: 886-933.
5. Kozeluhova M, Peichl P, Cihak R, et al. Catheter ablation of electrical storm in patients with structural heart disease. *Europace* 2011; 13: 109-13.
6. Szumowski L, Sanders P, Walczak F, et al. Mapping and ablation of polymorphic ventricular tachycardia after myocardial infarction. *J Am Coll Cardiol* 2004; 44 (8): 1700-6.
7. Bode K, Hindricks G, Piorkowski C, et al. Ablation of polymorphic ventricular tachycardias in patients with structural heart disease. *Europace* 2011; 13: 109-13.
8. Sela R, Gellerman M, Kalfon E, Atar S. Extreme electrical storm in a patient with an implantable cardioverter defibrillator. *IMAJ* 2014; 16: 513-15.
9. Bogun F, Good E, Reich S, et al. Role of Purkinje fibers in post-infarction ventricular tachycardia. *J Am Coll Cardiol* 2006; 48 (12): 2500-7.
10. Sinha A-M, Schmidt M, Marschang H, et al. Role of left ventricular scar and purkinje-like potentials during mapping and ablation of ventricular fibrillation in dilated cardiomyopathy. *PACE* 2009; 32: 286-90.

Capsule

Problems making proteins kills nerve cells

Neurodegeneration is associated with a variety of different diseases, but its cellular roots are often obscure. Ishimura and co-authors found that mutant mice whose brain cells start to die rapidly soon after birth have lost the function of two vital cellular components. The first is a protein that releases stalled ribosomes stuck on messenger RNA (mRNA); the second is a transfer RNA (tRNA), which reads the code for arginine in the mRNA. This tRNA is expressed predominantly in the central nervous system. The lack of the tRNA leads to increased ribosomal stalling at arginine codons, which, when left uncorrected, blocks protein synthesis and proves fatal.

Science 2014; 345: 455

Eitan Israeli

"I'm selfish, impatient, and a little insecure. I make mistakes, I'm out of control, and at times hard to handle. But if you can't handle me at my worst, then you sure as hell don't deserve me at my best"

Marilyn Monroe (1926-1962), American actress, model and singer, who became a major sex symbol

Extreme Electrical Storm in a Patient with an Implantable Cardioverter Defibrillator

Ron Sela MD, Mark Gellerman MD, Eli Kalfon MD and Shaul Atar MD

Department of Cardiology, Western Galilee Medical Center, Nahariya, affiliated with Bar-Ilan University Faculty of Medicine in the Galilee, Safed, Israel

KEY WORDS: electrical storm (ES), ablation, implantable cardioverter defibrillator (ICD)

IMAJ 2014; 16: 513–515

For Editorial see page 511

The implantable cardioverter defibrillator is highly effective in primary and secondary prevention of life-threatening ventricular arrhythmias. About 40–70% of patients with an ICD will receive appropriate therapy following implantation [1]. Most of the time these therapies are limited to a small number of shocks or anti-tachycardia pacing. However, some patients receive multiple treatments over a short period. This situation has been defined as an "electrical storm" which consists of three or more distinct episodes of ventricular tachycardia and/or ventricular fibrillation within a 24 hour period. ES is a life-threatening situation that adversely affects the short and long-term prognosis and is a clinical and therapeutic challenge [2].

We report the case of a patient with ischemic cardiomyopathy and severe ES caused by repeated short coupled premature ventricular complexes that triggered polymorphic VT and VF, which were resistant to anti-arrhythmic drugs and complete percutaneous coronary revascularization. Successful treatment was finally achieved with rapid pacing and extensive catheter ablation.

ICD = implantable cardioverter defibrillator
ES = electrical storm
VT = ventricular tachycardia
VF = ventricular fibrillation

PATIENT DESCRIPTION

A 59 year old man with ischemic cardiomyopathy, status post-coronary artery bypass graft surgery and an ICD (Virtuoso® DR, Medtronic, Inc. USA) for primary prevention of sudden cardiac death 2 years earlier was admitted to the intensive cardiac care unit due to non-ST elevation myocardial infarction, acute heart failure and cardiogenic shock. Left ventricular ejection fraction was estimated to be 15%. He was intubated and urgently transferred to the cardiac catheterization lab where an intra-aortic balloon pump was inserted, followed by coronary angiography that demonstrated severe native three-vessel disease, a patent left internal mammary graft to the left anterior descending artery, and a patent vein graft to a marginal branch. Percutaneous coronary intervention to an occluded diagonal artery was performed.

On his seventh day of hospitalization he developed severe ES that started with rapid atrial fibrillation. Subsequent episodes usually began with short coupled PVC of right bundle branch morphology [Figure A] that triggered PMVT and were terminated by appropriate shocks from his ICD. Attempts to reduce the frequency of ventricular tachyarrhythmias with anti-arrhythmic drugs such as amiodarone and procainamide were unsuccessful. The only anti-arrhythmic drug that seemed to reduce the number of ventricular tachyarrhythmic events was lidocaine, which was administered as a continuous infusion. Overall, the patient received a total of 104 shocks from the device over a 4 day period until the battery of the device reached its end of service and electric shocks had to be administered by an external defibrillator. In an attempt to reduce the ischemic burden, the patient underwent a second successful percutaneous coronary intervention to the right coronary artery.

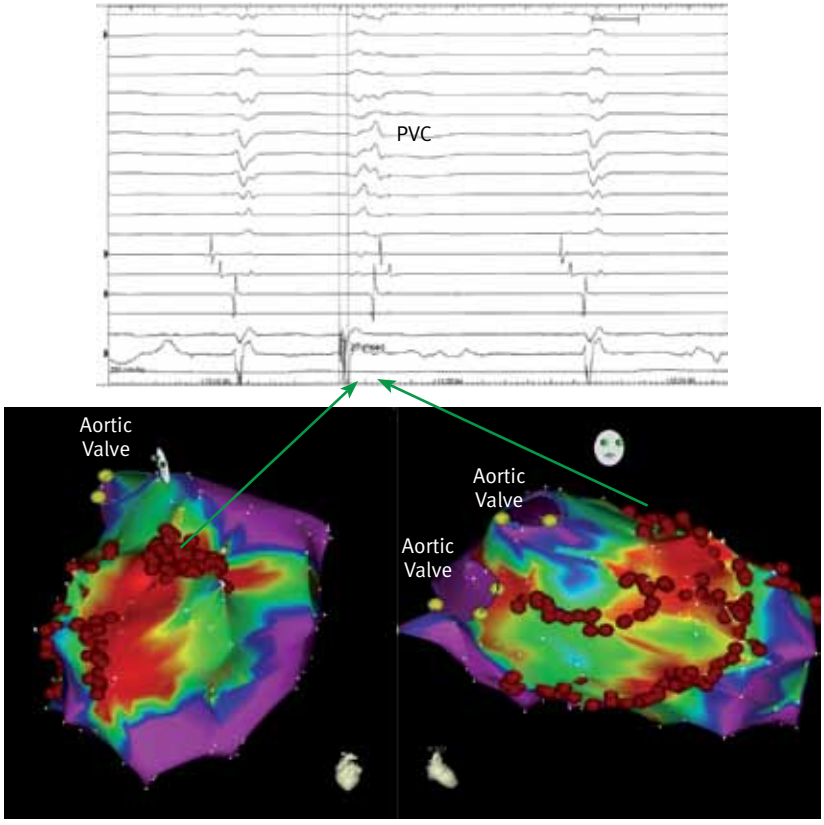
PVC = premature ventricular complexes
PMVT = polymorphic ventricular tachycardia

Although the ICD reached its end of service and the device could no longer deliver shocks, the pacing mechanism of the device was still functioning and reprogrammable. The managed ventricular pacing (MVP®, Medtronic) mode was turned off to eliminate the possibility for long-short episodes and the device was programmed to DDD mode 90/110 beats per minute lower/upper rate, respectively, with a long atrioventricular delay to prevent short coupled PVCs and reduce the chance of right ventricular pacing. The combination of rapid atrial pacing with the administration of intravenous lidocaine seemed to reduce, but did not eliminate, the episodes of ventricular tachyarrhythmias.

As a final recourse, the patient was taken to the electrophysiology lab for electrophysiology study and catheter ablation. Administration of lidocaine was stopped and the rate of pacing was slowed. Since we could not map the ventricular tachycardia, the strategy of the electrophysiology study was to create a substrate mapping of the left ventricle using 3-D electroanatomic voltage mapping (CARTO 3TM, Biosense Webster, Diamond Bar, CA, USA). Scar areas were defined by local voltage < 0.48 mV. Healthy tissue was defined as local voltage > 1.5 mV.

Mapping the site where the PVC originates was facilitated by an early electrocardiogram that preceded the QRS onset during PVC. We also created lines of ablation at the border of the scars and through

[A] Voltage map of the left ventricle using the CARTO 3 system, in left lateral and right anterior oblique views. The red colored areas represent the scar zone, the yellow-green the borderline zone, and purple indicates healthy tissue. The red dots show ablation applications. The endocardial map illustrates a large anterior-lateral-septal infarct. The arrows indicate the origin of the initiating PVC corresponding to the early electrocardiogram that preceded the QRS onset by 37 msec during the PVC. We also created lines of ablation at the border of the scars and through areas that could create re-entry tachycardia



areas that could create re-entry tachycardia [3-5] [Figure A].

At the end of the ablation procedure we recorded stable sinus rhythm, without PVCs or ventricular arrhythmias. We performed a modest programmed extra-stimulation from the right ventricular apex without triggering any ventricular tachyarrhythmias and stopped the procedure at that point. The ICD was reprogrammed back to high pacing rate and the patient was placed on mexiletine 200 mg orally four times a day and metoprolol. Following the catheter ablation, the patient underwent prolonged intensive rehabilitation without any ventricular arrhythmic events. After a few weeks, his ICD was replaced, gradually lowering the lower pacing rate to 70 beats per minute, and mexiletine and metoprolol were continued.

After 2 months of hospitalization the patient was gradually weaned from the ventilator and discharged to an inpatient rehabilitation facility. At 2 months follow-up after the implantation of his new ICD, there was no evidence of recurrent ventricular arrhythmias. Transthoracic echocardiography showed some improvement in left ventricular function.

COMMENT

We report the case of a severe unrelenting electrical storm in a patient with ischemic cardiomyopathy. Recurrent episodes of PMVT and VF were initiated by short coupled PVCs that seemed to be monomorphic.

Our comprehensive approach to this difficult situation included administering anti-arrhythmic drugs, maximal achievable revascularization, rapid pacing to reduce the possibility of early PVCs and, finally, extensive catheter ablation as a rescue procedure. The outcome was remarkable.

The catheter ablation was based on substrate-voltage mapping since we were unable to map during VT. We defined dense scar areas with bipolar potentials < 0.48 mV, drawing lines of ablation on the border of the dense scar tissue and through areas that could create re-entry tachycardia. We also looked for areas with early potentials during PVC and pace mapping compared to the 12 lead electrocardiogram morphology of the PVC that initiated the PMVT. We believe that the success of this ablation procedure was mainly due to targeting the origin of this PVC.

The scar area shown in the voltage map does not explain the patient's low cardiac function. A possible explanation is the deleterious effect of 104 consecutive shocks that could further impair the contractile properties of the left ventricle. Hibernating or stunned myocardium post-myocardial infarction is another possibility. Repeat echocardiography did show some improvement in ventricular function.

In conclusion, this case supports the use of catheter ablation as a life-saving rescue procedure in an extreme situation of refractory VT or VF, effectively abolishing the electrical storm.

Correspondence
Dr. R. Sela
Dept. of Cardiology, Western Galilee Medical Center, Nahariya 22100, Israel
Phone: (972-4) 910-7438
email: ron.sela@naharia.health.gov.il

References

1. Connolly SJ, Dorian P, Roberts RS, et al. Comparison of beta blockers, amiodarone plus beta blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: The OPTIC study: a randomized trial. *JAMA* 2006; 295: 165-71.

2. Gatzoulis KA, Andrikopoulos GK, Apostolopoulos T, et al. Electrical storm is an independent predictor of adverse long-term outcome in the era of implantable defibrillator therapy. *Europace* 2005; 7: 184-92.
3. Peichl P, Cihák R, Kozeluhová M, Wichterle D, Vancura V, Kautzner J. Catheter ablation of arrhythmic storm triggered by monomorphic ectopic beats in patients with coronary artery disease. *J Interv Card Electrophysiol* 2010; 27: 51-9.
4. Carbucicchio C, Santamaria M, Trevisi N, et al. Catheter ablation for the treatment of electrical storm in patients with implantable cardioverter-defibrillators: short and long-term outcomes in a prospective single-center study. *Circulation* 2008; 117: 462-9.
5. Enjoji Y, Mizobuchi M, Shibata K, et al. Catheter ablation for an incessant form of antiarrhythmic drug-resistant ventricular fibrillation after acute coronary syndrome. *Pacing Clin Electrophysiol* 2006; 29: 102-5.

Capsule

Parasites make it hard to fight viruses

Microbial co-infections challenge the immune system – different pathogens often require different flavors of immune responses for their elimination. Two teams studied what happens when parasitic worms and viruses infect mice at the same time. Reese et al. (Science 2014; 345: 73) found that parasite co-infection woke up a dormant virus. Osborne et al. (Science p. 517) found that mice already infected with parasitic worms were worse at fighting off viruses. In both cases, worms skewed the immune response so that the immune cells and the molecules they secreted created an environment favorable for the worm at the expense of antiviral immunity.

Eitan Israeli

Capsule

The long and short of hair growth

The length of your eyelashes probably differs from the length of the hair on your head – and unlike your hair, your eyelashes can never reach your shoulders. What controls how long hair can get? To find out, Higgins et al. studied people with a rare disorder called familial trichomegaly, who have very long eyelashes and longer hair on the arms. They found that these people had a mutation in the gene that encodes fibroblast growth factor 5 (FGF5). When human hair follicles produce FGF5, they stop growing hair. Targeting FGF5 could potentially control the growth and rest phases of hair follicles, preventing unwanted hair from sprouting or growing longer lashes and locks.

Proc Natl Acad Sci USA 2014;10.1073/pnas.1402862111

Eitan Israeli

Capsule

Mycobacterium make not-so-painful ulcers

Buruli ulcer disease causes extensive skin lesions and can be deadly, but the lesions themselves don't hurt, which can stop patients from seeking the appropriate care. The pathogen Mycobacterium ulcerans causes Buruli ulcers and also alleviates the pain. Although many scientists studying this disease thought the pathogen caused nerve damage that blocked the pain, Marion et al. show that the mycobacteria produce the mycolactone toxin, which causes analgesia by blocking the function of pain-responsive nerves. The findings could potentially help researchers develop a whole new class of painkillers.

Cell 2014;157: 1565

Eitan Israeli

Capsule

A neuropeptide kills patient's motivation

Chronic pain is not only extremely disturbing and unpleasant, it can also make people depressed and demotivated. What causes these effects? Schwartz and co-researchers discovered that chronic pain causes changes in the way a neuropeptide called galanin affects certain neurons in a brain region called the nucleus accumbens. Galanin influences a variety of behaviors, including feeding and certain aspects of pain. In this case, it depresses synaptic transmission at specific excitatory synapses. It does so, in part, by changing the ratio of subunits of an important receptor protein.

Science 2014; 345: 535

Eitan Israeli

Bilateral Traumatic Optic Neuropathy in an Unconscious Patient: A Diagnostic Challenge

Gilad Allon MD[1], Nir Seider MD[1,2], Eytan Z. Blumenthal MD[1,2] and Itzchak Beiran MD[1,2]

[1]Department of Ophthalmology, Rambam Health Care Campus, Haifa, Israel
[2]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

KEY WORDS: optic neuropathy, trauma, unconsciousness, visual loss, bilateral involvement

IMAJ 2014; 16: 516–517

Traumatic optic neuropathy is the result of an indirect optic injury caused by a contusion necrosis of the nerve fibers related to the shearing forces generated during the trauma, especially in the intracanalicular part of the optic nerve. TON may be a consequence of a relatively mild injury, especially in the case of trauma to the forehead region. TON usually causes immediate and severe visual loss which is unilateral in most cases [1].

In retrobulbar TON the optic disk appears normal at onset and atrophies within 4–8 weeks. In unilateral cases the affected eye demonstrates a relative afferent pupillary defect. Transethmoidal optic canal decompression and/or high dose intravenous corticosteroids were suggested as possible treatments for TON, in addition to follow-up. The International Optic Nerve Trauma study, a non-randomized multicenter comparative analysis of treatment outcomes, did not demonstrate a beneficial effect of either of these treatments [2,3]. The Corticosteroid Randomization After Significant Head Injury (CRASH) study included over 10,000 head injury victims. The study compared the effect of high dose corticosteroids administered within 8 hours of the trauma compared to placebo. The study was aborted because the group treated with corticosteroids was found to have a statistically significant higher mortality rate compared to the placebo group [4]. This means that not only is the treatment with high dose corticosteroids not beneficial in cases of TON, it may in fact be harmful when given to patients with severe head trauma and brain injury.

We present the case of a patient with bilateral TON. Bilateral TON is far less common than unilateral TON but is more meaningful functionally due to the likelihood of severe bilateral visual loss as its final outcome. In this case the diagnosis was difficult because the patient was anesthetized and could not verbalize his visual loss following the trauma and visual acuity could not be examined.

Bilateral involvement is not typical of traumatic optic neuropathy and is more commonly seen in other optic neuropathies such as arteritic optic neuropathy, infectious optic neuropathy in children, and toxic optic neuropathy [5].

TON = traumatic optic neuropathy

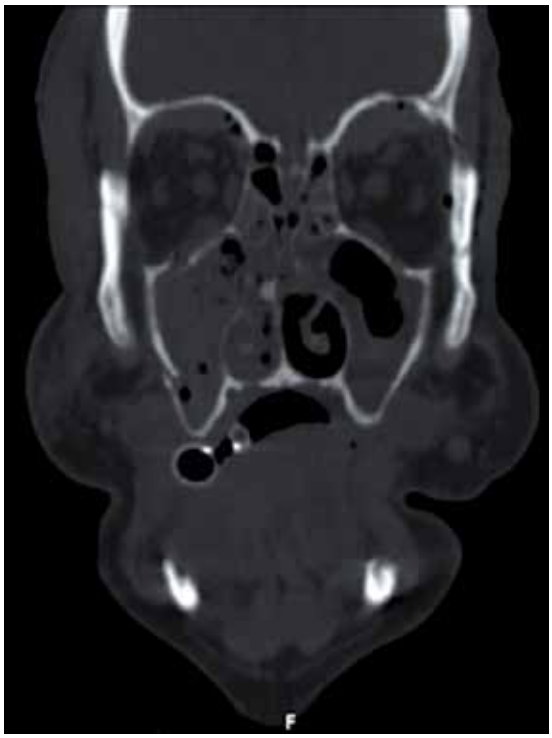
PATIENT DESCRIPTION

A 75 year old Caucasian man experienced direct head, face and chest injury upon falling forward after stumbling on a low fence. His past medical history included lymphoma in full remission for 10 years and no other known ocular or systemic pathologies.

The patient arrived at the trauma unit 30 minutes after the fall. Gross neurologic examination was normal except for dilated unresponsive pupils. The patient was anesthetized and ventilated because of restlessness and nose-bleeding. Computed tomography revealed a subarachnoid hemorrhage without a mass effect. Chest radiograph showed stable lymphadenopathy and a large volume of pleural effusion. A chest drain was inserted into the right pleural cavity. Blood analysis, including complete blood count, clotting function, electrolytes, glucose, renal function, liver function, erythrocyte sedimentation rate and C-reactive protein, showed that all were within normal limits.

Ophthalmic evaluation 4 hours following the trauma, conducted while the patient was anesthetized and ventilated, revealed a deep laceration above the right eyebrow and normal intraocular pressure bilaterally as measured by palpation. Forced duction test was impossible because of soft tissue swelling. Bilateral periorbital hematomas, subconjunctival hemorrhage and chemosis were observed. Both pupils were 8 mm wide and unresponsive to light. The anterior segments of both eyes were otherwise within normal limits. Fundus examination was normal. Head CT showed bilateral medium-sized subperiosteal hematomas in the upper anterior orbits, right orbital floor fracture, left orbital lateral wall fracture and left orbital floor fracture. The eyeball and optic nerve were intact bilaterally. Air in the orbits was found adjacent to all fractures. The hematomas and the air did not compress the optic nerves [Figure].

Ophthalmic evaluation following extubation and cessation of anesthesia 4 days after the original trauma revealed visual acuity of no light perception in both eyes. The intraocular pressure was 15 mmHg in both eyes. Eye movements were full and normal in all directions of gaze in both eyes. Periorbital hematomas, subconjunctival hemorrhages, clear corneas and nor-



Head CT demonstrates subperiosteal hematomas and orbital fractures

mal depth clear anterior chambers were observed in both eyes. Both eyes demonstrated maximal mydriasis unresponsive to light and accommodation. Lenses were clear and fundus examinations appeared normal bilaterally. Magnetic resonance imaging examination showed bilateral subperiostal hematomas in the upper part of the orbits without signs of optic nerve compression. Visual evoked potential showed no visual potentials in response to light stimulation.

The patient was diagnosed with bilateral TON. There was no contact between the hematomas and the nerve, and there was no direct compression on the nerve. The injury was facial, similar to previous reports of TON.

COMMENT

The differential diagnosis of post-traumatic bilateral severe visual loss includes cavernous sinus syndrome and cortical blindness, both of which show typical findings on CT. The CT assists in early diagnosis in the emergency room.

Bilateral severe injury to both optic nerves is a rare event. The case presented here should alert physicians to this rare possibility. Early diagnosis may be beneficial in allowing early treatment in the future. In victims of severe head trauma unable to undergo a visual acuity test a high index of suspicion is the key for early diagnosis.

VEP results confirm the presence of optic neuropathy, while MRI results rule out other possible causes for the observed optic nerve damage. MRI may imply TON by demonstrating facial, intracranial and intraorbital injuries.

Bilateral TON is a rare condition with only a few cases reported in the literature [2]. Bilateral TON should be considered in the differential diagnosis of post-traumatic blindness, even in a case of relatively minor trauma.

No signs on physical examination are expected in the early phase apart from bilateral mydriasis. If TON is suspected and the patient's cooperation is limited, early MRI and VEP studies are indicated. RAPD (relative afferent pupillary defect) examination can provide the diagnosis in the case of unilateral TON; however, this exam is not possible in bilateral TON because the pupils are dilated and not responsive to light.

In an unconscious patient with bilateral TON, decisions are much more complicated. Treatment of TON with steroids is strictly contraindicated in cases where severe head trauma accompanies the ocular damage. In cases without head trauma steroid treatment may be applied, although its benefit is questionable. Further research is required to establish the appropriate treatment approach for this condition.

VEP = visual evoked potential

Correspondence
Dr. G. Allon
Dept. of Ophthalmology, Rambam Health Care Campus, Haifa 31906, Israel
Phone: (972-4) 854-2668
Fax: (972-4) 854-2142
email: drgiladallon@gmail.com

References

1. Carta A, Ferringo L, Salvo M, Biachi-Marzoli S, Boschi A, Carta F. Visual prognosis after indirect traumatic optic neuropathy. *J Neurol Neurosurg Psychiatry* 2003; 74 (2): 246-8.
2. Levin LA, Beck RW, Joseph MP, Seiff S, Kraker R. The treatment of traumatic optic neuropathy: the International Optic Nerve Study. *Ophthalmology* 1999; 106 (7): 1268-77.
3. Cook MW, Levin LA, Joseph MP, Pinczower EF. Traumatic optic neuropathy. A meta-analysis. *Arch Otolaryngol Head Neck Surg* 1996; 122 (4): 389-92.
4. Edward P, Arango M, Balica L, et al., CRASH trial collaborators. Final results of MRC CRASH, a randomized placebo-control trial of intravenous corticosteroids in adults with head injury – outcomes at 6 months. *Lancet* 2005; 365: 1957-9.
5. Pillar G, Toubi E. Vaccination-induced bilateral optic neuritis: rare but existing. *IMAJ* 2012; 14 (11): 690-1.

"I learned long ago that being Lewis Carroll was infinitely more exciting than being Alice"

Joyce Carol Oates (b. 1938), American writer

Immediate Recovery of an "Ischemic Stroke" Following Treatment with Intravenous Thiamine (vitamin B1)

Arnon Blum MD, Michal Ovadia BSc, Gil Rosen MD and Claudia Simsolo MD

Department of Medicine, Poriah Medical Center, Tiberias, affiliated with Bar-Ilan University Faculty of Medicine in the Galilee, Safed, Israel

KEY WORDS: bariatric surgery, sleeve gastrectomy, vitamin B (thiamine), acute ischemic stroke, Wernicke-Korsakoff syndrome

IMAJ 2014; 16: 518–519

Bariatric surgery for weight loss has proven to be a highly efficient solution for morbid obesity, type 2 diabetes mellitus and other related comorbidities. However, the rapid weight loss after the surgery may lead to side effects, namely, vomiting, and vitamin deficiency. Low levels of B complex vitamins may cause neurologic complications such as Wernicke-Korsakoff syndrome and peripheral neuropathy [1,2].

We describe a 59 year old man who, 9 months after bariatric restrictive surgery for weight loss (sleeve gastrectomy), was admitted with a clinical presentation of recent (twice within the previous 5 days) recurrent left-sided acute ischemic cerebral stroke.

PATIENT DESCRIPTION

A 59 year old man of North African Jewish descent was admitted to the Department of Medicine with left-sided motor and sensory deficiency defined as left hemisyndrome. His symptoms had appeared 5 days earlier and he was admitted to another hospital with a diagnosis of a transient ischemic attack; he was discharged with statins and aspirin after resolution of the symptoms. However, 3 days after discharge his symptoms returned and he was admitted to our department.

Examination revealed left-sided motor weakness with sensory deficit and paresthesias and numbness in his left arm and leg, but no signs of extra-pyramidal pathological reflexes. A brain computed tomography and carotid and cerebral arteries CT angiography were normal and did not show any abnormality. Past medical history included type 2 diabetes mellitus and essential hypertension for 12 years, which were resolved following restrictive gastric bariatric surgery (sleeve gastrectomy) 9 months prior to the present admission. Since his operation he was taking multivitamins and exercised daily. Blood tests showed hemoglobin 13.6 g/dl, mean corpuscular volume 85.4 Fl, mean corpuscular hemoglobin 28.6 pg/dl, leukocytes 8340/mm^3 and platelets 227,000/mm^3. Vitamin B12 and folic acid levels were normal (380 pg/ml and 12.6 ng/ml respectively), thyroid hormone levels were normal (free thyroxine 1.29 ng/dl and thyroid stimulating hormone 0.083 mIU/ml). International normalized ratio was 1.37 and partial thromboplastin time 32.10 seconds. T-troponin was normal (0.001 ng/ml). Vitamin B1 level was not measured.

We suspected vitamin deficiency and immediately administered an intravenous injection of thiamine (vitamin B1 100 mg). Surprisingly, towards the end of the vitamin B1 infusion he declared that all his symptoms were gone and that he feels "great" without any motor or sensory deficits, parethesias or numbness. We continued to treat him with intravenous vitamin B1 as well as other B complex vitamins and vitamin B12 sublingually, and folic acid. He felt perfectly well without any neurological deficit and was discharged after 1 week of hospitalization with a diagnosis of a vitamin deficiency-related neurological event mimicking acute ischemic stroke.

DISCUSSION

We describe a patient who was admitted to two different hospitals with the diagnosis of an acute neurologic vascular event [3]. We suspected that the patient suffered from post-gastrectomy Wernicke's encephalopathy due to vitamin B1 deficiency and initiated vitamin supplementation: an intravenous injection of vitamin B1, sublingual vitamin B12 and folic acid. The immediate clinical response towards the end of the vitamin B1 infusion was convincing, with disappearance of the neurological complaints. We believe that the "neurovascular" event was caused by vitamin B1 deficiency. This syndrome has been described in patients undergoing gastric bypass surgery for weight loss who did not continue with vitamin supplementation after the operation. Most patients present with atypical neurological symptoms, which hamper rapid diagnosis [4,5].

A variety of neurological complications have been reported following weight loss surgery. These include Wernicke's syndrome, Korsakoff encephalopathy, neurologic beriberi, Guillain-Barre syndrome, and polyneuropathy [2,4,5]. These disorders usually appear in patients who suffered from vomiting in the first few months after the surgery. In many cases weakness is the primary feature, followed by hyporeflexia, numbness, and extremity pain [5]. Most of the neurologic syndromes appear 6–10 months post-surgery. However, Choi and Scarborough [4] reported an 18 year old

female who presented 4 months post-laparoscopic Roux-en-Y gastric bypass surgery with generalized seizures and stroke, and the brain CT demonstrated a brain infarction [4].

The clinical presentation in our case indicated an acute ischemic stroke (but without any lesions documented by brain CT scan). The administration of intravenous vitamin B1 (100 mg) led to the immediate resolution of all the symptoms.

Correspondence
Dr. A. Blum
Dept. of Medicine, Poriah Medical Center, Tiberias, Lower Galilee 15208 Israel
Phone: (972-4) 665-2688
Fax: (972-4) 665-2929
email: ABlum@poria.health.gov.il

References

1. Scarano V, Milone M, Di Minno MN, et al. Late micronutrient deficiency and neurological dysfunction after laparoscopic sleeve gastrectomy: a case report. *Eur J Clin Nutr* 2012; 66 (5): 645-7.
2. Sekiyama S, Takagi S, Kondo Y. Peripheral neuropathy due to thiamine deficiency after inappropriate diet and total gastrectomy. *Tokai J Exp Clin Med* 2005; 30 (3): 137-40.
3. Streifler JY, Raphaeli G, Bornstein NM, et al. Is the evaluation and treatment of transient ischemic attack performed according to current knowledge? A nationwide Israeli registry. *IMAJ* 2013; 15 (5): 236-40.
4. Choi JY, Scarborough TK. Stroke and seizure following a recent laparoscopic Roux-en-Y gastric bypass. *Obes Surg* 2004; 14: 857-60.
5. Kuhn AL, Hertel F, Boulanger T, Diederich NJ. Vitamin B1 in the treatment of Wernicke's encephalopathy due to hyperemesis after gastroplasty. *J Clin Neurosci* 2012; 19(9): 1303-5.

Capsule

A vitamin's dark side in liver disease

Too much of a good thing can be bad for the liver. Chen et al. found that mice with high levels of thiamine (vitamin B1) in their livers develop fatty liver disease, a metabolic disorder that affects one-third of adults in the United States. A protein called organic cation transporter 1 (*OCT1*) carries dietary thiamine into the liver. When the researchers deleted the Oct1 gene in mice or fed mice a diet low in thiamine, the mice did not develop the disease. OCT1 also carries the diabetes drug metformin into the liver, which might explain why metformin decreases symptoms of fatty liver disease: By competing with thiamine for OCT1, metformin reduces the amount of dietary thiamine that reaches the liver.

Proc Natl Acad Sci USA 2014;10.1073/pnas.1314939111

Eitan Israeli

Capsule

Reprogrammed heart cells set the pace

Pacemakers have revolutionized the care of patients with slow or abnormal heart rhythms, but these devices can break or become infected. With these patients in mind, Hu et al. created biological pacemakers to provide temporary, hardware-free support until a damaged electronic device can be replaced. They inserted a gene for a human transcription factor into heart muscle cells. This gene reprogrammed the cells to become pacemakers – cells that emit rhythmic electrical impulses to drive the beating heart. These biological pacemaker cells restored normal heart rate in pigs with complete heart block, a problem with the heart's electrical system.

Sci Transl Med 2014; 6: 245ra94

Eitan Israeli

Capsule

The latent reservoir of HIV

HIV-infected cells linger even in the face of therapy, and this persistence, termed the latent reservoir, is a major hurdle for curing HIV. HIV integrates itself into the DNA of its host cells. Could that affect the latent reservoir? To find out, Maldarelli and collaborators drew blood from five HIV patients on antiretroviral therapy and analyzed sites where HIV had inserted itself into the blood cells' DNA. In many cases, these sites were not random; HIV often weaseled its way into genes that help cells grow and proliferate. Where HIV integrates into the host genome may thus determine the size of the latent reservoir.

Science 2014; 345; 1790

Eitan Israeli

"So long as you have food in your mouth, you have solved all questions for the time being"

Franz Kafka (1883-1924), Czeck writer regarded as one of the most influential authors of the 20th century. Most of his works, such as *The Metamorphosis*, *The Trial* and *The Castle*, are filled with the themes and archetypes of alienation, physical and psychological brutality, parent-child conflict, characters on a terrifying quest, labyrinths of bureaucracy, and mystical transformations

Amyloid Heart: Heart Failure with Preserved Ejection Fraction – A Rare Cause of a Common Illness

Ronit Koren MD, Oran Tzuman MD and Ronit Zaidenstein MD

Department of Internal Medicine A, Assaf Harofeh Medical Center, Zerifin, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

KEY WORDS: amyloidosis, heart failure, diastolic dysfunction

IMAJ 2014; 16: 520–521

The importance of heart failure with preserved ejection fraction is gaining increasing recognition since it is responsible for half the cases of heart failure. Valvular and pericardial heart diseases, as well as right heart failure and diastolic dysfunction, are etiologies of this entity. Diastolic heart failure is more common in the elderly, in women, and in patients with hypertension. Hypertrophic cardiomyopathy, coronary heart disease, diabetes mellitus, hypertension, restrictive cardiomyopathy and infiltrative cardiomyopathies can all cause diastolic heart failure [1].

Amyloidosis can affect the heart in 50% of patients with systemic amyloidosis. Clinical manifestations include heart failure, syncope, angina, pericardial disease, involvement of the conduction system, and thromboembolism. Since the extent of cardiac involvement is a major prognostic factor in these patients, efforts should be made to reach the diagnosis as early as possible [2].

PATIENT DESCRIPTION

PATIENT 1

A 64 year old woman was admitted to our department after several months of malaise. Her clinical history included poliomyelitis in her childhood resulting in right leg weakness, back surgery at the age of 12 for spina bifida and occasional urinary incontinence with recurrent urinary tract infections since the surgery, multinodular goiter, and monoclonal gammopathy of undetermined significance for 20 years.

On arrival the patient reported weakness and twitching of her legs, loss of appetite and nausea with weight loss of 4 kg over a period of 1 month, dysphagia for fluids and solids, reflux, cough and hoarseness. A thorough ambulatory investigation revealed anemia with hemoglobin 10 g/dl (11.7–15.7 g/dl) and erythrocyte sedimentation rate 84. Thyroid ultrasound demonstrated a multinodular goiter; chest X-ray and abdominal ultrasound were normal. Electrophoresis of her urine showed 2.8 g of immunoglobulin G lambda protein, which correlated well with previous and recurrent studies over the last 20 years since MGUS was first described. On admission the patient showed no sign of distress, and apart from hypoesthesia and weakness of her legs (that were attributed to the polio) her physical examination was normal. Laboratory test revealed creatinine 0.71 mg/dl (0.5–0.9 mg/dl), albumin 30 mg/dl (34–48 mg/dl), protein 80 mg/dl (64–83 mg/dl). Electrolytes and liver function tests were normal. Electrocardiography revealed small complexes. Echocardiography demonstrated left ventricular hypertrophy with diastolic dysfunction. Soon after admission the patient underwent a fat-pad biopsy that was negative for amyloid by Congo-red stain; gastroscopy was scheduled for 2 weeks.

On her second admission, gastroscopy revealed erosive gastritis and duodenitis, and gastric biopsies were also sent for amyloid. Bone marrow biopsy was performed. During this admission she developed leg edema and was discharged although the biopsy results were pending. The gastric biopsy revealed abundant amyloid type AL, and the bone marrow biopsy showed monoclonal plasma cells lambda type with up to 60% cellularity. Blood vessels stained positive for Congo-red. The patient received fluids with allopurinol and started on a regimen of bortezomib, dexamethasone and cyclophosphamide. Dyspnea developed, peripheral leg edema worsened, and chest X-ray was consistent with pulmonary congestion and bilateral pleural effusions. The patient developed atrial fibrillation that was restored to sinus rhythm with amiodarone. She was transferred to the intermediate care chest unit with a diagnosis of amyloid heart. After stabilization she was referred to a tertiary hospital for completion of therapy where she is currently being treated.

MGUS = monoclonal gammopathy of undetermined significance

PATIENT 2

A 75 year old woman was admitted to our department with dyspnea, cough, bilateral leg edema and abdominal distension. The patient had been hospitalized repeatedly in the preceding months due to dyspnea that was attributed to heart failure exacerbations, and each time diuretics were administered but with no improvement. She suffered from hypertension, diabetes mellitus, dyslipidemia, morbid obesity, and diastolic heart failure. Her regular medications included acetylsalicylic acid, furosemide, statins, repaglinide, losartan, and inhalations of ipratropium. Prior to her first admission she underwent cardiac scintigraphy that revealed no ischemia, and chest computed tomography that demonstrated mild pericardial effusion, bilateral

moderate pleural effusion, signs of pulmonary hypertension and a small left lower lobe consolidation. Echocardiography showed left ventricular hypertrophy with mild left atrial enlargement. On admission the patient was tachycardic, tachypneic and dyspneic, and had rales on auscultation, with prolonged expiratory phase and wheezes and severe bilateral leg edema. Blood tests were consistent with creatinine levels of 2.7 mg/dl (0.5–0.9), protein 57 mg/dl (64–83), albumin mg/dl 27 (34–48), and hemoglobin 9.6 g/dl (11.7–15.7). ECG showed sinus tachycardia with no ST changes and inverted T wave in V6.

Chest X-ray revealed pulmonary congestion with bilateral pleural effusion. We found 3.9 g of protein in a 24 hour urine collection. Echocardiography showed diastolic dysfunction with left ventricular hypertrophy and a restrictive pattern. The patient was treated with diuretics and her kidney function deteriorated. She was then transferred to the intensive care cardiac unit and underwent right-sided heart catheterization with a finding of high pulmonary capillary wedge pressure. She became dialysis dependent.

Serum protein electrophoresis showed monoclonality of lambda chains. A fat-pad biopsy was positive for amyloidosis. The patient developed line sepsis and deep vein thrombosis of her right leg followed by heparin-induced thrombocytopenia. Her leg became necrotic and an above-knee amputation was performed. She was then admitted to the intensive care unit but died several days later due to septic shock.

COMMENT

We describe two women with amyloid heart presenting with heart failure and preserved ejection fraction, who differ by presentation and outcome. The 64 year old patient developed rapidly progressive heart failure and atrial fibrillation during treatment with steroids, fluids and bortezomib for systemic AL amyloidosis. The other patient, 75 years old, was hospitalized recurrently because of symptomatic heart failure unresponsive to therapy. This patient was diagnosed too late in the grim pathway of this disease.

AL amyloidosis is the most common and severe among the increasing number of amyloidosis subtypes. It often targets the heart, with an estimated survival of a few weeks after the onset of overt heart failure. Early diagnosis is of the utmost importance to improve survival. Since cardiac involvement determines both survival and treatment tolerability, risk stratification is based on troponin and N-terminal pro-brain natriuretic peptide levels [3]. Bortezomib combinations are the mainstay of therapy with reports of long-term survival, although studies are still lacking. Intermediate risk patients can either undergo autologous stem cell transplantation or combination chemotherapy. High risk patients with markedly elevated levels of NT-Pro-BNP are extremely sensitive to treatment toxicity. Since early diagnosis is of great importance, it is possible that changing the monitoring approach to MGUS will hasten diagnosis and improve survival [4].

Heart failure is a leading cause of morbidity and mortality among hospitalized patients and diastolic heart failure comprises half of those cases. Cardiac amyloidosis should be considered in adults with unexplained heart failure, left ventricular hypertrophy and low voltage on electrocardiography [2].

Correspondence
Dr. R. Koren
9/10 Pilichovsky St., Tel Aviv 69341, Israel
Fax: (972-8) 977-9429
email: ronitkoren@gmail.com

References

1. Aurigemma GP, Gaasch WH. Clinical practice. Diastolic heart failure. *N Engl J Med* 2004; 351 (11): 1097-105.
2. Dubrey SW, Cha K, Anderson J, Chamarthi B, Reisinger J, Skinner M, Falk RH. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. *QJM* 1998; 91 (2): 141-57.
3. Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J Clin Oncol* 2004; 22 (18): 3751-7.
4. Merlini G, Wechalekar AD, Palladini G. Systemic light chain amyloidosis: an update for treating physicians. *Blood* 2013; 121 (26): 5124-30.

NT-Pro-BNP = N-terminal pro-brain natriuretic peptide

Capsule

Regulation of the hepatitis C virus RNA replicase by endogenous lipid peroxidation

Oxidative tissue injury often accompanies viral infection, yet there is little understanding of how it influences virus replication. Yamane et al. show that multiple hepatitis C virus (HCV) genotypes are exquisitely sensitive to oxidative membrane damage, a property distinguishing them from other pathogenic RNA viruses. Lipid peroxidation, regulated in part through sphingosine kinase-2, severely restricts HCV replication in Huh-7 cells and primary human hepatoblasts. Endogenous oxidative membrane damage lowers the 50% effective concentration of direct-acting antivirals in vitro, suggesting critical regulation of the conformation of the NS3-4A protease and the NS5B polymerase, membrane-bound HCV replicase components. Resistance to lipid peroxidation maps genetically to transmembrane and membrane-proximal residues within these proteins and is essential for robust replication in cell culture, as exemplified by the atypical JFH1 strain of HCV. Thus, the typical, wild-type HCV replicase is uniquely regulated by lipid peroxidation, providing a mechanism for attenuating replication in stressed tissue and possibly facilitating long-term viral persistence.

Nature Med 2014; 20: 927

Eitan Israeli

Cat Scratch Disease Associated with Retinal Vein Occlusion

Avi Rubinov MD[1], Eytan Z. Blumenthal MD[1] and Itzchak Beiran MD[1,2]

[1]Department of Ophthalmology, Rambam Health Care Campus, Haifa, Israel
[2]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

KEY WORDS: retinal vein occlusion, cat scratch disease, bevacizumab

IMAJ 2014; 16: 522–523

Cat scratch disease is a zoonotic infection caused by the gram-negative rod *Bartonella henselae*. It is typically a benign, self-limiting, acute febrile illness that is accompanied by regional lymphadenopathy. Ocular manifestations of this disease usually do not involve severe visual loss. Classically, a papule or pustule initially develops at the site of a cat scratch followed by regional lymphadenopathy with or without fever. The affected nodes may become suppurative [1]. In about 5–10% of cases CSD may present with ocular symptoms, ranging from primary oculoglandular syndrome to neuroretinitis and, rarely, vascular occlusions due to localized vasculitis [2]. Neuroretinitis manifests as optic nerve head swelling and the partial or complete formation of a macular star, usually within 2–4 weeks [2]. Systemic antibiotic treatment with doxyline 100 mg twice a day, rifampin 300 mg twice a day, ciprofloxacin 750 mg four times day, or azithromycin 500 mg four times a day is the treatment of choice [2]. The role of systemic corticosteroids in the treatment of CSD is controversial [3].

CSD = cat scratch disease

A 34 year old Caucasian male presented with acute painless loss of vision in his right eye 4 days earlier. Upon examination the best corrected visual acuity was counting fingers 1.5 m in the right eye and 20/20 in the left eye. He had a +2 right relative afferent pupillary defect and the intraocular pressure was 16 mmHg in the right eye and 12 mmHg in the left. Anterior segments were normal in both eyes. Dilated fundus examination showed a central vein occlusion with macular edema and blurred disk margins in the right eye [Figure 1A]. The left eye fundus was normal.

The patient reported a febrile illness of 6 days duration 4 weeks prior to his initial ocular examination and recalled being scratched by a cat several weeks earlier. Laboratory workup was normal except for elevated liver enzymes (alanine and aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase), elevated erythrocyte sedimentation rate, C-reactive protein, complement C3, as well as positive serology for *B. henselae* (immunoglobulin M and G). Herpes simplex type 1, cytomegalovirus and varicella zoster virus were all IgG positive but negative for IgM, suggestive of past infection. An extended coagulation panel was normal. Fluorescein angiography of the right eye demonstrated peripapillary leakage and signs of retinal vasculitis in the inferior half of the retina [Figure 2]. Macular spectral domain optical coherence tomography of the right eye demonstrated severe macular edema [Figure 3].

Antibiotic treatment was started with doxyline 100 mg and rifampin 300 mg twice daily for 1 month. Two intravitreal bevacizumab injections were given to the right eye 1 month apart, resulting in amelioration of the macular edema. Best corrected visual acuity at last follow-up was 20/60. Repeat blood workup showed

Ig = immunoglobulin

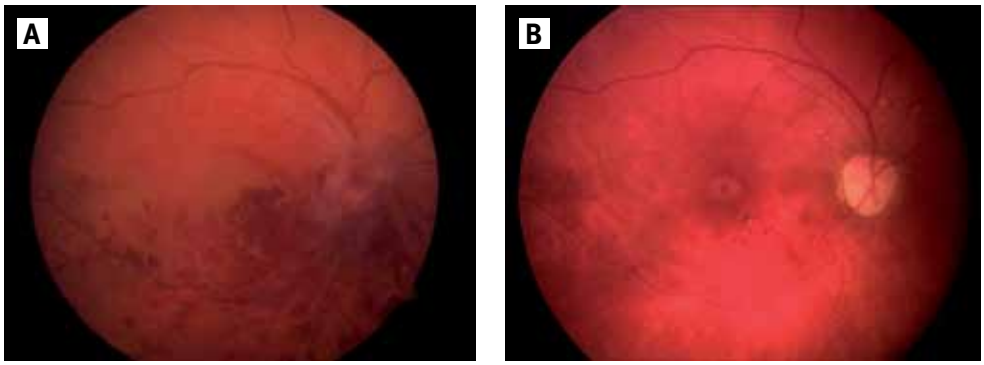


Figure 1. Fundus **[A]** at presentation and **[B]** 5 months later

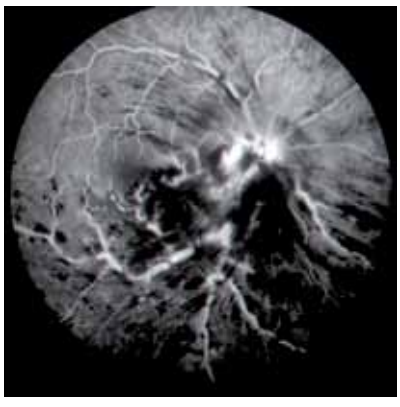


Figure 2. Fundus at presentation showing signs of vasculitis mostly in the inferior half of the retina

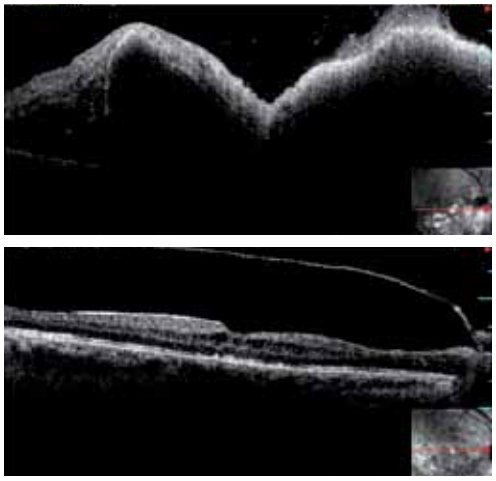


Figure 3. Serial optical coherence tomography report showing marked amelioration of macular edema 5 months after initial presentation

normalization of erythrocyte sedimentation rate and C-reactive protein.

Rarely, vasculitis caused by *B. henselae* leads to a decrease in vision [1]. One reported case of retinal vein occlusion due to *B. henselae* was treated with laser photocoagulation and bevacizumab [1]. The present case supports the use of intravitreal bevacizumab injection for the treatment of macular edema caused by venous occlusion secondary to *B. henselae* neuroretinitis. In young patients with arterial or venous retinal occlusive disease, cat scratch disease should be included in the differential diagnosis.

Correspondence
Dr. A. Rubinov
Dept. of Ophthalmology, Rambam Health Care Campus, Haifa 31096, Israel
Phone: (972-4) 854-2668
email: avi@rubinov.com

References

1. Kalogeropoulos C, Koumpoulis I, Mentis A, Pappa C, Zafeiropoulos P, Aspiotis M. Bartonella and intraocular inflammation: a series of cases and review of literature. *Clin Ophthalmol* 2011; 5: 817-29.
2. Batsos G, Kabanarou SA, Fotiou P, Rouvas A, Xirou T. Retinal arterial occlusive disease in a young patient with cat scratch disease. *Case Rep Ophthalmol* 2013; 4 (2): 87-92.
3. Curi AL, Machado D, Heringer G, et al. Cat-scratch disease: ocular manifestations and visual outcome. *Int Ophthalmol* 2010; 30 (5): 553-8.

Capsule

Two signals for maximal T cell activation

T cell activation requires increased intracellular calcium and the activity of various enzymes, such as the kinase Itk. Wang et al. report that two signals, calcium and lipids, converged on Itk for maximal activation of T cells. The same region of the Itk protein bound to the signaling lipid PI(3,4,5)P3 and to the calcium-binding protein calmodulin. PI(3,4,5)P3 and calmodulin enhanced the binding of each other to Itk. The binding of both PI(3,4,5)P3 and calmodulin was necessary so that T cells produced maximal levels of an inflammatory cytokine, interleukin-17A.

Sci Signal 2014; 7: ra74
Eitan Israeli

Capsule

Putative cis-regulatory drivers in colorectal cancer

The cis-regulatory effects responsible for cancer development have not been as extensively studied as the perturbations of the protein coding genome in tumorigenesis. To better characterize colorectal cancer (CRC) development Ongen et al. conducted an RNA-sequencing experiment of 103 matched tumor and normal colon mucosa samples from Danish CRC patients, 90 of which were germline-genotyped. By investigating allele-specific expression (ASE) the authors show that the germline genotypes remain important determinants of allelic gene expression in tumors. Using the changes in ASE in matched pairs of samples they discovered 71 genes with excess of somatic cis-regulatory effects in CRC, suggesting a cancer driver role. The authors correlated genotypes and gene expression to identify expression quantitative trait loci (eQTLs) and found 1693 and 948 eQTLs in normal samples and tumors, respectively. They estimate that 36% of the tumor eQTLs are exclusive to CRC and show that this specificity is partially driven by increased expression of specific transcription factors and changes in methylation patterns. They also show that tumor-specific eQTLs are more enriched for low CRC genome-wide association study (GWAS) P values than shared eQTLs, which suggests that some of the GWAS variants are tumor-specific regulatory variants. Importantly, tumor-specific eQTL genes also accumulate more somatic mutations when compared to the shared eQTL genes, raising the possibility that they constitute germline-derived cancer regulatory drivers. Collectively the integration of genome and the transcriptome reveals a substantial number of putative somatic and germline cis-regulatory cancer changes that may have a role in tumorigenesis.

Nature 2014; 512: 87
Eitan Israeli

IMAJ • VOL 16 • AUGUST 2014

12th Mediterna International Meeting: What Did we Learn?

Maria João Oliveira[1], Tiago Borges[2] and Carlos Dias[3]

[1]Department of Internal Medicine, Curry Cabral Hospital, CHLC, Lisbon, Portugal
[2]Department of Internal Medicine, São João Hospital Centre, Porto, Portugal
[3]Department of Internal Medicine, Centro Hospitalar São João, Porto, Portugal

IMAJ 2014; 16: 524–526

The12th Mediterna International Meeting took place in Porto, Portugal, from 27 February to 1 March 2014. This annual conference is organized by the Mediterna Association and sponsored by São João Hospital Centre. Different topics in Autoimmunity were discussed over the three days.

The first day of the meeting, 27 February, was dedicated to arthritis, specifically rheumatoid arthritis, risk cardiovascular factors in RA, and the relationship between bone, cartilage and osteoporosis.

WHAT DID WE LEARN ON FEBRUARY 27?

Vasculitis was the theme of the first morning of the meeting. João Viana (Lisbon, Portugal) spoke about the variability in autoantigens, antibodies and measurement tests, resulting in conflicting laboratory results in autoimmunity. The need for standardization and uniformity of these tests to help clinicians in daily practice was also reinforced.

The subject of the second session was pulmonary involvement in sarcoidosis. Athol Wells (London, UK) talked about the lack of understanding of treatment goals in this disease and the difficulty to predict which patients will progress to severe disease. The main treatment indications were noted, as was the unacceptable loss of quality of life and the danger of long-term disability.

Yehuda Shoenfeld (Tel Aviv, Israel) talked about vitamin D as an immunomodulating agent in autoimmune diseases. Several studies have demonstrated the association of vitamin D deficiency, infections and autoimmune diseases. However, discussion was centered on the hypothesis that low vitamin D is a result of the disease and not a cause itself, serving as a biological marker more than a therapeutic one.

The subject of the next two sessions was Sjögren syndrome. Jan Damoiseaux and Jan Willem Cohen Tervaert (Maastricht, The Netherlands) used a clinical case to exemplify the changes in classification criteria in this syndrome, with special attention to the antibodies. The importance of the antibodies in pregnancy leading to two major complications, neonatal systemic lupus erythyematosus and congenital heart block, was emphasized. Cees Kallenberg (Groningen, Netherlands) reviewed the biological therapeutic tools in Sjögren syndrome, presenting several studies that used rituximab, epratuzumab, belimumab and abatacept with promising results.

The afternoon proceeded with Bruno Vidal and Diana Fernandes (Lisbon, Portugal) presenting some preliminary results of their work on nano-inflammation. Animal models of arthritis were used to prove the role of cytokines implicated in this disease in bone structure and in atherosclerosis.

Monika Ostensen (Kristiansand, Norway) highlighted the importance of adequate contraception and pregnancy planning in patients with rheumatic diseases, discussing the need for risk stratification in these patients according to disease activity and antibodies. The contraindications of some drugs in pregnancy were also reviewed, including those that are not used due to lack of knowledge or because of proven teratogenecity.

After a brief revision of thrombocytopenic idiopathic purpura, Ducla Soares (Lisbon, Portugal) spoke about the paradigm shift in diagnosis and treatment. Attention was focused on the importance of decreased platelet production in the pathogenesis of this disease as well as on the thrombopoietin analogues as promising therapeutic targets.

The next subject, presented by Carlo Perricone (Rome, Italy), was ASIA syndrome, an autoinflammatory syndrome induced by adjuvants. He discussed the current data which support the role of various environmental factors in the pathogenesis of immune mediated diseases. Some examples were given, such as Gulf War syndrome, siliconosis and post-vaccination syndrome.

Pedro Vita (Porto, Portugal) concluded the first day of the meeting with a talk on RA treatment, with particular emphasis on interleukin-6 inhibition with tocilizumab. Some studies demonstrating the superiority of tocilizumab in monotherapy and in controlling systemic manifestations of the disease were presented.

WHAT DID WE LEARN ON FEBRUARY 28?

Systemic sclerosis was the topic of the morning and part of the afternoon. Luc Mouthon (Paris, France) focused on muscle involvement in Systemic sclerosis (SSc), naming the three components that are responsible for its pathogenesis: vascular hyperreactivity, fibrosis, and autoantibodies. Skeletal involvement in SSc is frequent, but often mild and related to diffuse cutaneous

RA = rheumatoid arthritis

SSc = systemic sclerosis

Table 1. Risk factors for digital ulcers in SSc

	dSSc	Male	Scl70	Early age at RP onset	ESR	Pulmonary disease	GI disease	Disease duration	mRSS	No vasodilator therapy
DAS-DU	+									
DUO Registry	+	+	+	+		+	+			
DNSS Registry		+	+	+		+	+			
Inter AIR Registry		+		+					+	
CSRG Registry			+	+		+		+	+	
EUSTAR group	+		+	+						
Hachulla et al.				+					+	+
Sunderkotter et al.		+	+	+	+	+	+			
Tiev et al.		+		+	+	+			+	
Caramaschi et al.										+

dSSc = diffuse systemic sclerosis, RP = Raynaud's phenomenon, ESR = erythrocyte sedimentation rate, GI = gastrointestinal, mRSS = modified Rodnan skin score, DAS-DU = Scleroderma Digital Ulcers Database, DUO = Digital Ulcers Outcome, DNSS = German Network for Systemic Sclerosis, CSRG = Canadian Scleroderma Research Group, EUSTAR = EULAR Scleroderma Trial and Research

SSc and anti-PM/Scl antibodies. Whenever skeletal muscle is involved, cardiomyopathy must be excluded. Moreover, muscle biopsy is warranted not only for diagnostic purposes but also for prognosis, since inflammation and necrosis predict response to treatment, while patients with non-inflammatory myopathy should not be treated with steroids.

Bodo Grimbacher (London, UK) spoke of the high prevalence of autoimmunity in patients with primary immunodeficiencies and that this immune dysregulation may manifest only during adulthood. LRBA mutations occur in common variable immune deficiency, establishing a possible link between autoimmunity and autophagy. On the other hand, autoimmune polyendocrine syndrome type 1 was mentioned to illustrate the role of cell cytokines in fungal control.

At the roundtable of the day, activity markers of SSc were discussed. Ignacio Martin Suárez (Huelva, Spain) listed which biomarkers are being considered in SSc and highlighted the need for validated biomarkers for diagnosis, disease classification and evaluation of organ involvement and therapeutic response. Isabel Almeida (Porto, Portugal) explained how activity can be evaluated in cutaneous and articular involvement, using tools as the durometer, the modified Rodnan skin score, ultrasonography or magnetic resonance imaging. Maria Jesús Castillo Palma (Sevilla, Spain) did the same for cardiopulmonary involvement, pointing out that damage occurs early in SSc and that lung and heart involvement are the major causes of SSc-related deaths.

Carlos Aguiar (Lisbon, Portugal) presented atherosclerosis as an inflammatory disease, emphasizing that the management of autoimmune diseases should address global cardiovascular risk since it may reduce coronary artery disease and potential morbidity. Examples were also given of how cardiovascular risk is increased in disorders such as psoriasis, RA or SLE.

Cândida Abreu (Porto, Portugal) talked about infection and vaccination by zoster virus in the elderly and in autoimmune diseases and showed how the number of specific memory T cells decrease with age below a threshold, which represents a significant risk for zoster infection. The complications of zoster infection were listed, and preventing infection through vaccination in patients aged 60 years or older was recommended.

After lunch, Ivone Silva (Porto, Portugal) described which risk factors are consistently associated with the development of digital ulcers [Table 1], the role of angiogenesis biomarkers, and how nailfold videocapillaroscopy patterns and scores may be used as an outcome measure. The treatment of digital ulcers was highlighted, through pain management, antibiotics, vasodilatation, tissue repair, iloprost for active ulcers, and either bosentan or iloprost for ulcer prevention.

Rui Baptista (Coimbra, Portugal) reinforced the idea that current available therapies for pulmonary hypertension are effective even in mildly symptomatic SSc patients; screening algorithms were explained in general, including the DETECT study which is a sensitive, non-invasive tool for detection of PAH. It should be remembered that all patients with SSc need to be screened for PAH which, if detected, will require right heart catheterization.

The rest of the afternoon was dedicated to antiphospholipid syndrome and SLE. Jo Berden (Nijmegen, The Netherlands) summarized the role of nucleosome as the driving autoantigen in SLE and how binding mechanisms occur. In clinical practice, anti-nucleosomes are more sensitive than anti-dsDNA with equal specificity, and the presence of nucleosome/autoantibody complexes is associated with the onset and exacerbations in lupus nephritis.

SLE = systemic lupus erythematous

PAH = pulmonary hypertension

Anisur Rahman (London, UK) brought the latest news about mechanisms of thrombosis in APS, based on the fact that the effects of antiphospholipids are not confined to thrombosis and that β2-glycoprotein 1 is a critical antigen. Other drugs besides anticoagulants may play a role in APS treatment, not only those that are already available (rivaroxaban, hydroxicloroquine, rituximab and complement inhibitors), but also new therapies such as DV inhibitors, DI variants, signaling inhibitors and TLR blockers.

George Bertsias (Crete, Greece) stressed the need for therapeutic targets for SLE to be as available as for other chronic diseases, giving examples of possible candidates. One should prevent damage to ensure long-term survival and this can be accomplished by lowering disease activity, preventing flares by using hydroxicloroquine, avoiding long exposures to steroids, assessing comorbidities, and improving quality of life. On the other hand, clinically stable and inactive SLE should be managed with watchful waiting.

APS = antiphospholipid syndrome

Finally, genetic factors in primary biliary cirrhosis were discussed by Pietro Invernizzi (Milan, Italy) who explained their importance in familial clustering, high concordance in monozygotic twins, sex chromosome defects (X-monosomy and Y-chromosome loss in males) and polymorphisms. In addition, the concept of a "second wave" represented by genome-wide association studies was highlighted because it has increased the genetic list, contrasting with the pre-GWAS era when only HLA-DRB1*08, HLA-DRB1*11 and HLA-DRB1*13 were known.

The next meeting on autoimmune diseases in Porto will be 12–14 February 2015.

Correspondence
Dr. Carlos Dias
Head, Dept. of Internal Medicine, Centro Hospitalar São João, 4200–319 Porto, Portugal
email: carlosdias@medinterna.org

GWAS = genome-wide association studies

Capsule

Hearing sounds can improve your vision

Sounds can draw our attention to a specific location and make us aware of something that we may otherwise overlook. But do auditory cues improve the function of other senses, such as sight? To find out, Feng et al. recorded the electrical activity in people's brains when they were seeing and hearing stimuli. The researchers played a sound from one side and then quickly flashed a visual stimulus either on the same side as the sound or on the opposite side. When the sound and the visual stimulus came on the same side, electrical activity in the brain increased and people correctly identified the visual stimulus more often. This suggests that sound helps the brain process co-localized visual input.

J Neurosci 2014; 34: 9817

Eitan Israeli

Capsule

Tumorigenicity and genetic profiling of circulating tumor cells in small-cell lung cancer

Small-cell lung cancer (SCLC), an aggressive neuroendocrine tumor with early dissemination and dismal prognosis, accounts for 15–20% of lung cancer cases and ~200,000 deaths each year. Most cases are inoperable, and biopsies to investigate SCLC biology are rarely obtainable. Circulating tumor cells (CTCs), which are prevalent in SCLC, present a readily accessible 'liquid biopsy'. Hodgkinson et al. show that CTCs from patients with either chemosensitive or chemorefractory SCLC are tumorigenic in immune-compromised mice, and the resultant CTC-derived explants (CDXs) mirror the donor patient's response to platinum and etoposide chemotherapy. Genomic analysis of isolated CTCs revealed considerable similarity to the corresponding CDX. Most marked differences were observed between CDXs from patients with different clinical outcomes. These data demonstrate that CTC molecular analysis via serial blood sampling could facilitate delivery of personalized medicine for SCLC. CDXs are readily passaged, and these unique mouse models provide tractable systems for therapy testing and understanding drug resistance mechanisms.

Nature Med 2014; 20: 897

Eitan Israeli

"I have one share in corporate Earth, and I am nervous about the management"

E.B. White (1899-1985), American writer and co-author of the English language style guide, *The Elements of Style*, commonly known as "Strunk & White." He also wrote books for children, including *Charlotte's Web*, *Stuart Little* and *The Trumpet of the Swan*

LANCET'S UNETHICAL BEHAVIOR

In light of the recent publication of the biased and unethical letter in *The Lancet*, we urge that this letter be retracted and that the editor who cleared it for publication step down. The editor R. Horton has proved once and again that he is prejudiced against Israel, and he is using *The Lancet*, a medical journal, for political ends. Horton is a member of the Lancet Palestinian Health Alliance at Bir Zeit University, and of course has conflict of interests in this matter. David Feifel, Professor of Psychiatry at the University of California, San Diego, summed up the facts pertaining to this issue and it merits citing in *IMAJ*.

> The letter, "An Open Letter for the People in Gaza" [1], is a highly partisan, demonstrably inaccurate and defamatory representation of the violence now taking place between the Israel Defense Forces and the terrorist group Hamas. The authors declared they had no competing interests, but Stall et al. [2] pointed out that two of the co-authors have affiliations with pro-Palestinian non-governmental organizations (NGOs). In fact, that barely scratches the surface in terms of the potentially biasing conflicts. For example, the letter's first author, Paola Manduca, receives funding from several anti-Israel NGOs including Interpal [3], which has been designated a terrorist entity by the governments of the United States, Canada and Australia [4]. U.S. Federal authorities describe the organization as a global clearing-house channeling money to Hamas, and a BBC investigation came to the same conclusion [5-7]. Interpal is a founding member of the so-called Union of Good, an umbrella organization that funds Islamic terrorists in Gaza [8]. Its leader, Yussef al-Qaradawi, is a notorious jihadist who has publically lauded Hitler for "putting Jews in their place" and has said of the Israeli-Palestinian conflict: "We must plant the love of death and the love of martyrdom in the Islamic nation." The organization actively encourages Palestinian children to become martyrs and suicide bombers [5-7]. Manduca not only receives funding from Interpal but also raises money for it [9].
>
> Is it any wonder then that Manduca is a signatory to the "Appeal for the removal of Hamas from the EU terror list" [10] and that her co-author, Mads Gilbert, is on record for supporting terror attacks against civilians including the 11 September 2001 attacks on the World Trade Center [11] which took the lives of nearly 3000 innocent civilians? These revelations totally belie the authors' description of themselves as merely "doctors and scientists, who spend our lives developing means to care and protect health and lives." Are some of them, in fact, doctors and scientists with intellectual and financial links to terrorist entities with genocidal agendas? In violating the Lancet's published Declaration of Interests policy [12], Manduca et al. deprived Lancet readers of crucial contextual information with which to judge their polemical correspondence.
>
> Considering these egregious omissions, The Lancet must immediately retract the Manduca letter in accordance with its own stated policy on such violations. Anything less would only add to the damage that has been done to Lancet's credibility by its editorial decision to publish this scurrilous correspondence which has been likened to a blood libel against the people of Israel [13,14]. This decision also violated both Elsevier's editorial policy of avoiding material that contains inaccuracy, bias and defamation [15], and the guidelines of the International Committee of Medical Journal Editors (ICMJE) – of which Lancet is a member – which states: "editors must make an effort to screen discourteous, inaccurate, or libelous comments" [16]. Indeed, in two previous letters we pointed to Lancet's unethical behavior and its bias against Israel for using a medical journal for its own political agenda [17,18]. In light of these breaches of ethical behavior, the editor who allowed this publication, R. Horton, should step down.

E. Israeli PhD[1], J. Shemer MD[2], G. Keren MD[3] and Y. Shoenfeld MD[1,4]
[1]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

PS. We are adding two references that were recently published in *The Lancet* [19,20].

References

1. Manduca P, Chalmers I, Summerfield D, Gilbert M, Ang S; on behalf of 24 signatories. An open letter for the people in Gaza. *Lancet* 2014; 384: 397-8. Published online July 22, 2014.
2. Stall NM, Berger PB, Ray JG, Bogler T, Bell C, on behalf of 1234 Canadian physicians. Open letter for the people in Gaza – more than a military conflict. *Lancet* 2014; 384: 398-9.
3. Manduca P, Naim A, Signoriello S. Specific association of teratogen and toxicant metals in hair of newborns with congenital birth defects or developmentally premature birth in a cohort of couples with documented parental exposure to military attacks: observational study at Al Shifa Hospital, Gaza, Palestine. *Int J Environ Res Public Health* 2014; 11 (5): 5208-23.
4. U.S. Designates Five Charities Funding Hamas and Six Senior Hamas Leaders as Terrorist Entities, Department of Treasury, 8/22/2003 http://www.treasury.gov/press-center/press-releases/Pages/js672.aspx Page Content
5. Levitt M. Hamas: Politics, Charity, and Terrorism in the Service of Jihad. New Haven/London: Yale Press, 2006: 157-64; http://books.google.com/books?id=Min9VpiravsC&pg=PA158&dq=interpal&hl=en&sa=X&ei=DATeU9y3FoSCogTX9YG4BQ&ved=0CCgQ6AEwAQ#v=onepage&q=interpal&f=false
6. http://news.bbc.co.uk/2/hi/programmes/panorama/5234586.stm
7. http://news.bbc.co.uk/panorama/hi/front_page/newsid_7915000/7915916.stm
8. US Department of Treasury, Treasury Designates the Union of Good, 11/ 12 /2008 http://www.treasury.gov/press-center/press-releases/pages/hp1267.aspx
9. https://groups.google.com/forum/#!topic/sempreconcontrolaguerra/jF_p5vbTQpU
10. Appeal for the removal of Hamas from the EU terror list; http://www.informationclearinghouse.info/article22138.htm
11. http://www.dagbladet.no/nyheter/2001/09/30/

284907.html

12. The Lancet Information for Authors. http://www.thelancet.com/lancet-information-for-authors/statements-permissions-signatures#conflicts-of-interest
13. Israel advocates get little space to respond to epistle in 'The Lancet', *Jersusalem Post*, http://www.jpost.com/Health-and-Science/Israel-advocates-get-little-space-to-respond-to-epistle-in-The-Lancet-369648
14. Cravatts R. Academic Lies and Distortions in the Cognitive War Against Israel. SPME http://spme.org/spme-research/academic-lies-distortions-cognitive-war-Israel/18116/ | SPME
15. Reed Elsevier Editorial Policy. http://www.reedelsevier.com/corporateresponsibility/Documents/policies/reed-elsevier-editorial-policy.pdf
16. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, Updated February 2006; International Committee of Medical Journal Editors http://www.icmje.org/recommendations/archives/2006_urm.pdf
17. Israeli E, Shoenfeld Y. The Lancet against Israel. *IMAJ* 2013; 15: 2.
18. Israeli E, Shoenfeld Y, Zimlichman E. *The Lancet* against Israel – again. *IMAJ* 2014; 16: 403-4.
19. Konikkoff T, Konikoff FM, Shoenfeld Y. Israel-Gaza conflict. *Lancet* 2014; 384 (9942): 491.
20. Blachar Y. Israel-Gaza Conflict. Lancet 2014; 384 (9943): 579-80. doi: 10.1016/S0140-6736(14)61310-6. Epub 2014 Aug 11. No abstract available. PMID: 25123775.

My Dear Friends,

We know each other as friends and colleagues, but this time I am writing to you as Gabriel Gurman, an Israeli citizen living in the south of the country. I decided to write to you because in the last month something quite unfortunate has occurred in our profession.

As you know, a small group of medical colleagues decided to publish in The Lancet an "open letter" to the people of Gaza, in which *"on the basis of our ethics and practice, we are denouncing what we witness in the aggression of Gaza by Israel."* For someone who does not know the reality on the ground, this open letter would seem a sincere manifestation of rage against the inhuman attitude of Israel towards Gaza's citizens and a declaration of solidarity with the poor, the oppressed and the victims of an unjustified aggression against a defenseless population by a cruel army.

It is not my intention to convince you to the contrary. You can check the facts and reach your own conclusions. I would just like to tell you what has been happening here in southern Israel over the past 9 years (or 14, depending on how one starts counting). For years, and without respite, we have been attacked. In 2001, 501 rockets were fired from Gaza into Israel. By 2008 this number had increased to 3278. The years in between were no more peaceful: from 661 rockets in 2002 to 2427 in 2007. This is the daily reality for those, like me, who live here.

The question is twofold: who is it that attacks us on a daily basis and why? The answer is complicated, but also very simple. Open the Hamas Charter of 1988. The full text can easily be found on the internet. The main goal of Hamas, as they themselves write, is to annihilate Israel and its population, to the very last Jew.

I am 75 years old, but I know my history. Hitler wanted to occupy Russia, but not kill *all* Russians. Stalin occupied Eastern Europe and transformed each country into a communist state, destroying their culture, civilization and economy and killing thousands and thousands of opponents, but he never wished to annihilate all the citizens of any of these countries. For the first time in modern history an ethnic group declares, in writing, that its core goal is to completely wipe a country entirely off the map and kill every citizen of Jewish origin.

But the Jews are not the only victims of this fanatic, fundamentalist, terror organization. The first and most tragic victims of Hamas' brutality are the citizens of Gaza themselves. As one of their leaders claimed, "The difference between us and the Israelis is that "they fight to live while we fight to die." While Israel was taking care of its citizens by creating effective means of defense, Hamas was building a cruel reality for Gazans characterized by:

- Merging its offensive weaponry among civilian population centers, knowing full well that innocent civilians would be the inevitable victims of Israeli retaliation
- Forcing civilians to defend Hamas military facilities
- Transforming every non-military building (houses, hospitals, UN schools, mosques) into caches for weapons, especially missiles
- Threatening Gaza residents against following IDF warnings (flyers, phone calls, etc.) to immediate evacuate buildings targeted for destruction.

The results of the last 45 days of combat in the south of Israel and the Gaza Strip show:

- On the Israeli side, almost 3000 missiles launched over the whole country, with three citizens killed
- In Gaza, some 5000 IDF air attacks, more than 2000 people killed, mostly citizens, women and children, most of whom lived in buildings transformed into arsenals and deposits for weaponry, and who did not have any means of defending themselves.

International law calls for Israel to attack proportionately. But international law did not envision an enemy that glorifies death and embraces it for its citizens. Nor does the terrible toll that Gazans have suffered make Israel's fight against Hamas unfair, just as NATO's offensive against Serbia was not unjust because of the civilian death toll that American air attacks inflicted.

My dear friends, I am not a politician, nor a strategist. I will not tell you about the danger that fundamentalist Islam represents to our civilization. But what I would ask you to do is write a letter to Dr. Richard Horton, editor of the Lancet, that esteemed scientific journal which published an article full of hate and bias, placing blame squarely at the hands of Israel and not with one of the most dangerous terrorist organizations in the world today.

In my opinion a doctor dedicated to his or her patient is someone who, before drawing a conclusion, checks the facts, makes a differential diagnosis, reads the pertinent literature and only then recommends a treatment. That is what I am

expecting from each of you and am sure you will not let me down.

G.M. Gurman MD
[gurman@bgu.ac.il]
Mayanei Hayeshuah Medical Center, Bnai Brak, and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

To the Editor:

We, a group of doctors and directors of hospitals in northern Israel, write this letter in response to the "Open Letter to the People of Gaza" ('the letter') published electronically in *The Lancet* on 23 July 1914. We too work every day for the saving of lives without respect to race, creed or nationality. In our hospitals about 1000 casualties of the Syrian civil war have been given medical treatment of the highest dedication and standard, without charge [1-4]. It is to be noted with sadness that the authors of the letter have not yet found time to vent their anger and concern regarding this particular cruel war that has so far cost more than 190,000 lives [1].

We, who live and work in a democracy and have various political views, are united in our opinion that the above "letter" contains disinformation and is deliberately and dishonestly misleading for the otherwise uninformed reader. The distortions are beyond anything reasonably expected of medical professionals.

Residents of Gaza have natural human rights including a dignified life, prosperity, freedom of movement and education. These they are daily denied by a ferociously violent terrorist regime (Hamas is so classified by the UN, EU, U.S. and others) that suppresses women, Christians, homosexuals and displays contempt for democratic values. Hamas has its declared object, as its own charter clearly states, the destruction of the State of Israel and killing of Jews [5,6]. The letter's authors do not mention or condemn, even in passing, the endless missile attacks (at the time of writing over 2500 rockets and missiles have been launched at Israel during the last two weeks) on cities and innocent citizens. Every missile is a war crime. This shows a lack of balance which is alien to a scientific journal. It shows the double standards adopted by the letter's authors, who claim to be motivated by moral, ethical, and humanistic considerations.

Displays of rage against Israel, whose three young boys were kidnapped and brutally murdered by Hamas at the outset of this tragedy, are misplaced and simply prolong the enormous damage sustained by the Palestinian population of Gaza, all of which is Hamas' responsibility. The attempt of the letter's authors to grant legitimacy to a terror group that sanctions these acts is unacceptable, especially in a respected medical journal.

A medical journal is also not a suitable arena for geopolitical debate, but we believe the general reader should know that in 2005 Israel unilaterally evacuated all Israeli civilians and military personnel from Gaza. Until Hamas took control in a military coup in 2007 [7] (in which nearly 1000 Palestinians were killed by Hamas), the residents of Gaza carried on close economic and trade relations with Israel. Many Gazans enjoyed (and many doctors from our hospitals were personally involved in) medical treatment in clinics and hospitals in Israel. The so-called military blockade on Gaza stems solely from Israel's need to prevent the entry of weapons and terror-tunnel building materials. This is crucial, since materials supposed to be used for civilian building have been diverted to the extensive network of underground military bunkers and terror tunnels throughout Gaza, currently being exposed and destroyed. Egypt has restricted its border for the same reasons [8,9].

Israel continues to supply food, medicines and other necessities, and continues to supply electricity to Gaza. Israel has opened a field hospital at the "Erez" crossing for the benefit of innocent Gazans and permits medical assistance in every way. Against this, hospitals in Gaza like Wafa Hospital have been documented as firing stages against Israeli forces [10]. In addition, in three cases missile caches have been found in the precincts of UNRWA schools [11,12], a finding that has been condemned by the UN Secretary-General. Hamas' refusal to agree to many cease-fires during the campaign reveals its murderous nature and cynical disregard for the lives of its own people. We are in the face of an unprecedented strategy designed to bring about the deaths of its own innocent people. This is a war crime without a name. Israel does not impede any third party (including Turkey) from importing supervised humanitarian aid into Gaza. One can only imagine the benefit the billions of dollars that have been given by donors to Gaza could have brought to Gazans if Hamas had not been the rulers.

We are saddened and pained by all victims of violence, especially children and women and other civilians who have been killed and injured in an unnecessary war that was forced on Israel by Hamas. We believe that when the world realizes that Israel is not fighting against Gazans but rather against a brutal Islamic terrorist organization that has taken an entire civilian population hostage, the true liberation of Gaza will begin.

V. Volach-Mena MD[1], O. Embon MD[2], E. Onn MD[3], M. Barhoum MD[3,4] and A. Luder MD[1,4]
[luder.a@ziv.health.gov.il]
[1]Ziv Medical Center, Safed, Israel
[2]Padeh Medical Center, Poriya, Israel
[3]Galilee Medical Center, Nahariya, Israel
[4]Faculty of Medicine in the Galilee, Bar Ilan University, Safed, Israel

References

1. On Israeli Humanitarian Aid to Syrians. American Thinker Feb. 11 2014. http://www.americanthinker.com/2014/02/on_israeli_humanitarian_aid_to_syrians.html (accessed July 30, 2014).
2. Israelis treating Syria's wounded confront complex injuries, cultural gaps. Jewish Telegraph Agency April 9, 2014. http://www.jta.org/2014/04/09/news-opinion/israel-middle-east/israelis-treating-syrias-wounded-confront-complex-injuries-cultural-gaps#ixzz38yh0MBQM (accessed July 30, 2014).
3. As Israeli doctors aid Syrians, humanitarianism trumps geopolitics. *Los Angeles Times* Feb 6, 2014. http://articles.latimes.com/2014/feb/06/world/la-fg-israel-syria-20140206 (accessed July 30, 2014).
4. Ziv Medical Center treats Syrian casualties. https://www.youtube.com/watch?v=qEll5kTC2S

Y&feature=youtube_gdata_player (accessed July 30, 2014).

5. Hamas Charter Information Division, Israel Foreign Ministry – Jerusalem. http://fas.org/irp/world/para/docs/880818a.htm (accessed July 30, 2014).
6. Hamas Charter Ariel Center for Policy Research. http://www.acpr.org.il/resources/hamascharter.html (accessed July 30, 2014).
7. Hamas takes control of Gaza. The Guardian June 15, 2007. http://www.theguardian.com/world/2007/jun/15/israel4 (accessed July 30, 2014).
8. Gunmen kill 21 Egyptian soldiers in checkpoint attack. *Yahoo News* July 19, 2014. http://news.yahoo.com/gunmen-kill-15-egyptian-soldiers-checkpoint-attack-171849046.html (accessed July 30, 2014).
9. Sinai Border: Hamas Kills 3 Egyptian Soldiers; Egypt Arrests 150 Hamas Operatives. *The Algemeiner* July 9, 2014. http://www.algemeiner.com/2013/07/09/sinai-border-hamas-kills-3-egyptian-soldiers-egypt-arrests-150-hamas-operatives (accessed July 30, 2014)Top of Form.
10. Wafa Hospital in Gaza used as fire base. Ynet July 25, 2014. www.ynetnews.com/headlines/1,7340,L-3082-88257,00.htm (accessed July 30, 2014).
11. UNRWA condemns placement of rockets, for a second time, in one of its schools. http://www.unrwa.org/newsroom/press-releases/unrwa-condemns-placement-rockets-second-time-one-its-schools (accessed July 30, 2014).
12. UNRWA admits finding more rockets hidden in Gaza school; second time in a week. The Algemeiner July 30, 2014. http://www.algemeiner.com/2014/07/22/unrwa-admits-finding-more-rockets-hidden-in-gaza-school-second-time-in-a-week (accessed July 30, 2014).Ariel Center for Policy Research (ACP

Capsule

Bad cholesterol: Bad for bacteria, too?

Why do viral infections, such as the common cold, leave people more susceptible to bacterial pneumonia? One reason is that type I interferons, secreted proteins that initiate antiviral immune responses, suppress other inflammatory molecules that protect against bacterial infection. Reboldi et al. investigated how this suppression occurs on a molecular level in mice. Interferons stimulated expression of a particular enzyme that catalyzes the production of the oxysterol 25-hydroxycholesterol (25-HC). 25-HC inhibits the function of the transcription factor SREBP, which normally drives expression of the gene that encodes interleukin-1, a secreted inflammatory protein with wide-ranging antibacterial functions.

Science 2014; 345: 679

Eitan Israeli

Capsule

A not so random integration for HIV

Even in the face of a cocktail of antiretroviral drugs, HIV manages to hang on. It does so by integrating its own genome into those of host cells, where it persists in a latent state. To better understand this process, Wagner et al. determined the sites where HIV integrated into three HIV-infected patients treated with antiretroviral drugs for more than a decade. They found an over-representation of sites where HIV integrated into genes associated with cancer and cell proliferation. Also, multiple cells in the same individual harbored the same integration sites. This suggests that integration into specific genes may drive cell proliferation and viral persistence.

Science 2014; 345: 570

Eitan Israeli

Capsule

Better blood thinner, without bleeding

Blood thinners prevent heart attacks and strokes by making it harder for blood to clot, but these drugs can put patients at risk of dangerous bleeding. Now Moeckle et al. describe an enzyme that can prevent clots without this perilous side effect. They engineered the enzyme apyrase to remove the pro-clotting molecule ADP from the blood quickly. In dogs and mice with heart attacks, apyrase stopped blood cells from aggregating, the first step in forming a clot. At the highest dose, the animals suffered less heart damage and did not bleed excessively. In comparison, clopidogrel, a blood thinner used currently in patients, protected the heart less well and did cause excessive bleeding.

Sci Transl Med 2014; 6: 248ra105

Eitan Israeli

"People are like stained glass windows: they sparkle and shine when the sun is out, but when the darkness sets in their true beauty is revealed only if there is a light within"

Elisabeth Kubler-Ross (1926-2004), American psychiatrist, a pioneer in near-death studies and the author of the groundbreaking book *On Death and Dying* (1969), where she first discussed her theory of the five stages of grief