Atrial Fibrillation in the Clinical Environment at the Beginning of the 21st Century

Shimon Rosenheck MD FACC FESC FHRS

Arrythmia Therapy Center, Heart Institute, Hadassah-Hebrew University (Ein Kerem Campus), Jerusalem, Israel

KEY WORDS: atrial fibrillation, rhythm control, rate control, cardioversion, emergency department

IMAJ 2012; 14: 313–314

A vast amount of knowledge has been accumulated on atrial fibrillation during the last two decades. From among 24,078 publications in 2000 until now, only 452 (0.019%) mention the words "emergency department" (PubMed) and very few describe the approach in an ambulatory cardiology clinic. Only a few publications (less than 100) question the epidemiology of the patients presenting with atrial fibrillation in the emergency department. For this reason the study published by Antoneli and colleagues in this issue of *IMAJ* may add to our understanding of the profile and behavior of patients with this arrhythmia in a clinical environment [1]. Their study describes the clinical presentation of patients with the primary diagnosis of atrial fibrillation in the ambulatory cardiology clinic at a large regional medical center.

Atrial fibrillation is the most common type of arrhythmia, affecting 0.89% of the population in the United States and probably anywhere in the industrialized world [2,3]. In the third world, atrial fibrillation is still frequent because of the high prevalence of rheumatic valvular disease [4]. In the western world the main etiology is hypertension [5].

A patient may be referred to the emergency room either because of a new onset of symptomatic atrial fibrillation persisting for at least 1–2 hours, or one of the chronic forms, i.e., paroxysmal or persistent. Patients with chronic permanent atrial fibrillation are mainly encountered in the outpatients' clinic or medicine ward as this is the sole diagnosis, and less in the emergency room. There is a continuous increase in the prevalence of atrial fibrillation, and the number of patients is expected to double by 2050 [3]. Parallel to the increase in frequency of total referrals to the emergency department, the number of patients presenting with atrial fibrillation is also continually increasing [6]. However, in the USA the percentage of patients admitted to hospital with atrial fibrillation was found to be constant during 10 years. This discrepancy suggests that the number of patients with atrial fibrillation treated in the emergency department is also continually increasing. Several reports from different regions in the world describe their treatment policy for patients with atrial fibrillation in the emergency department [7-11].

The approach to these patients in the emergency department is determined by the patient's clinical condition, duration of the fibrillation episode, previous medical treatment, associated clinical conditions, previous medical history and previous history of atrial fibrillation. If the patient is unstable, accelerated processing and termination of the atrial fibrillation is required. A minimal evaluation is followed by electric cardioversion. If the patient is not on chronic anticoagulation, transesophageal echocardiography may be needed. If the patient is not on anti-arrhythmic treatment there is a high probability of fibrillation recurrence. The third concern in emergency cardioversion is the associated clinical condition, e.g., acute coronary syndrome, decompensated heart failure, disturbed thyroid function, or acute exacerbation of obstructive lunge disease. In all these conditions the success of cardioversion is limited and hospitalization to stabilize the clinical condition must precede the electric shock. The percent of patients in a compromised clinical condition is about 11% [11].

If the patient is stable hemodynamically, the duration of the episode must be determined. The duration for acute cardioversion without previous anticoagulation should not exceed 24–48 hours. Two types of episode may qualify for acute cardioversion: recent-onset first episodes, or episodes with a previous history of atrial fibrillation. Patients with recurrent episodes of atrial fibrillation may or may not be on chronic anticoagulation, depending on the $CHADS_2$ or $CHADS_2$-vasc score. If the patient is on anticoagulation he or she may be electrically cardioverted 6 hours after the last oral intake. Medical cardioversion may be performed at any time subject to the patient being suitable.

Patients with longer episodes and without previous anticoagulation are discharged from the emergency department with the recommendation for anticoagulation and future cardioversion. However, the natural history of the atrial fibrillation in these patients is not well described, and publications like that of Antonelli et al. in this issue of *IMAJ* may contribute to our knowledge on this subject [1].

In the clinic, the cardiologist decides upon cardioversion or rate control. Unfortunately, there is no unanimously accepted approach to the decision whether or not to cardiovert.The safety of cardiover-

sion is very high if the patient is appropriately prepared with anticoagulation. Transesophageal echo is not necessary in these patients [12]. Several studies have suggested that the outcome of patients on rate control or rhythm control regime is similar [13-15]. However, the outcome is not similar in patients with sinus rhythm or atrial fibrillation [16]. This means that we still need a safe and effective therapy for rhythm control [17].

The second group of patients presenting to the cardiology clinic are those who were successfully cardioverted in the emergency department or in hospital. The follow-up clinician decides on the length of anticoagulation and intervention if the fibrillation reoccurs.

The third group of patients is referred for further intervention, such as catheter ablation. Since catheter ablation has become a routine treatment for atrial fibrillation, a significant number of patients referred to the cardiology clinic are further referred for an invasive approach.

The study by Antonelli et al. [1] presents a snapshot picture of patients with atrial fibrillation in the cardiology clinic. The outcome of these patients, the length of anticoagulation, the therapeutic approach taken, the decision on rate or rhythm control, and referral to catheter ablation are not provided in their article and future large clinical studies are needed.

Address for correspondence:
Dr. S. Rosenheck
Heart Institute, Hadassah Hebrew-University Medical Center, P.O. Box 12000, Jerusalem 91120, Israel
Phone: (972-2) 677-6564
Fax: (972-2) 641-1028
email: shimonr@ekmd.huji.ac.il

References

1. Antonelli D, Peres D, Turgeman Y. Atrial fibrillation in ambulatory cardiology clinics. *IMAJ Isr Med Assoc J* 2012; 14: 290-3.
2. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. *Arch Intern Med* 1995; 155: 469-73.
3. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults. National implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *JAMA* 2001; 285: 2370-5.
4. Seckeler M, Hoke TR. The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. *Clin Epidemiol* 2011; 3: 67-84.
5. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM, for the Collaborative Research Group. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol* 1994; 74: 236-41.
6. McDonald AJ, Pelletler AJ, Ellinor PT, Camargo CA. Increasing US emergency department visit rates and subsequent hospital admission for atrial fibrillation from 1993 to 2004. *Ann Emerg Med* 2008; 51: 58-65.
7. Stiell IA, Clement CM, Brison RJ, et al. Variations in management of recent-onset atrial fibrillation and atrial flutter among academic hospital emergency departments. *Ann Emerg Med* 2011; 57: 13-21.
8. Arendts G, Krishnaraj M, Paull G, Rees D. Management of atrial fibrillation in acute setting. Findings from an Australasian Survey. *Heart Lung Circ* 2010; 19: 423-7.
9. Decker WW, Smars PA, Valdyanathan L, et al. A prospective randomized trial of an emergency department observation unit for acute onset atrial fibrillation. *Ann Emerg Med* 2008; 52: 322-8.
10. Deasy C. Emergency department protocolised management of acute atrial fibrillation: How many patients in a tertiary hospital are eligible? *Ir Med J* 2006; 99: 272-3.
11. del Arco C, Martin A, Laguna P, Gargantilla P, on behalf of the investigators in the Spanish atrial fibrillation in emergency medicine study group (GEFAUR). *Ann Emerg Med* 2005; 46: 424-30.
12. Nagarakanti R, Ezekowitz MD, Oldgren Y, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation* 2011; 123: 131-6.
13. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002; 347: 1825-33.
14. van Gelder IC, Hagens VE, Bosker HA, et al. A comparision of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002; 347: 1834-40.
15. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008; 358: 2667-77.
16. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel B, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998; 98: 946-53.
17. Reiffel JA. Atrail fibrillation: what have recent trials taught us regarding pharmacologic management of rate and rhythm control? *Pacing Clin Electrophysiol* 2011; 34: 247-59.

Capsule

A fine-scale chimpanzee genetic map from population sequencing

To study the evolution of recombination rates in apes, Auton et al. developed methodology to construct a fine-scale genetic map from high-throughput sequence data from 10 Western chimpanzees, *Pan troglodytes verus*. Compared to the human genetic map, broad-scale recombination rates tend to be conserved, but with exceptions, particularly in regions of chromosomal rearrangements and around the site of ancestral fusion in human chromosome 2. At fine scales, chimpanzee recombination is dominated by hotspots, which show no overlap with those of humans even though rates are similarly elevated around CpG islands and decreased within genes. The hotspot-specifying protein PRDM9 shows extensive variation among western chimpanzees, and there is little evidence that any sequence motifs are enriched in hotspots. The contrasting locations of hotspots provide a natural experiment, which demonstrates the impact of recombination on base composition.

Science 2012; 336: 193
http://www.sciencemag.org/content/336/6078/193
Eitan Israeli

"An honest man in politics shines more there than he would elsewhere"

Mark Twain (1835-1910), American author and humorist, most noted for his novels, *The Adventures of Tom Sawyer* and its sequel, *Adventures of Huckleberry Finn*

Alcohol Consumption in Israel: A Public Health and Medical Problem

Yehuda Neumark PhD MPH

Braun School of Public Health and Community Medicine, Hadassah-Hebrew University, Jerusalem, Israel

KEY WORDS: alcohol, Israel, fetal alcohol spectrum disorder (FASD), screening, epidemiology

IMAJ 2012; 14: 315–317

In this publication, Jaworowski et al. present alcohol-screening findings from a sample of patients (aged 14 years and older) in a university-affiliated hospital in Israel [1]. Using the four-item CAGE questionnaire [2] with a cutoff of two or more positive responses, 22% of 178 patients referred for psychiatric consultation (95% confidence interval 17–29%, calculated), and 13% of 105 randomly recruited emergency room patients (CI 8–21%), were classified as having an alcohol use disorder. Extrapolation from data presented in Table 3 of their report reveals a particularly high positive CAGE result among divorced/separated/widowed patients (43%) and among those born in the Former Soviet Union/Russia (37%).

In a recent survey of women in three hospital maternity wards in Israel (N=3815), 14% reported having consumed alcohol during their pregnancy, and 26 women were identified as being at high risk for hazardous alcohol consumption (based on the T-ACE screening tool, a modified CAGE questionnaire designed to screen pregnant women for alcohol use) [3]. According to these results, the authors estimated that over 1000 babies are born annually in Israel at high risk for fetal alcohol spectrum disorder.

Tenenbaum and colleagues [4] investigated a high risk pediatric population of 100 infants referred to the Hadassah University Hospital's Medical Adoption Unit for clinical manifestations of FASD. Four children met FASD criteria: two exhibited fetal alcohol syndrome in the absence of a known history of maternal alcohol exposure, and two exhibited partial FAS with confirmed (self-reported) maternal alcohol consumption [5]. Another 11 were classified as "highly likely to receive a FASD diagnosis." The authors maintain that the prevalence of FASD is likely to be higher as most of these infants had not yet reached one year of age when FASD becomes more apparent. They estimate that 22 to 225 FASD "at-risk" babies are born annually in Israel. Yet, during the 10 year period 1998–2007, only 4 FASD cases were recorded in 17 Israeli hospitals and 6 cases were diagnosed at the primary care level [6]. This discrepancy may be due to insufficient knowledge and awareness among health care professionals, as reported by the heads of all (but one) of the 43 child development centers and genetic counseling clinics in Israel [6], who estimated that there are "tens" of undiagnosed FASD cases, and some put the number at "hundreds."

Regardless of the actual numbers of high risk drinkers and FASD cases, it is clear that physicians and other health professionals, particularly those who serve the adolescent population – those most vulnerable to alcohol-related harms – should be playing a more central role in the prevention, diagnosis, treatment, as well as research, of harmful drinking and alcohol-related disorders. There is ample evidence of effectiveness for brief behavioral counseling interventions for harmful alcohol use among adolescent and adult primary care patients [7,8]. Yet, these programs are rarely implemented, and general practitioners and other health care providers, owing to numerous clinical and administrative barriers, often fail to identify, counsel and refer patients who misuse alcohol [9]. Perhaps paramount among these barriers are lack of training, time constraints, and in some settings reimbursement issues [10]. Recent initiatives by the Ministry of Health in addiction medicine teaching for physicians will hopefully overcome the barrier posed by the limited training received by medical and paramedical students.

Having said that, we must be careful, however, not to confuse screening tests with diagnostic tests. Screening tests are designed to identify persons who are *likely* to have the condition being screened for, and who should then be referred for diagnostic confirmation and appropriate treatment when necessary. While the CAGE is a highly sensitive test (i.e., nearly all persons with alcohol dependence will have a positive CAGE result), the positive predictive value of the CAGE (using a 2+ cutoff) has consistently been shown to be about 85% among hospital-based and other high risk samples. This means that of the 54 patients identified by Jaworowski et al. [1] with a positive CAGE score, 46 can be expected to actually have an alcohol use disorder. Unlike sensitivity and specificity, the PPV of a screening test – and thus, its efficacy as

CI = confidence interval

FASD = fetal alcohol spectrum disorder
FAS = fetal alcohol syndrome

PPV = positive predictive value

a screening tool – is largely influenced by the underlying prevalence of the condition in the population. Application of the CAGE screening tool to the general adult population of Israel, where the prevalence of an alcohol-related disorder is about 4% [11], would produce a large number of false positives who might be unnecessarily referred for diagnostic assessment and/or treatment.

Epidemiological findings and anecdotal evidence suggest that Israeli society, long known to be relatively sober (and drug-free) by western standards, is no longer immune to the deleterious outcomes of alcohol (and drug) misuse. In recent years drinking has become a central element of entertainment and nightlife among Israeli adolescents and adults alike, with a concomitant growth in the number of drinking sites, and a burgeoning phenomenon of youthful drinking and harmful drinking. Indeed, the impression one gets from Israeli internet news is that Israel is drowning in alcohol: "Experts say Israel is now among world leaders in per capita consumption of vodka…" [Ynet, 2/17/08]; "Alcohol is killing Israel" [Ynet, 11/11/09]; "Alcohol abuse at Israel's military bases is spiraling out of control" [Ynet, 12/29/11].

The available epidemiological evidence is almost equally alarming. Findings from the HBSC 2005/2006 survey of 5350 Israeli school-attending youth in grades 6, 8 and 10 rank Israel second out of 40 countries (behind only Ukraine) in the percent of youth who report drinking alcohol at least once a week – 19% and 8% of 11 year old Israeli boys and girls, respectively [12]. In the latest national school survey (grades 7–12) conducted in 2009 by the Israel Anti-Drug Authority, about 40% of adolescents reported drinking alcohol in the past month (apart from religious ceremonies), and one-third had gotten drunk at least once in the past year [13]. Relatively high rates of binge drinking and getting drunk were noted among Arab respondents, long believed to be immune to excessive drinking due to religious and cultural restrictions. IADA survey results also show that school-going youth who drink are much more likely than non-drinkers to smoke (36% vs. 5%), and to use illicit drugs (17% vs. 3%), inhalants (22% vs. 9%) and non-prescription medications (10% vs. 2%). In turn, a history of harmful alcohol consumption patterns (drunkenness and binge drinking) and drug use strongly predicts violence among Israeli adolescents, particularly among Arab girls [14].

Particularly troubling patterns of alcohol consumption are seen among immigrant youth from the Former Soviet Union [15] and Ethiopia [16] for whom the challenges of acculturation and integration into Israeli society, coupled with typical adolescent turmoil, contribute to a greater likelihood of social maladjustment and the development of risk-taking behavior patterns [17].

Perhaps most worrisome is the finding that nearly one-quarter (22%) of school-going youth surveyed by the IADA in 2005 believed there is little or no danger in drinking alcohol several times a week [18]. Similarly, approximately 70% of Israeli college/university students nationwide perceive drinking as carrying no harm or only minor harm, despite 35% admitting to drink-driving and 20% admitting that they had driven while they knew they were too drunk to do so [19].

In the IADA 2009 national household survey of 18–40 year old adults, just over half (53%) reported any past-month drinking (this has remained virtually unchanged over the past two decades); however, one-quarter reported having gotten drunk at least once in the past year, and 21% had at least one episode of binge drinking (5+ drinks within a few hours) [13].

While none of these sources address drink-driving or drug-driving directly, the findings certainly describe a culture in which dangerous drinking patterns are common among adolescents (including pre-teens) and adults, and clearly suggest the likelihood of the dangerous mix between alcohol, drugs and driving. Indeed, evidence from various sources suggests that the proportion of alcohol-related road accidents is growing [20].

Harmful patterns of drinking and drug use and associated behaviors such as drink-driving, particularly among young adults, pose a potential serious social threat and a real challenge for public health practitioners, health service providers and public policy makers. The consequences of such behavior are increasingly felt in many spheres of life at the level of the individual, the family and society as a whole.

Physicians, epidemiologists and public health professionals in Israel should be playing a more prominent role in the prevention, diagnosis, treatment as well as research of harmful drinking and alcohol-related disorders. The medical community must become more active in bringing their collective clinical experience regarding alcohol (and the misuse of other psychoactive drugs) to policy makers, health educators and the general public.

HBSC = Health Behaviour in School-Aged Children

IADA = Israel Anti-Drug Authority

Address for correspondence:
Dr. Y. Neumark
Braun School of Public Health and Community Medicine, Hadassah-Hebrew University,
P.O. Box 12272, Jerusalem 91120, Israel
Phone: (972-2) 643-9103
Fax: (972-2) 643-1086
email: yneumark@ekmd.huji.ac.il

References

1. Jaworowski S, Raveh D, Gomard J-L, Gropp C, Mergui J. Alcohol use disorder in an Israeli general hospital: sociodemographic, ethnic and clinical characteristics. *IMAJ Isr Med Assoc J* 2012; 14: 294-8.
2. Ewing JA. Detecting alcoholism. The CAGE questionnaire. *JAMA* 1984; 252: 1905-7.
3. Sokol RJ, Martier SS, Ager JW. The T-ACE questions: practical prenatal detection of risk-drinking. *Am J Obstet Gynecol* 1989; 160: 863-71.
4. Tenenbaum A, Hertz P, Dor T, Castiel Y, Sapir A, Wexler ID. Fetal alcohol spectrum disorder in Israel: increased prevalence in an at-risk population. *IMAJ Isr Med Assoc J* 2011; 13: 725-9.
5. Chudley AE, Conry J, Cook JL, et al. Public Health Agency of Canada's National Advisory Committee on Fetal Alcohol Spectrum Disorder. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. *CMAJ* 2005; 172 (5 Suppl): S1-21.
6. Senecky Y, Inbar D, Diamond G, Basel-Vanagaite L, Rigler S, Chodick G. Fetal alcohol spectrum disorder in Israel. *IMAJ Isr Med Assoc J* 2009; 9: 619-22.

7. Whitlock EP, Polen MR, Green CA, Orleans T, Klein J. Behavioral counseling interventions in primary care to reduce risky/harmful alcohol use by adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2004; 140: 557-68.
8. Screening and Behavioral Counseling Interventions in Primary Care to Reduce Alcohol Misuse: Recommendation Statement, U.S. Preventive Services Task Force. *Ann Intern Med* 2004; 140: 554-6.
9. Babor TF, Higgins-Biddle JC. Alcohol screening and brief intervention: dissemination strategies for medical practice and public health. *Addiction* 2000; 95: 677-86.
10. Seale JP, Shellenberger S, Clark DC. Providing competency-based family medicine residency training in substance abuse in the new millennium: a model curriculum. *BMC Med Educ* 2010; 10: 33-44.
11. Neumark YD, Lopez-Quintero C, Grinshpoon A, Levinson D. Alcohol drinking patterns and prevalence of alcohol-abuse and dependence in the Israel National Health Survey. *Isr J Psychiatry Relat Sci* 2007; 44: 126-35.
12. Curie C, Gabhainn SN, Godeau E, et el. Inequalities in young people's health: Health Behavior in School-aged Children International Report from the 2005/2006 Survey. 2008 Health Policy for Children and Adolescents, No. 5, WHO Regional Office for Europe. Available at: www.euro.who.int/en/what-we-do/health-topics/Life-stages/child-and-adolescent-health/publications2/2011/inequalities-in-young-peoples-health.-hbsc-international-report-from-the-20052006-survey.
13. Bar-Hamburger R, Ezrahi Y, Rosiner I, Nirel R. Illegal use of drugs and alcohol in Israel, 2009. Seventh national epidemiological survey. Report for the Anti-Drug Authority of Israel, 2009; Available at: http://www.antidrugs.gov.il/template/default.asp?maincat=12&catId=41&pageId=1554&parentId=224.
14. Molcho M, Harel Y, Lash D. The co-morbidity of substance use and youth violence among Israeli school children. *Int J Adolesc Med Health* 2004; 16: 223–51.
15. Horowitz T, Brosh T, Bar-Hamburger R. Patterns of drug and alcohol abuse among youth from the Former Soviet Union. 2011; Available at: http://www.antidrugs.gov.il/template/default.asp?maincat=12&catId=41&pageId=1697&parentId=224.
16. Edelstein O. Patterns of psychoactive-drug use among Ethiopian immigrant youth in Israel (Hebrew). National Anti-Drug Authority 2007; Available at: http://www.antidrugs.gov.il/download/files/microsoft_word_-_-אתיופים_נוער-_מחקר_שימוש_-_עם_סמל_הרשות.pdf.
17. Tartakovsky E. A longitudinal study of acculturative stress and homesickness: high-school adolescents immigrating from Russia and Ukraine to Israel without parents. *Soc Psychiatry Psychiatr Epidemiol* 2007; 42: 485-94.
18. Bar-Hamburger R, Ezrahi Y, Roziner A, Nirel R. The use of psychoactive substances among Israeli residents, 2005. Report for the Anti-Drug Authority of Israel, 2005; Available at: http://www.antidrugs.gov.il/template/default.asp?maincat=12&catId=41&pageId=1554&parentId=224.
19. Bar-Hamburger R. Survey of attitudes and use of psychoactive drugs among students in institutes of higher learning in Israel – 2003 (Hebrew). Available at: http://www.antidrugs.gov.il/download/files/2003-סטודנטים.zip.
20. Jaffe DH, Savitsky B, Zaistev K, Hiss J, Peleg K. Alcohol and driver fatalities in Israel: an examination of the current problem. *IMAJ Isr Med Assoc J* 2009; 9: 725-9.

Capsule

The Cancer Cell Line Encyclopedia enables predictive modeling of anticancer drug sensitivity

The systematic translation of cancer genomic data into knowledge of tumor biology and therapeutic possibilities remains challenging. Such efforts should be greatly aided by robust preclinical model systems that reflect the genomic diversity of human cancers and for which detailed genetic and pharmacological annotation is available. Barretina et al. describe the Cancer Cell Line Encyclopedia (CCLE): a compilation of gene expression, chromosomal copy number and massively parallel sequencing data from 947 human cancer cell lines. When coupled with pharmacological profiles for 24 anticancer drugs across 479 of the cell lines, this collection allowed identification of genetic, lineage, and gene expression-based predictors of drug sensitivity. In addition to known predictors, we found that plasma cell lineage correlated with sensitivity to IGF1 receptor inhibitors; *AHR* expression was associated with MEK inhibitor efficacy in *NRAS*-mutant lines; and *SLFN*11 expression predicted sensitivity to topoisomerase inhibitors. Together, these results indicate that large, annotated cell-line collections may help to enable preclinical stratification schemata for anticancer agents. The generation of genetic predictions of drug response in the preclinical setting and their incorporation into cancer clinical trial design could speed the emergence of 'personalized' therapeutic regimens.

Nature 2012; 483: 603

Eitan Israeli

Capsule

Atg7 modulates p53 activity to regulate cell cycle and survival during metabolic stress

Withdrawal of nutrients triggers an exit from the cell division cycle, the induction of autophagy, and eventually the activation of cell death pathways. The relation, if any, among these events is not well characterized. Lee et al. found that starved mouse embryonic fibroblasts lacking the essential autophagy gene product Atg7 failed to undergo cell cycle arrest. Independent of its E1-like enzymatic activity, Atg7 could bind to the tumor suppressor p53 to regulate the transcription of the gene encoding the cell cycle inhibitor $p21^{CDKN1A}$. With prolonged metabolic stress, the absence of Atg7 resulted in augmented DNA damage with increased p53-dependent apoptosis. Inhibition of the DNA damage response by deletion of the protein kinase Chk2 partially rescued postnatal lethality in $Atg7^{-/-}$ mice. Thus, when nutrients are limited, Atg7 regulates p53-dependent cell cycle and cell death pathways.

Science 2012; 336: 225

http://www.sciencemag.org/content/336/6078/225

Eitan Israeli

Inflammation and Early Brain Injury in Term and Preterm Infants

Itai Berger MD[1], Ofra Peleg MD[2] and Noa Ofek-Shlomai MD[2]

[1]Neonatal Neurology Clinic, Neuro-Cognitive Center, Pediatric Wing, and [2]Department of Neonatology, Hadassah-Hebrew University Medical Center (Mount Scopus Campus), Jerusalem, Israel

KEY WORDS: inflammation, early brain injury, microglia, cytokines, white matter damage

IMAJ 2012; 14: 318–323

Early brain injury occurring during the prenatal, perinatal and postnatal periods is the most commonly recognized cause of severe, long-term neurological deficits in children [1,2]. There is no single cause for early brain injury, but a multiplicity of potential causes with complex underlying mechanisms [1,3]. The major proposed pathogenetic mechanisms are hypoxia-ischemia and inflammation [4-6]. Several lines of evidence suggest that neuronal injury related to inflammation can induce a cascade of immune responses that are involved in the pathogenesis of early brain injury [2,3,5,7]. However, until recently, the fetal-neonatal brain was viewed as an immune-privileged organ [2]. It is now clear that neuroinflammation is linked to the aggravation of early brain injury following hypoxia-ischemia and alone serves as a cause for brain injury [2]. Moreover, the unique anatomy and physiology of the fetal-neonatal brain underlies an exquisite sensitivity for inflammation [1,3,7]. In many neonates, both preterm and term, inflammation results in cell proliferation, cell differentiation and cell death, causing long-term brain injury leading to cerebral palsy, seizure disorders, sensory impairments and cognitive limitations [1,5,8,9]. However, neuroinflammatory responses are not necessarily harmful and provide beneficial results as well [10].

Neuronal injury related to inflammation can induce a cascade of immune responses, in both term and preterm infants, which is involved in the pathogenesis of early brain injury

We assume that better understanding of the nature and mechanisms causing early brain injury will lead to the development of future pathways for improved prevention and treatment. In this review we focus on the relationships between inflammation and early brain injury, demonstrating the dominant role of inflammatory processes involved in early brain injury, which might lead to management strategies designed to limit early inflammatory responses and reduce the risk of early brain injury. Most studies and reviews on this subject focus solely on either term or preterm infants. We would like to introduce an unusual joint discussion of both term and preterm infants, since although different in many aspects of response and outcome they share basic mechanisms of early brain injury.

INFLAMMATION AND EARLY BRAIN INJURY

The common mechanism of early brain injury in both term and premature neonates is impaired cerebral blood flow [2,10]. At the cellular level, reduction of cerebral blood flow and oxygen delivery initiates a cascade of biochemical events leading to acidosis and cell death [10]. This is an evolving process, since it is usually followed by a phase of secondary energy failure [1,10]. The mechanisms involved in the secondary phase may involve mitochondrial dysfunction, calcium influx, excitatory neurotoxicity, oxygen free radicals, and nitric oxide formation [10]. During the secondary phase, neurons and oligodendroglia continue to die over hours, days, or possibly weeks and months [1,10]. The biochemical processes involved in cell death are numerous. Improved investigative methods enable detection of previously unrecognized factors that may have a role in causing brain injury among preterm and term neonates [2]. Animal models demonstrated several changes in hypoxia-inducible factors, among them pro-inflammatory cytokine expression in conjunction with neuronal damage [2,9]. In these models ischemia or hypoxia alone are not enough to cause cerebral damage, but additional inflammatory signals contribute to cell death [11]. We know that the brain is a major target for inflammatory mediator actions and that inflammation/cytokines could be neurotoxic with direct effects on the nerve cells; therefore, they have been associated with early brain damage [12]. Although the mechanisms involved in inflammation-induced early brain injury are not clearly understood, recent evidence has shown that inflammatory responses in the fetus and neonate can contribute towards inflammatory cerebral white matter damage [1,5,13]. During inflammation, systemic up-regulation of pro-inflammatory cytokines and diffuse activation of microglia in the neonatal brain occur, releasing inflammatory mediators, which enhance

brain injury [1,5,14]. Cytokine-activated cells release toxic substances (reactive oxygen species, proteolytic enzymes, myeloperoxidase) and activate cytotoxic T cells, natural killer cells, and lymphokine-activated killer cells, which enhance excessive cellular and tissue damage [8]. Significant 'key-players" in this process are:

MICROGLIA, PRO-INFLAMMATORY CYTOKINES AND INFLAMMATORY MEDIATORS

At the heart of this mechanism is a systemic up-regulation of pro-inflammatory cytokines and diffuse activation of microglia following an acute hypoxic insult [1,7,14]. When stimulated, the neonatal immune system can function in a fashion rather similar to the adult system and can lead to injury or death of neurons and premyelinating oligodendrocytes [1,5]. Microglia, the brain's resident immune cells, progressively populate the brain mainly during the second trimester [1,14]. These cells, present in large numbers in the developing periventricular white matter, are antigen-presenting cells in the brain [15]. They are known to be active macrophages that remove cellular debris during normal development as well as in pathological conditions [15]. Besides their role as active phagocytes, the presence of microglia has been associated with active myelination in the developing brain [15,16]. Microglial cells have been detected in periventricular lesions in children with signs of periventricular leukomalacia [17]. Microglia cells play an important role in the development of an inflammatory response in the developing brain [15-17]. It has been reported that microglia may be responsible for the early phase of an inflammatory response and enhance hypoxic injury by expressing inflammatory mediators such as tumor necrosis factor-alpha, interleukins 1 alpha and 1 beta (IL-1β), interleukins 2, 6, 8, 18, and lipopolysaccharide [1,5,8,14,15,17]. The inflammatory mediators enhance damage to the developing brain in different pathways, such as TNFα, which seems to play a key role in the immune cascade leading to periventricular white matter damage in the fetus/neonate [15,17]. The cytotoxic and inflammatory actions of TNFα are mediated through membrane receptors, among them TNF receptor-1 [15,18]. TNF-R1 has an intracellular death domain and its activation leads to cell apoptosis [15]. Aberrant TNFα/TNF-R1 signaling has a potentially major role in the early brain injury pathogenesis in which oligodendrocyte death and demyelination are primary pathological features [15]. The expression of TNF-R1 in oligodendrocytes increased significantly in the periventricular white matter in the developing brain [19]. This is coupled with increased cell death by apoptosis and necrosis in the periventricular white matter. Therefore, it seems that the pathway includes production of TNFα by microglial cells in hypoxic conditions which induce oligodendrocyte apoptosis via TNF-R1 [15,16,19]. An example of a different pathway is IL-1. Unlike TNFα, IL-1β is non-toxic to oligodendrocytes, but it can block oligodendrocyte proliferation [20]. A significant increase in IL-1β production by microglial cells along with expression of IL-1 receptor-1 on oligodendrocytes in periventricular white matter of the neonatal brain was observed [19]. It was suggested that activation and pro-inflammatory orientation of the IL-1 produced by microglial cells in hypoxic conditions delay the white matter development and recovery in hypoxic conditions [20,21].

Cytokine-activated cells may release toxic substances, such as reactive oxygen species and toxic granules including proteolytic enzymes and myeloperoxidase, resulting in cell injuries [8]. Moreover, these pro-inflammatory cytokines activate cytotoxic T cells, natural killer cells, lymphokine-activated killer cells and more phagocytes, which enhance excessive cellular and tissue damage in the inflammatory lesions [8]. The process induces responses such as cell proliferation, cell differentiation, and cell death, leading to the occurrence of early brain injury with severe damage especially to the vulnerable white matter, leading to long-term neurological damage [1,5,8,14].

Hypoxia alone is not enough. There is an association between antenatal inflammation, white matter damage and long-term motor and cognitive deficits

TOLL-LIKE RECEPTOR

Innate immunity, the Toll-like receptors in particular, are vital players in the immune response in the brain [12]. It is not just that TLRs are important mediators of neuro-inflammation and tissue damage during infectious and non-infectious brain disease, but the dysregulation of this immunological response against brain-associated antigens could play a significant role in neonatal cerebral white matter damage [5]. Innate immunity in the brain depends, as mentioned above, primarily on the functions of glial cells such as astrocytes and microglia, which are important for the early control of pathogen replication, directing, recruiting and activating cells of the adaptive immune system [12]. Moreover, the activation of innate immunity via TLRs could play a role in pathology acquired after an infection and might initiate or amplify neuroinflammation [12].

ENDOPLASMIC RETICULUM

ER stress promotes cell survival in fully myelinated mature oligodendrocytes; on the other hand however, ER stress leads actively myelinating oligodendrocytes to cell death [22]. Non-inflammatory stimuli such as hypoxia can initiate inflammatory phenomena via ER stress, leading to the unfolded protein response, which might then lead to brain damage [23]. The

TNFα = tumor necrosis factor-alpha
TNF-R1 = TNF receptor-1
IL = interleukin
TLR = Toll-like receptors
ER = endoplasmic reticulum

neonatal brain might be especially vulnerable to ER stress because of the abundant protein synthesis by pre-oligodendrocytes and myelinating oligodendrocytes [23]. Moreover, TNFα can induce the unfolded protein response, which in turn, is able to attenuate interleukin-1 and interferon-gamma signaling – all causing or enhancing early brain injury [19,20,23,24]. So it is suggested that non-inflammatory stimuli (hypoxia) can lead to ER stress, promoting systemic inflammation that contributes to early brain injury [23]. There are specific and sometimes different aspects related to neonatal age.

CNS INFLAMMATION IN TERM INFANTS

Several major events can induce inflammation in the term infant brain.

ISCHEMIA

Ischemia induces microglial activation, initiating an inflammatory response, increases regional cerebral blood flow, induces perivascular inflammatory reactions with chemotactic activity, and alters both neuronal and glial function, causing brain injury [10]. Endothelial cells further contribute to the inflammatory response by producing pro-inflammatory mediators, which alter vascular permeability and regional blood flow and promote leukocyte adhesion [7]. Cytokines are injurious to the white matter by inhibiting differentiation of developing oligodendrocyte precursors, inducing glial apoptosis, and causing myelin degeneration [1,25].

Better understanding of the nature and mechanisms leading to inflammatory early brain injury will help focus and develop future pathways for improved prevention and treatment

Term newborn infants who suffer from hypoxic-ischemic encephalopathy were found to have elevated cerebrospinal fluid IL-6 and TNFα levels [14,25]. Shalak et al. [26] reported a significant association between abnormalities in the neurological examination and cytokine concentrations, with the highest cytokine concentrations (IL-6, IL-8) in term infants who developed clinical encephalopathy with seizures.

INFECTION

Ascending infections causing inflammation occur most commonly in the presence of rupture of membranes, but they are also possible with intact membranes [27]. The immune suppression inherent in pregnancy, which prevents rejection of the fetus by the mother, might explain how vaginal and lower genital tract organisms overcome natural barriers and gain access to the uterine cavity, and why the mother tolerates the presence of these organisms over long periods without showing any clinical manifestations [28]. Other routes of infection include hematogenous or transplacental infection, retrograde infection from the pelvis, and even transuterine infection caused by medical procedures [29]. Intraamniotic infection is usually polymicrobial and in most cases is caused by a combination of anaerobic and aerobic organisms [28,29]. The most frequently isolated pathogens are found in the vaginal flora [28,29]. The presence of bacteria induces the release of pro-inflammatory cytokines (IL-1 and TNF), causing an inflammatory process [27,28]. Prolonged fetal exposure to these microorganisms might contribute to prolonged inflammation and to neonatal brain injury and subsequent cerebral palsy [28]. Chorioamnionitis is strongly associated with brain injury leading to CP among term infants, and increases the risk by two to twelvefold through multiple pathways [28]. Involved mechanisms include elevated fetal cytokine levels, which cause direct injury to the fetal brain, and inflammation of the placental membranes, which results in hypoxic-ischemic brain injury in the fetus [26,29]. This might result in compromised placental circulation or the exacerbation of existing hypoxic brain injury [28].

CNS INFLAMMATION IN PRETERM INFANTS

Inflammation has an important role in inducing both preterm labor and brain injury in the premature infant, especially at very low gestation [28]. Prematurity is a major cause of neonatal morbidity and mortality, and cerebral white matter damage is the predominant pattern of brain injury and a major clinical issue [1,30]. The risk of CP is 70 times greater at delivery < 28 weeks compared to delivery at term [28,29]. WMD is also associated with an increased risk for cognitive limitations, behavioral problems, and visuospatial difficulties [1,30]. Epidemiological studies show that perinatal infections, chorioamnionitis and early-onset sepsis are associated with an increased risk of PVL [17]. Early models of WMD etiology were based on the assumption that much of WMD occurrence among preterm infants is attributable to brain vulnerability associated with prematurity itself [7]. Dammann and Leviton [7] suggested that a certain "factor" might lead to both prematurity and WMD, thus increasing the possibility of damage to the premature brain. Prenatal inflammatory response might be a candidate for this "factor," leading to both preterm birth and brain damage [9]. The presence of pro-inflammatory cytokines in the CNS inhibits proliferation of neuronal precursor cells, activates astrogliosis and stimulates oligodendrocyte cell death, all of which increase the risk of WMD [28]. The oligodendrocyte appears to be particularly vulnerable [15,28,29]. Activation of cytokine receptors on the surface of oligodendrocytes may result in early cell death. Overproduction of pro-inflammatory cytokines TNFa, IL-1β, IL-6 and IL-2, along with adhesion molecules such as intercellu-

CP = cerebral palsy
WMD = white matter damage
PVL = periventricular leukomalacia

lar adhesion molecule-1 and vascular cell adhesion molecule-1 can decrease the number of oligodendrocyte progenitors by causing their apoptosis and has been implicated in the pathogenesis of PVL [6,7,9,13,15].

Intraamniotic bacterial endotoxins trigger a release of cytokines in maternal and fetal tissue that leads to a release of additional cytokines, leukocyte migration, and prostaglandin [31]. This prostaglandin release leading to rupture of the fetal membranes and to the initiation of uterine contractions can be one of the direct mechanisms causing preterm labor [30,31]. Together with the evidence that inflammation can damage the developing white matter, it means that prenatal inflammation is involved in both directly causing brain WMD in preterm infants and in causing preterm labor, which is associated with WMD, as suggested by Leviton and Damman [7].

INTRAUTERINE INFECTION

Intrauterine infections increase the risk for cystic PVL and CP [23]. The rate of these complications increases dramatically with decreasing gestational age at delivery. The mechanism whereby infection appears to lead to neurological injury in the fetus and neonate is similar to the mechanism believed to cause premature rupture of membranes and preterm labor [28]. The presence of bacteria induces the release of pro-inflammatory cytokines (IL-1 and TNF) by macrophages, amnion, decidua and myometrium. IL-1 and TNFα as well as endotoxins released by the bacteria induce an increased production of prostaglandins, endothelin and corticotropin-releasing hormone in decidual, chorionic and amniotic cells [27]. Furthermore, IL-1 and TNFα induce the release of IL-6 from decidual and chorionic cells, which increases the placental secretion of prostaglandins and endothelin and mediates the release of IL-8 from decidual, chorionic, amniotic and cervical cells [28]. Elevated concentrations of bacterial endotoxins and pro-inflammatory cytokines as well as prostaglandins and endothelin in the amniotic fluid are detectable in patients with chorioamnionitis [27,28]. This leads to the activation and recruitment of granulocytes that release elastase in high concentrations and contribute to the reduction of the extracellular matrix, causing preterm labor [27]. As mentioned above, this also facilitates the process that leads to WMD.

INTRAUTERINE INFLAMMATION

As in the term infant, pro-inflammatory cytokines in the premature brain inhibit proliferation of neuronal precursor cells, activate astrogliosis, and stimulate oligodendrocyte cell death [3]. It has been suggested that neurological damage in the preterm infant results from the innate and adaptive immune systems reinforcing each other [5]. Innate immune mechanisms include the inflammatory reactions of neutrophils and monocytes triggered by microbial infectious products, such as endotoxin and nucleic acids. Adaptive immunity refers to the responses of lymphocytes that recognize specific microbial antigens. Leviton and Damman [5] suggest that the interaction between these immune systems provides a more intense and prolonged inflammatory response. Much of this mutual reinforcement occurs peripherally and does not require the presence of lymphocytes or a foreign inflammatory stimulus in the infant's brain [5,9].

Infants born at 23–29 weeks gestation and who developed WMD in the first days after birth were found to have an increased level of memory T cells [32]. The presence of these cells in cord blood is presumptive evidence for antigen exposure in utero. Another support is the presence of IL-2, produced exclusively by activated T lymphocytes, which is toxic to oligodendrocytes and myelin in areas of cerebral WMD in newborns, even when lymphocytes were not identified [5]. These findings suggest that IL-2 originated outside the brain. Activated microglia are found in high concentrations in the immature brain and produce various inflammatory mediators, including IL-1β, TNFα, and IL-6 [14,27]. This is particularly true in PVL-affected areas. In addition, these cells produce free radicals, which potentially amplify white matter injury by up-regulating the production of cytokines [14]. Oligodendrocytes appear to be particularly vulnerable to this injury, causing PVL in both in vitro and in vivo studies [28].

POSTNATAL INFECTION AND INFLAMMATION

The majority of premature (especially very low birth weight) infants develop at least one neonatal infection during their hospital stay [33]. An overwhelming systemic inflammatory response may be generated in response to early or late-onset sepsis, meningitis or necrotizing enterocolitis, resulting in brain injury or death. In a large cohort study from the NICHD Neonatal Research Network, Stoll et al. [33] reported that premature infants with neonatal infections were more likely to have cerebral palsy, lower cognitive scores, lower psychomotor developmental index scores, visual impairment, and impaired growth compared with those who were not infected [27].

DOES INFLAMMATION ALWAYS MEAN 'BAD NEWS'?

Intuitively, if the neonatal immune system is capable of producing an inflammatory response, the blockade of inflammatory chemokines may contribute to the prevention of early brain damage. However, the same cytokines causing the unfavorable inflammation in the neonatal brain appear to have a beneficial neurotropic effect [10]. Cytokines play a vital role in elimination of cellular debris, and in growth and repair, thus contributing to tissue recovery [10,15]. Some researchers could not find an association between histological inflammation of placenta and lesions and regional volumes of the brain in very preterm infants, or a direct association between the risk

of white matter injury and the severity of fetal and maternal inflammatory responses [34]. Others have demonstrated that the activation of glial cells triggers release of factors, such as colony-stimulating factor-1 and IL-6, resulting in marked neuroprotection, and is necessary for neuron survival [10]. Compensatory antioxidants and IL-8 elevation could be protective of perinatal asphyxic brain injury [35]. This dual effect complicates the task of developing targeted interventions to reduce the inflammatory response [10].

WHAT CAN BE DONE?

There is no clear answer to this question but several aspects of treatment and prevention have been suggested in the literature: namely, prevention of perinatal infection and inflammation and anti-inflammatory treatment such as corticosteroids, indomethacin and recombinant human erythropoietin. There has even been a suggestion regarding endogenous protectors and genetic regulation of inflammatory processes, but this is beyond the scope of this review [36-40].

CONCLUSIONS

Early brain injury is a continuous process, initiated most probably by in utero preconditioning in many neonates, born premature or at term. The injury is initiated during the primary insult and extends through the recovery phase. Hypoxia alone is not enough. There is an association between antenatal inflammation, WMD and long-term motor and cognitive deficits. Clearer understanding of the mechanisms and roles of key cellular and vascular components is crucial for the development of more effective prophylactic and therapeutic strategies. Better markers are needed for a reliable, earlier and more certain diagnosis of the newborn at risk. The hope is that there are interventions that might help to minimize the intensity and extent of damage, thereby decreasing morbidity and mortality in term and preterm infants alike.

Corresponding author:
Dr. I. Berger
Neuro-Cognitive Center, Pediatric Wing, Hadassah-Hebrew University Medical Center, Mount Scopus, P.O. Box 24035, Jerusalem 91240, Israel
Phone: (972-2) 584-4903
Fax: (972-2) 532-8963
email: itberg@hadassah.org.il

References

1. Khwaja O, Volpe JJ. Pathogenesis of cerebral white matter injury of prematurity. *Arch Dis Child. Fetal Neonatal Ed* 2008; 93: F153-61.
2. Degos V, Favrais G, Kaindl AM, et al. Inflammation processes in perinatal brain damage. *J Neural Transm* 2010; 117: 1009-17.
3. Alvarez-Díaz A, Hilario E, de Cerio FG, Valls-i-Soler A, Alvarez-Díaz FJ. Hypoxic-ischemic injury in the immature brain – key vascular and cellular players. *Neonatology* 2007; 92: 227-35.
4. Volpe JJ. Cerebral white matter injury of the premature infant – more common than you think. *Pediatrics* 2003; 112: 176-80.
5. Leviton A, Dammann O, Durum SK. The adaptive immune response in neonatal cerebral white matter damage. *Ann Neurol* 2005; 58: 821-8.
6. Adén U, Favrais G, Plaisant F, et al. Systemic inflammation sensitizes the neonatal brain to excitotoxicity through a pro-/anti-inflammatory imbalance: key role of TNF-alpha pathway and protection by etanercept. *Brain Behav Immun* 2010; 24: 747-58.
7. Dammann O, Leviton A. Inflammatory brain damage in preterm newborns – dry numbers, wet lab, and causal inferences. *Early Hum Dev* 2004; 79: 1-15.
8. Okazaki K, Nishida A, Kato M, et al. Elevation of cytokine concentrations in asphyxiated neonates. *Biol Neonate* 2006; 89: 183-9.
9. Dammann O, Durum S, Leviton A. Do white cells matter in white matter damage? *Trends Neurosci* 2001; 24: 320-4.
10. Perlman JM. Intervention strategies for neonatal hypoxic-ischemic cerebral injury. *Clin Ther* 2006; 28: 1353-65.
11. van den Tweel ER, Kavelaars A, Lombardi MS, et al. Bilateral molecular changes in a neonatal rat model of unilateral hypoxic-ischemic brain damage. *Pediatr Res* 2006; 59: 434-9.
12. Yuan TM, Sun Y, Zhan CY, Yu HM. Intrauterine infection/inflammation and perinatal brain damage: role of glial cells and Toll-like receptor signaling. *J Neuroimmunol* 2010; 229: 16-25.
13. Rezaie P, Dean A. Periventricular leukomalacia, inflammation and white matter lesions within the developing nervous system. *Neuropathology* 2002; 22: 106-32.
14. Silveira RC, Procianoy RS. Interleukin-6 and tumor necrosis factor-alpha levels in plasma and cerebrospinal fluid of term newborn infants with hypoxic-ischemic encephalopathy. *J Pediatr* 2003; 143: 625-9.
15. Kaur C, Ling EA. Periventricular white matter damage in the hypoxic neonatal brain: role of microglial cells. *Prog Neurobiol* 2009; 87: 264-80.
16. Deng YY, Lu J, Ling EA, Kaur C. Microglia-derived macrophage colony stimulating factor promotes generation of proinflammatory cytokines by astrocytes in the periventricular white matter in the hypoxic neonatal brain. *Brain Pathol* 2010; 20: 909-25.
17. Kadhim H, Tabarki B, Verellen G, De Prez C, Rona AM, Sébire G. Inflammatory cytokines in the pathogenesis of periventricular leukomalacia. *Neurology* 2001; 56: 1278-84.
18. Kadhim H, Khalifa M, Deltenre P, Casimir G, Sebire G. Molecular mechanisms of cell death in periventricular leukomalacia. *Neurology* 2006; 67: 293-9.
19. Deng Y, Lu J, Sivakumar V, Ling EA, Kaur C. Amoeboid microglia in the periventricular white matter induces oligodendrocyte damage through expression of proinflammatory cytokines via MAP kinase signaling pathway in hypoxic neonatal rats. *Brain Pathol* 2008; 18: 387-400.
20. Vela JM, Molina-Holgado E, Arévalo-Martín A, Almazán G, Guaza C. Interleukin-1 regulates proliferation and differentiation of oligodendrocyte progenitor cells. *Mol Cell Neurosci* 2002; 20: 489-502.
21. Girard S, Sébire G, Kadhim H. Proinflammatory orientation of the interleukin 1 system and downstream induction of matrix metalloproteinase 9 in the pathophysiology of human perinatal white matter damage. *J Neuropathol Exp Neurol* 2010; 69: 1116-29.
22. Lin W, Kemper A, Dupree JL, Harding HP, Ron D, Popko B. Interferon-gamma inhibits central nervous system remyelination through a process modulated by endoplasmic reticulum stress. *Brain* 2006; 129: 1306-18.
23. Bueter W, Dammann O, Leviton A. Endoplasmic reticulum stress, inflammation, and perinatal brain damage. *Pediatr Res* 2009; 66: 487-94.
24. Lin W, Harding HP, Ron D, Popko B. Endoplasmic reticulum stress modulates the response of myelinating oligodendrocytes to the immune cytokine interferon-gamma. *J Cell Biol* 2005; 169: 603-12.
25. Tekgul H, Yalaz M, Kutukculer N, et al. Value of biochemical markers for outcome in term infants with asphyxia. *Pediatr Neurol* 2004; 31: 326-32.
26. Shalak LF, Laptook AR, Jafri HS, Ramilo O, Perlman JM. Clinical chorioamnionitis, elevated cytokines, and brain injury in term infants. *Pediatrics* 2002; 110: 673-80.
27. Holst D, Garnier Y. Preterm birth and inflammation – the role of genetic polymorphisms. *Eur J Obstet Gynecol Reprod Biol* 2008; 141: 3-9.

28. Wu YW, Escobar GJ, Grether JK, Croen LA, Greene JD, Newman TB. Chorioamnionitis and cerebral palsy in term and near-term infants. *JAMA* 2003; 290: 2677-84.
29. Girard S, Kadhim H, Roy M, et al. Role of perinatal inflammation in cerebral palsy. *Pediatr Neurol* 2009; 40: 168-74.
30. Elovitz MA, Mrinalini C, Sammel MD. Elucidating the early signal transduction pathways leading to fetal brain injury in preterm birth. *Pediatr Res* 2006; 59: 50-5.
31. Nelson KB, Grether JK, Dambrosia JM, et al. Neonatal cytokines and cerebral palsy in very preterm infants. *Pediatr Res* 2003; 53: 600–7.
32. Duggan PJ, Maalouf EF, Watts TL, et al. Intrauterine T-cell activation and increased proinflammatory cytokine concentrations in preterm infants with cerebral lesions. *Lancet* 2001; 358: 1699-700.
33. Stoll BJ, Hansen NI, Adams-Chapman I, et al; for National Institute of Child Health and Human Development Neonatal Research Network. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA* 2004; 292: 2357-65.
34. Chau V, Poskitt KJ, McFadden DE, et al. Effect of chorioamnionitis on brain development and injury in premature newborns. *Ann Neurol* 2009; 66: 155-64.
35. Hussein MH, Daoud GA, Kakita H, et al. High cerebrospinal fluid antioxidants and interleukin 8 are protective of hypoxic brain damage in newborns. *Free Radic Res* 2010; 44: 422-9.
36. Watterberg K. Anti-inflammatory therapy in the neonatal intensive care unit: present and future. *Semin Fetal Neonatal Med* 2006; 11: 378-84.
37. Miller SP, Mayer EE, Clyman RI, Glidden DV, Hamrick SE, Barkovich AJ. Prolonged indomethacin exposure is associated with decreased white matter injury detected with magnetic resonance imaging in premature newborns at 24 to 28 weeks' gestation at birth. *Pediatrics* 2006; 117: 1626-31.
38. Arad I, Bar-Oz B, Ergaz Z, Nir A, Barak V. Interleukin-6 and N-terminal pro-brain natriuretic peptide cord blood levels in premature infants: correlations with perinatal variables. *IMAJ Isr Med Assoc J* 2010; 12: 419-23.
39. Cohen-Hillel E, Yron I, Meshel T, Ben-Baruch A. Interleukin 8 and cell migration to inflammatory sites: the regulation of focal adhesion kinase under conditions of migratory desensitization. *IMAJ Isr Med Assoc J* 2007; 9: 579-83.
40. Dammann O, Bueter W, Leviton A, Gressens P, Dammann CE. Neuregulin-1: a potential endogenous protector in perinatal brain white matter damage. *Neonatology* 2008; 93: 182-7.

Capsule

Amino acid position 11 of HLA-DRβ1 is a major determinant of chromosome 6p association with ulcerative colitis

The major histocompatibility complex (MHC) on chromosome 6p is an established risk locus for ulcerative colitis (UC) and Crohn's disease (CD). Achkar and team aimed to better define MHC association signals in UC and CD by combining data from dense single-nucleotide polymorphism (SNP) genotyping and from imputation of classical human leukocyte antigen (HLA) types, their constituent SNPs and corresponding amino acids in 562 UC, 611 CD and 1428 control subjects. Univariate and multivariate association analyses were performed, controlling for ancestry. In univariate analyses, absence of the rs9269955 C allele was strongly associated with risk for UC ($P = 2.67 \times 10^{-13}$). rs9269955 is an SNP in the codon for amino acid position 11 of HLA-DRβ1, located in the P6 pocket of the HLA-DR antigen binding cleft. This amino acid position was also the most significantly UC-associated amino acid in omnibus tests ($P = 2.68 \times 10^{-13}$). Multivariate modeling identified rs9269955-C and 13 other variants in best predicting UC vs. control status. In contrast, there was only suggestive association evidence between the MHC and CD. Taken together, these data demonstrate that variation at HLA-DRβ1, amino acid 11 in the P6 pocket of the HLA-DR complex antigen binding cleft is a major determinant of chromosome 6p association with UC.

Genes Immun 2012; 13: 245

Eitan Israeli

Capsule

NLRC4 driven production of IL-1β discriminates between pathogenic and commensal bacteria and promotes host intestinal defense

Intestinal phagocytes transport oral antigens and promote immune tolerance, but their role in innate immune responses remains unclear. Franchi and collaborators found that intestinal phagocytes were anergic to ligands for Toll-like receptors (TLRs) or commensals but constitutively expressed the precursor to interleukin 1β (pro-IL-1β). After infection with pathogenic Salmonella or Pseudomonas, intestinal phagocytes produced mature IL-1β through the NLRC4 inflammasome but did not produce tumor necrosis factor (TNF) or IL-6. BALB/c mice deficient in NLRC4 or the IL-1 receptor were highly susceptible to orogastric but not intraperitoneal infection with Salmonella. That enhanced lethality was preceded by impaired expression of endothelial adhesion molecules, lower neutrophil recruitment and poor intestinal pathogen clearance. Thus, NLRC4-dependent production of IL-1β by intestinal phagocytes represents a specific response that discriminates pathogenic bacteria from commensal bacteria and contributes to host defense in the intestine.

Nature Immunol 2012; Volume:13: Pages:449

Eitan Israeli

"What I am remains to be proved by the good I do"

Mary Baker Eddy (1821-1910), founder of Christian Science, a Protestant American system of religious thought

Radical Trachelectomy: A Fertility-Sparing Option for Early Invasive Cervical Cancer

Javier Mejia-Gomez MD, Tomer Feigenber MD, Sagit Arbel-Alon MD, Liron Kogan MD and Abraham Benshushan MD

Department of Obstetrics and Gynecology, Hadassah-Hebrew University Medical Center (Ein Kerem Campus), Jerusalem, Israel

ABSTRACT: For the past 15 years gynecological oncologists have been seeking ways to preserve woman's fertility when treating invasive cervical cancer. For some women with small localized invasive cervical cancers, there is now hope for pregnancy after treatment. Many cases of cervical cancer are diagnosed in young woman who wish to preserve their fertility. As more women are delaying childbearing, fertility preservation has become an important consideration. The standard surgical treatment for stage IA2-IB1 cervical cancer is a radical hysterectomy and bilateral pelvic lymphadenectomy. This surgery includes removal of the uterus and cervix, radical resection of the parametrial tissue and upper vagina, and complete pelvic lymphadenectomy. Obviously, the standard treatment does not allow future childbearing. Radical trachelectomy is a fertility-sparing surgical approach developed in France in 1994 by Dr. Daniel Dargent for the treatment of early invasive cervical cancer. Young women wishing to bear children in the future may be candidates for fertility-preservation options. The radical trachelectomy operation has been described and performed abdominally, assisted vaginally by laparoscopy and robotically. In this review we discuss the selection criteria for radical trachelectomy, the various possible techniques for the operation, the oncological and obstetric outcomes, and common complications.

IMAJ 2012; 14: 324–328

KEY WORDS: cervical cancer, fertility preservation, vaginal trachelectomy, trachelectomy, laparoscopy, robotic trachelectomy

Cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in females worldwide, accounting for 9% (529,800) of the total new cancer cases responsible for 275,100 deaths in 2008. More than 85% of these cases and deaths occur in developing countries [1]. In the United States, each year 12,200 new cases of cervical cancer are diagnosed and 4200 women die from this disease annually. It is estimated that 43% of all cases of invasive cervical cancer in the U.S. are diagnosed in women younger than 45 years of age.

HISTORICAL PERSPECTIVES OF THE TRACHELECTOMY

In 1948 Novak proposed that cervicectomy was a reliable treatment approach for cervical intraepithelial neoplasias. In the 1950s a Romanian gynecologist, Aburel, described a technique called subfundic radical hysterectomy for the management of microcarcinoma and in situ carcinoma of the cervix. In 1977, Bughardt and Holzer reported that removal of the uterine fundus and adnexa was not required for the management of small cervical tumors. In 1994 Daniel Dargent in Lyon [2,3] first described vaginal radical trachelectomy with laparoscopic lymph node dissection as a fertility-preserving technique. The technique was modified by Shepherd et al. [4] in London, and subsequently Roy and Plante [5] in Quebec showed that successful pregnancy could occur after this treatment. As a result, the technique of radical trachelectomy with laparoscopic pelvic lymph node evaluation has become established as a possible alternative for the surgical management of small early-stage cervical cancers in women anxious to conserve their fertility.

PROPOSED SELECTION CRITERIA FOR RADICAL TRACHELECTOMY

- A desire for future fertility
- A proven diagnosis of cervical cancer
- Squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma
- Tumor size less than 2 cm
- Stage IA1 disease with lymph vascular space invasion, stage IA2 disease or stage IB1 disease
- Tumor limited to the cervix as confirmed by preoperative pelvic magnetic resonance imaging or PET-CT
- No evidence of clinical pelvic lymph node metastases
- No previous documentation of infertility

All patients must be aware that the chances of successful fertility after radical trachelectomy are lower. Patients older than 40 years of age are counseled regarding their inherent risk of fertility based on age alone [2].

RADICAL TRAHCELECTOMY: SURGICAL TECHNIQUE

Radical trachelectomy may be performed either abdominally, vaginally, laparosocpically, or robotically. The feasibility and safety of some of these techniques have been well established, whereas for others the oncological data on outcome are only

PET-CT = positron emission tomography-computed tomography

preliminary. The decision to use newer techniques should be directed by patient variables as well as the surgeon's training and competence with laparoscopy, robotics, or vaginal surgery [6].

- *Radical abdominal trachelectomy*. The procedure begins with the inspection and removal of the pelvic lymph nodes that are then sent for frozen section. If any grossly positive nodes are detected the procedure is aborted. The round ligaments are transected and the paravesical and pararectal spaces are developed. The uterine arteries are ligated and transected bilaterally at their origin from the internal iliac arteries so the ureters can be separated from the parametria. A bladder flap is created, and the bladder is pushed away from the cervix and the rectovaginal space is developed. The cervix is amputated approximately a centimeter below the uterine-cervical junction. The uterosacral ligaments are transected and the bladder is pushed even lower. The vagina is cut in such a manner as to leave enough clear margins. The surgeon removes the cervix, parametrium and upper 2 cm of the vagina. After the cervix is amputated the trachelectomy specimen is sent for frozen section evaluation to assure that the cervical margins are free of disease. The uterine corpus with its blood supply from the uterine and ovarian arteries is retained and anastomosed to the remaining vagina. A cerclage is placed where the cervix used to be to allow the patient to carry a pregnancy. Future delivery is achieved by cesarean section.

- *Radical vaginal trachelectomy*. This procedure begins with laparoscopic pelvic lymphadenectomy. The vaginal procedure is started by placing the patient in the lithotomy position. A circumferential incision is made in the upper vagina. The supracervical ligament is cut, and the bladder base is mobilized. Posteriorly, the pouch of Douglas is opened and the pararectal spaces are exposed. The uterosacral ligaments are then divided. The vesicovaginal ligaments are then identified, and the paravesical spaces are entered laterally. At this point, the ureters are identified by palpation after which the vesicovaginal ligaments are separated from the cervix. The uterine artery is identified, and a right-angle forceps is passed through the para-isthmic window just underneath the uterine artery to define the upper limit of the cardinal ligaments. The cardinal ligaments are then divided. The cervix is amputated below the cervical isthmus, and the trachelectomy specimen is sent for frozen section

Radical trachelectomy should be regarded as an optional surgical approach in the management of early cervical cancer in a young patient who wants to preserve her fertility

ONCOLOGIC OUTCOMES FOR RADICAL VAGINAL TRACHELECTOMY

A review published in 2007 by Dursun and collaborators [7] summarized the oncological outcome of 520 patients who had undergone a radical vaginal trachelectomy. The median age for all patients reported was 31 years. The median follow-up time was 48 months. The majority of patients (60%) had a diagnosis of squamous cell carcinoma, with adenocarcinoma being the second most common histological subtype (40%). Similar results were reported by Beiner et al. [8] in a study where 90 patients underwent radical vaginal trachelectomy; 50% of their patients were reported to have adenocarcinomas.

In a study of 100 patients who underwent radical vaginal trachelectomy combined with laparoscopic pelvic lymphadenectomy, Hertel and team [9] reported that the recurrence rate after radical vaginal trachelectomy was not significantly different between squamous cell carcinoma and adenocarcinoma. Overall, in 24% of patients undergoing a radical vaginal trahcelectomy the preoperative biopsy specimen showed lymph-vascular space invasion. The majority of patients (88%) had tumors less than 2 cm in size. The median time of surgery was 213 minutes. With a median follow-up time of 48 months, the overall recurrence rate was 4.2% and the death rate from cervical cancer was 2.8% These results are comparable to those of radical hysterectomies for similarly sized lesions, with the advantages of less aggressive surgery, shorter hospital stay, lower blood loss, quicker return of bladder function, and fertility preservation.

In another study, Diaz and colleagues [10] compared the outcomes of 40 patients with stage IB1 cervical cancer, who underwent radical trachelectomy (radical vaginal hysterectomy in 28 and radical abdominal hysterectomy in 12) and 110 patients with stage IB1 cervical cancer who underwent radical hysterectomy. The median follow-up time was 44 months. The 5 year recurrence-free survival rate was 96% for the radical trachelectomy group compared to 86% for the radical hysterectomy group. The authors concluded that for selected patients with stage IB1 cervical cancer, fertility-sparing radical trachelectomy appears to produce oncologic outcomes similar to those after radical hysterectomy. Table 1 summarizes these studies.

There is increasing evidence in the literature that not only is radical trachelectomy feasible and safe but the oncologic outcomes are similar to those of equivalent patients undergoing radical hysterectomy.

RECURRENCE

Recent reviews of the published literature totaling more than 600 cases confirm an overall recurrence rate of < 5% and death rate of < 3% [9-12]. These results are comparable to those of radical hysterectomies for similarly sized lesions [12].

Nearly 40% of recurrences after vaginal radical trachelectomy occur in the parametrium or pelvic sidewall, possibly due to insufficient parametrial excision or to the presence of microscopic lymph-vascular space invasion, and 25% occur in the pelvic, para-aortic and/or supraclavicular nodes [12]. Sentinel node

Table 1. Oncologic outcomes after vaginal radical trachelectomy

Author [ref]	No. of patients	Median follow-up (mon)	Histology	Recurrence rate (%)	Death rate (%)
Dursun et al. [7]	520	48	Squamous cell carcinoma 60% Adenocarcinoma 40%	4.2	2.8
Beiner et al. [8]	90	51	Adenocarcinoma 50% Squamous cell carcinoma 43% Adenosquamous carcinoma 7%	5.5	3.3
Hertel et al. [9]	100	48	Squamous cell carcinoma 69% Adenocarcinoma 31%	4.2	2.8
Diaz et al. [10]	40*	44	Squamous cell carcinoma 50% Other 50%	4	2.5

* The study population comprised 28 patients who had radical vaginal hysterectomy and 12 patients who had radical abdominal hysterectomy

Table 2. Risk factors for recurrence and histology after vaginal trachelectomy

Lesion size	Lesions ≥ 2 cm have a higher risk of recurrence [13,22,23,28-30]
Lymph-vascular space invasion	The presence of LVSI also appears to be associated with a higher risk of recurrence (12% vs. 2%) [23,28,30]
Adenocarcinomas	Not clearly associated with a higher risk of recurrence [9]
Adenosquamous histology	Does not seem to increase recurrence rate either [23,30]
Neuroendocrine tumors	A very aggressive variant of cervical cancer. These patients should probably not be offered fertility-sparing surgery (22,23,28,30]

LVSI = lymph vascular space invasion

mapping in the surgical management of cervical cancer may reduce the risk of potentially missing nodal micrometastasis and aberrant lymph node draining sites [13,14]. Table 2 summarizes the risk factors for recurrence after vaginal trachelectomy.

OBSTETRIC OUTCOME AFTER RADICAL VAGINAL TRACHELECTOMY

Although most patients become pregnant spontaneously after radical vaginal trachelectomy, some may require the help of assisted reproductive technologies. In two recent series, 70–79% of all women attempting to conceive succeeded spontaneously [15-17]. The main concern with pregnancies following radical vaginal trachlectomy is the higher rate of premature labor and delivery.

Current literature supports the feasibility and safety of radical trachelectomy

It has been estimated that 10–15% of patients may develop cervical stenosis following vaginal radical trachelectomy [18]. The lack of cervical mucus during pregnancy may cause cervical incompetence and ascending infections, leading to prematurity and/or fetal death.

There are no guidelines for the management of pregnancies following radical vaginal trachelectomy. Routine genital tract infection screening, prophylactic antibiotics, bed rest and routine administration of steroids for fetal lung maturation have been suggested. Most authors agree that a specialist in fetal-maternal medicine should be involved in the early care of these patients.

Table 3. Obstetric outcomes after radical vaginal trachelectomy

Author [ref]	Cases	Pregnancies	Live births	< 32 weeks	Term
Milliken & Shepherd [17]	790	320	24%	9%	–
Plante [19]	256	256	40%	12%	65%

Milliken and Shepherd [17] published a review in 2008 on the obstetric outcomes in 790 radical vaginal trachelectomy procedures with 302 pregnancies and 190 live births described in the literature. Nine percent (27 patients) were significantly premature. It has been estimated that 63% of pregnancies following radical vaginal trachelectomy will result in live births. According to another review, performed by Plante [19], of 256 pregnancies following vaginal radical trachelectomy 65% of pregnancies will reach term.

As reported by Dornhofer and Hockel [20] in a more recent review, the most important obstetric outcome parameter is the rate of very premature infants related to the overall number of babies born, which is 15%. Despite major medical progress, children born at 24–28 weeks of gestation are still at significant risk to develop cognitive and motoric deficiencies, and the treatment costs for these infants are very high. In order to minimize the rate of very premature infants after radical trachelectomy, the authors propose the preservation of at least 1 cm of residual cervical tissue. Table 3 summarizes the obstetric outcome following radical trachelectomy.

RADICAL ABDOMINAL TRACHELECTOMY

Far fewer cases of abdominal trachelectomy have been reported in the literature. Technically, abdominal trachelectomy is very similar to the abdominal radical hysterectomy, making this surgery a viable option for the gynecologic oncologist with limited experience in vaginal radical surgery [21].

Abdominal radical trachelectomy is the technique of choice in pediatric patients, and in cases of distorted vaginal anatomy, bulky exophytic tumor, or cervical cancer in the first half of pregnancy [22].

The results of 10 abdominal radical trachelectomies performed in the Massachussetts General Hospital from 1999 to 2008 were published by Olawaiye et al. [23]. A high infertility rate in patients after abdominal radical trachelectomies was reported by the authors. They concluded that the high infertility rate may merely be secondary to the small sample size, but may also be attributed to a larger amount of cervix taken during the abdominal approach, leading to cervical factor as a cause of infertility. It should be noted that no cancer recurrences were found in this group after abdominal radical trachelectomy.

Einstein and co-authors [22] reported that radical abdominal trachelectomy provides similar surgical and pathological outcomes with a wider parametrial resection in comparison with the radical vaginal approach.

Another disadvantage of the radical abdominal trachelectomy is the necessity for laparotomy. Most authors consider that an abdominal approach is preferable in units with limited experience with vaginal surgical procedures.

Although premature deliveries are the main obstetric complication of radical trachelectomy, abundant successful pregnancies have been reported

ROBOTIC RADICAL TRACHELECTOMY

The advantages of minimally invasive surgery have been well documented and include decreased blood loss, decreased pain medication requirements, reduced length of hospital stay, quicker return of bowel function, and faster return to daily activities. Ramirez et al. [24] reported their experience in performing four cases of robotic radical trachelectomy. The robot offers excellent visualization of the vasculature and parametrial tissues, which must be isolated during this procedure, while still offering a minimally invasive technique that has a quick recovery and is likely to help preserve fertility [25]. The use of robotic surgical systems has allowed surgeons to perform complex gynecologic oncology procedures using a minimally invasive approach.

The first to report on robotic radical trachelectomy was Geisler et al. [26] from St. Vicente Hospital in Indianapolis, USA. They described a patient with stage IB1 adenosarcoma of the cervix. Persson et al. [27] from the Lund University Hospital in Sweden presented two patients who underwent robotic radical trachelectomy. One patient was diagnosed with stage IB1 adenocarcinoma of the cervix and the other with a stage IA2 squamous carcinoma of the cervix. This group of investigators was the first to describe robotic radical trachelectomy in conjunction with lymphatic mapping and sentinel identification. Ramirez and co-scientists [24], from the M.D. Anderson Cancer Center in Houston, USA, recently reported a case series of four patients who underwent robotic radical trachelectomy. The authors of these case reports agree that robotic surgery is a feasible and safe option for gynecologic oncology procedures with reasonable operative times, low blood loss, and short hospital stays [24-26].

FOLLOW-UP AFTER TRACHELECTOMY

Contraception is recommended for 6 months before colposcopic assessment + vaginal vault and isthmic smear are carried out. Magnetic resonance imaging is performed and if there is no evidence of recurrent disease then the patient is free to conceive. MRI assessment with colposcopy and smears are performed at 6, 12 and 24 months [17].

COMPLICATIONS

The typical complications reported in patients undergoing radical trachelectomy include dysmenorrhea (24%), dysplastic Pap smears (24%), irregular or intermenstrual bleeding (17%), problems with cerclage sutures (14%), excessive vaginal discharge (14%), isthmic stenosis (10%), and amenorrhea (7%). Another potential complication unique to this procedure is occasional reports of deep dyspareunia. Deep dyspareunia occurs because the uterus and the ovaries are much lower in the pelvis; this, accompanied by cervical stenosis, causes deep dyspareunia [18].

CONCLUSIONS

The accumulating data in the literature support the notion that radical trachelectomy is a safe option for the treatment of carefully selected women diagnosed with early cervical cancer who want to preserve their fertility. In view of the series reported in the literature, we believe that it is safe to claim that the oncologic outcome of radical trachelectomy is not inferior to radical hysterectomy in well-selected cases.

The data comparing the two main surgical approaches – radical vaginal trachelectomy versus radical abdominal trachelectomy – are not sufficient to determine which surgical approach is superior, and the decision will usually be made by the surgeon's preference and experience. It has yet to be proven whether the use of a robot carries any advantage over the traditional surgical approaches. Until more data are published, we contend that robotic radical trachelectomy should be considered an experimental procedure.

With regard to fertility, it appears that conception rates after radical trachelectomy are high, and the main obstetric obstacle remains premature delivery. Due to the relatively high premature birth rates, it is prudent to follow pregnancies after radical trachelectomies as high risk pregnancies.

Corresponding author:
Dr. A. Benshushan
Dept. of Obstetrics and Gynecology, Hadassah-Hebrew University Medical Center (Ein Kerem Campus), P.O. Box 12000, Jerusalem 91120, Israel
Phone: (972-2) 677-6424/5
Fax: (972-2) 643-3337
email: abs@hadassah.org.il

References

1. Ferlay J, Shin HR, Forman D, et al. Estimates of worldwide burden of cancer in 2008: Globocan 2008. *Int J Cancer* 2010; 127 (12): 2893-917.
2. Ramirez P, Schmeler K, Soliman P, et al. Fertility preservation in patients with early cervical cancer: radical trachelectomy. *Gynecol Oncol* 2008; 110: S25-8.
3. Abu-Rustum NR, Sonoda Y, Black D, et al. Fertility-sparing radical abdominal trachelectomy for cervical carcinoma: technique and review of the literature. *Gynecol Oncol* 2006; 103: 807-13.
4. Shepherd JH, Crawford RAF, Oram DH. Radical trachelectomy: a way to preserve fertility in the treatment of early cervical cancer. *Br J Obstet Gynaecol* 1998; 105: 912-16.
5. Roy M, Plante M. Pregnancies after radical vaginal trachelectomy for early stage cervical cancer. *Am J Obstet Gynecol* 1998; 179: 1491-6.
6. Zakashansky K, Bradley WH, Chuang l, et al. recent advances in the surgical management of cervical cancer. *Mt Sinai J Med* 2009; 76 (6): 567-76.
7. Dursun P, LeBlanc E, Nogueira MC. Radical vaginal trachelectomy (Dargent's operation): a critical review of the literature. *Eur J Surg Oncol* 2007; 33: 933-41.
8. Beiner ME, Hauspy J, Rosen B, et al. Radical vaginal trachelectomy vs. radical hysterectomy for small early stage cervical cancer: a matched case-control study. *Gynecol Oncol* 2008; 110 (2): 168-71.
9. Hertel H, Kohler C, Grund D, et al. Radical vaginal trachelectomy (RVT) combined with laparoscopic pelvic lymphadenectomy: postoperative multicenter study of 100 patients with early cervical cancer. *Gynecol Oncol* 2006; 103: 506-11.
10. Diaz JP, Sonoda Y, Leitao MM, et al. Oncologic outcome of fertility-sparing radical trachelectomy versus radical hysterectomy for stage IB1 cervical carcinoma. *Gynecol Oncol* 2008; 111: 255-60.
11. Marchiole P, Benchaib M, Buenerd A, et al. Oncological safety of laparoscopic-assisted vaginal radical trachelectomy (LAVRT or Dargent's operation): a comparative study with laparoscopic assisted vaginal radical hysterectomy (LARVH). *Gynecol Oncol* 2007; 106: 132-41.
12. Hauspy J, Beiner M, Harley I, et al. Sentinel lymph nodes in early stage cervical cancer. *Gynecol Oncol* 2007; 105: 285-90.
13. Plante M, Renaud MC, Harel F, Roy M. Vaginal radical trachelectomy: an oncologically safe fertility-preserving surgery. An updated series of 72 cases and review of the literature. *Gynecol Oncol* 2004; 94: 614-23.
14. Beiner ME, Covens A. Surgery insight: radical vaginal trachelectomy as a method of fertility preservation for cervical cancer. *Nat Clin Pract Oncol* 2007; 4: 353-61.
15. Sonoda Y, Chi DS, Carter J, et al. Initial experience with Dargent's operation: the radical vaginal trachelectomy. *Gynecol Oncol* 2008; 108: 214-19.
16. Boss EA, van Golde RJ, Beerendonk CC, et al. Pregnancy after radical trachelectomy: a real option? *Gynecol Oncol* 2005; 99: S152-6.
17. Milliken D, Shepherd J. Fertility preserving surgery for carcinoma of the cervix. *Curr Opin Oncol* 2008; 20: 575-80.
18. Alexander-Sefre F, Chee N, Spencer C, et al. Surgical morbidity associated with radical trachelectomy and radical hysterectomy. *Gynecol Oncol* 2006; 101: 450-4.
19. Plante M. Vaginal radical trachelectomy: an update. *Gynecol Oncol* 2008; 111: S105-10.
20. Dornhofer N, Hockel M. New developments in the surgical therapy of cervical carcinoma. *Ann N Y Acad Sci* 2008; 1138: 233-52.
21. Cibula D, Slama J, Fischerova D. Update on abdominal radical trachelectomy. *Gynecol Oncol* 2008; 111: S111-15.
22. Einstein MH, Park KJ, Sonoda Y, et al. Radical vaginal versus abdominal trachelectomy for stage IB1 cervical cancer: a comparison of surgical and pathologic outcomes. *Gynecol Oncol* 2009; 112: 73-7.
23. Olawaiye A, Del Carmen M, Tamburet R, et al. Abdominal radical trachelectomy: success and pitfalls in general gynecologic oncology practice. *Gynecol Oncol* 2009; 112: 506-10.
24. Ramirez PT, Schmeler KM, Malpica A, et al. Safety and feasibility of robotic radical trachelectomy in patients with early-stage cervical cancer. *Gynecol Oncol* 2010; 116 (3): 512-15.
25. Bandera CA, Magrina JF. Robotic surgery in gynecologic oncology [Review]. *Curr Opin Obstet Gynecol* 2009; 21 (1): 25-30.
26. Geisler JP, Orr CJ, Manahan KJ. Robotically assisted total laparoscopic radical trachelectomy for fertility sparing in stage IB1 adenosarcoma of the cervix. *J Laparoendosc Adv Surg Tech A* 2008; 18 (5): 727-9.
27. Persson J, Kannisto P, Bossmar T. Robot-assisted abdominal laparoscopic radical trachelectomy. *Gynecol Oncol* 2008; 111 (3): 564-7.
28. Shepherd JH, Spencer C, Herod J, et al. Radical vaginal trachelectomy as a fertility-sparing procedure in women with early-stage ovarian cancer – cumulative pregnancy rate in a series of 123 women. *Br J Obstet Gynaecol* 2006; 113: 719-24.
29. Burnett AF. Radical trachelectomy with laparoscopic lymphadenectomy: review of oncologic and obstetrical outcomes. *Curr Opin Obstet Gynecol* 2006; 18: 8-13.
30. Beiner ME, Covens A. Surgery insight: radical vaginal trachelectomy as a method of fertility preservation for cervical cancer. *Nat Clin Pract Oncol* 2007; 4: 353-61.

Capsule

Joint decisions in a group of people

In many instances, decisions made by relatively homogeneous groups (two or more people) coalesce around the choice that people are most confident in, and this in turn stems from the sampling of representations that individuals perform when making their choices. Koriat found that if most of the group members are able to form accurate judgments, then confidence and accuracy coincide and the consensus choice is the correct one. By contrast, if few people know the right answer, then heterogeneity in people's representations appeared to offer a surer path to accuracy.

Science 2012; 336: 360

Eitan Israeli

"Flatter me, and I may not believe you. Criticize me, and I may not like you. Ignore me, and I may not forgive you. Encourage me, and I will not forget you"

William Arthur Ward (1921-1994), American college administrator and writer and one of the most quoted writers of inspirational maxims

Imaging Modalities in the Diagnosis of Transient Central Retinal Artery Occlusion

Elad Moisseiev MD, Dafna Goldenberg MD, Daniel Gold MD, Meira Neuderfer MD and Zohar Habot-Wilner MD

Department of Ophthalmology, Tel Aviv Sourasky Medical Center, Tel Aviv, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

KEY WORDS: transient central retinal artery occlusion, cotton wool spots, optical coherence tomography, fluorescein angiography, indocyanine green angiography

IMAJ 2012; 14: 329–330

Central retinal artery occlusion is an ophthalmic emergency, causing acute painless loss of vision. Typical clinical findings include retinal pallor, appearance of a foveal "cherry-red spot," and in some cases narrow and segmented arteries [1]. Hayreh and Zimmerman [1] divided CRAO into four distinct subtypes: non-arteritic, non-arteritic with cilioretinal sparing, arteritic, and transient. The diagnosis of transient CRAO is challenging as it lacks the aforementioned classical findings. It occurs when the central retinal artery is not completely occluded and retinal perfusion pressure is reduced, but not enough to cause complete retinal infarction as seen in complete CRAO. The peripapillary and periarterial regions remain perfused, and beyond them the retina becomes ischemic. At the border between the perfused and ischemic retina the axoplasmic transport is interrupted, which results in the appearance of cotton wool spots [2]. Oji and McLeod [3] described seven patients with transient CRAO who presented with acute mild decrease of vision, a ring-like pattern of CWS around the optic disk and along the arcades, and perifoveal ischemia. Several causes of transient CRAO and retinal hypoperfusion have been suggested, such as transient emboli that dislodge or dissolve, nocturnal arterial hypotension, or transient vasospasm induced by serotonin released from atherosclerotic plaques [4].

A literature review revealed only a few studies that acknowledge this diagnosis; most studies consider all subtypes of CRAO as a single clinical entity. We present a case of transient CRAO and demonstrate the imaging modalities that were used to confirm this unique diagnosis.

CRAO = central retinal artery occlusion
CWS = cotton wool spots

PATIENT DESCRIPTION

A 58 year old man presented to our clinic with a 3 day history of acute painless decreased vision in his right eye. The patient was otherwise healthy and did not use any medications. Ocular history included only presbyopia.

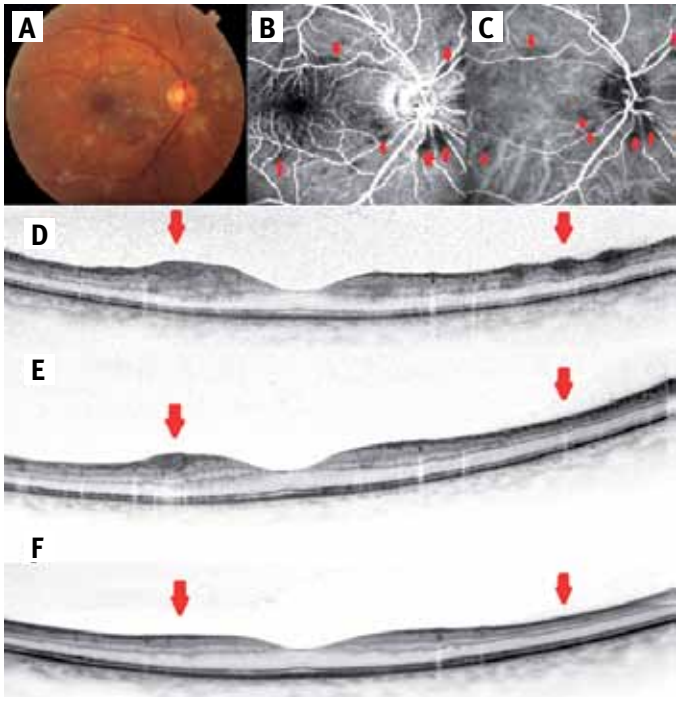
Best corrected visual acuity at presentation was 20/70 in the right eye and 20/20 in the left eye. There was no afferent pupillary defect or ocular movement limitation, anterior segments were both normal, and applanation tonometry was normal. Dilated fundus examination of the right eye revealed multiple fluffy whitish lesions around the optic disk and along the arcades, with perifoveal ischemia [Figure A]. The left eye was normal. HR-OCT (high resolution optical coherence tomography) (Spectralis, Heidelberg, Germany) of the retinal lesions demonstrated focal thickening and hyper-reflectivity of the nerve fiber layer, compatible with CWS [Figure D]. The macula appeared normal. Fluorescein angiography demonstrated focal areas of hypofluorescence which matched the size and location of the CWS [Figure B]. There was no leakage from the blood vessels or the optic disk. Importantly, a marked delay of 24 seconds in the arterial filling time was documented. Indocyanine green angiography demonstrated areas of hypofluorescence that matched the size and location of the CWS [Figure C]. No disturbance in choroidal filling or other chorioretinal pathology was detected. Automated visual field testing demonstrated decreased sensitivity of the right eye (mean deviation -4.7 dB OD compared with -0.7 dB OS), with no scotoma.

The following laboratory tests were normal: complete blood count, kidney and liver function tests, lipid profile, blood clotting test, erythrocyte sedimentation rate, C-reactive protein, collagenogram, and serology testing for human immunodeficiency virus and syphilis. Homocysteine levels were normal and there was no hypercoagulability. Echocardiography and carotid ultrasound Doppler were normal. Ultrasound Doppler of the orbital vessels revealed no vascular abnormalities in the ophthalmic, posterior choroidal and central retinal arteries. To demonstrate any vascular abnormalities that may have been undetected by the previous modalities, magnetic resonance angiography of the head and neck was performed, and was found normal.

A diagnosis of transient CRAO was made, and the patient was treated with aspirin. He was followed closely for 6 weeks, during which BCVA improved to 20/20, the CWS completely resolved, and only mild foveal retinal pigment epithelial changes remained. HR-OCT documented the gradual disappearance

BCVA = best corrected visual acuity

[A] Presentation of the right eye with multiple cotton wool spots around the optic disk and along the arcades. **[B]** Fluorescein angiography at end-transit time, demonstrating areas of hypofluorescence (arrows) that match the size and location of the cotton wool spots seen in [A]. **[C]** ICG demonstrating areas of hypofluorescence (arrows) that match the size and location of the cotton wool spots. Choroidal filling is normal. **[D–F]** Spectralis HR-OCT scans demonstrating the gradual absorption of two cotton wool spots (arrows) and restoration of normal retinal configuration, **[D]** at presentation, **[E]** after 2 weeks, and **[F]** after 6 weeks



of the cotton wool spots and restoration of normal retinal configuration [Figure D-F]. Repeated visual field testing after 6 weeks was normal.

COMMENT

We report a case of multiple CWS secondary to transient CRAO. To our knowledge, this is the first case in which multiple imaging modalities were used to confirm the suspected diagnosis. This is the first report on the use of ultrasound Doppler of orbital vessels and MRA to ascertain patency of the central retinal artery in transient CRAO.

HR-OCT is a valuable tool for identifying retinal abnormalities, and a review of the literature revealed a few studies, which used this modality, on the appearance of CWS. Only two studies have shown that HR-OCT is efficient in demonstrating CWS in both acute and late stages [5]. HR-OCT has also been shown to detect retinal hyper-reflectivity even after CWS resolution, consistent with residual retinal damage [5]. Our data are consistent with these studies.

Fluorescein angiography and ICG aided in establishing the diagnosis of transient CRAO. The arterial filling delay is highly suggestive of CRAO (both complete and transient). ICG ruled out ocular ischemic syndrome and other chorioretinal pathology. Unique to our case is the demonstration of CWS by ICG, which were seen as focal areas of hypofluorescence.

After CWS resolution, foveal retinal pigment epithelial changes were noted, which may result from an initial perifoveal ischemia [1,3]. It has been suggested that foveal retinal thickening may prevent reperfusion of the fovea, which may result in foveal ischemia. This mechanism has been dubbed "no-reflow phenomenon," and may explain residual ischemic changes or even a central scotoma [4]. As occurred in most reports of patients with transient CRAO, our patient's BCVA improved and his visual field returned to normal.

In summary, our case emphasizes the role of different imaging techniques in establishing the rare diagnosis of transient CRAO. HR-OCT is very helpful in identifying and monitoring CWS. Fluorescein angiography and ICG aid in ruling out other potential causes for a similar clinical presentation. Ultrasound Doppler of the orbital vessels may be a significant adjunct to these tests, as it may directly demonstrate occlusion or patency of the arteries in question. MRA may be useful in finding the cause of CRAO, but since it is relatively expensive and less available we suggest it be reserved for cases in which all other modalities fail to reveal any significant findings and where the clinical picture supports its use.

Acknowledgments

The authors thank Mrs. Galit Yair-Pur for her photographic and technical support.

Corresponding author:
Dr. E. Moisseiev
Dept. of Ophthalmology, Tel Aviv Sourasky Medical Center, 6 Weizmann St., Tel Aviv 64239, Israel
Phone: (972-3) 697-3408
Fax: (972-3) 697-3870
email: elad_moi@netvision.net.il

References

1. Hayreh SS, Zimmerman MB. Fundus changes in central retinal artery occlusion. *Retina* 2007; 27: 276-89.
2. McLeod D. Why cotton wool spots should not be regarded as retinal nerve fiber layer infarcts. *Br J Ophthalmol* 2005; 89: 229-37.
3. Oji EO, McLeod D. Partial central retinal artery occlusion. *Trans Ophthal Soc UK* 1978; 98: 156-9.
4. Hayreh SS. Prevalent misconceptions about acute retinal vascular occlusive disorders. *Prog Ret Eye Res* 2005; 24: 493-519.
5. Kozak I, Bartsch DU, Cheng L, Freeman WR. Hyperreflective sign in resolved cotton wool spots using high-resolution optical coherence tomography and optical coherence tomography ophthalmoscopy. *Ophthalmology*. 2007; 114: 537-43.

MRA = magnetic resonance angiography

ICG = indocyanine green (angiography)

Giant Colon Diverticulum: Rare Manifestation of a Common Disease

Ahmad Mahamid MD[1], Itamar Ashkenazi MD[1], Nasser Sakran MD[1] and Abdel-Rauf Zeina MD[2]

[1]Division of Surgery and [2]Department of Radiology, Hillel Yaffe Medical Center, Hadera, affiliated with Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

KEY WORDS: giant colonic diverticulum, giant sigmoid diverticulum, diverticular disease, diverticulitis, multi-detector computed tomography

IMAJ 2012; 14: 331–332

Diverticular disease of the colon is a common condition, with a prevalence of about 60% in people over the age of 70 [1]. Its incidence appears to be increasing, especially in the western world [2]. A giant colonic diverticulum is defined as a diverticulum larger than 4 cm in diameter [2]. The GCD can be congenital with a muscular layer, or acquired as a rare complication of the diverticular disease. GCD mostly presents after the sixth decade, has an equal gender distribution, and affects the sigmoid colon in 90% of the cases. It is a rare entity, with fewer than 200 cases discussed in the literature since it was first reported by Bonvin and Bonte in 1946 [3]. In this article we present the case of a patient with giant sigmoid diverticulum complicated with diverticulitis, and describe the clinical presentation, diagnosis and treatment of this uncommon condition.

PATIENT DESCRIPTION

A 62 year old man was referred from a psychiatric institution to our emergency department because of diffuse abdominal pain and constipation, without fever. His past medical history was positive for major depression, diverticulosis and diverticulitis of the descending colon that was treated conservatively. One year before his admission, he underwent a colonoscopy and a benign polyp was removed. Since then he suffered intermittently from dull lower abdominal pain, with no history of anorexia, nausea, vomiting, weight loss, or change in bowel habit or gastrointestinal blood loss. Abdominal examination revealed a soft, non-tender abdomen with normal peristalsis and without a palpable abdominal mass. Digital rectal examination was normal. Blood tests showed leukocytosis and elevated C-reactive protein. Plain abdominal radiograph showed a large, oval, homogenous radiolucency in the right upper quadrant that was smoothly marginated [Figure A]. For further evaluation, contrast-enhanced computed tomography of the abdomen using a 64-multi-detector CT scanner was performed. The CT scan revealed an 11 × 10 cm, predominantly gas-filled structure in the right upper abdomen, containing a small amount of fluid and communicating with the sigmoid colon [Figure B]. The wall of this gas-filled structure and the surrounding fat were thickened, indicating recent inflammation [Figure C]. The appearance was of a giant sigmoid diverticulum, complicated by infection. The patient was treated conservatively with intravenous antibiotics. Several weeks later, he underwent an uneventful laparoscopic sigmoidectomy. Intraoperative findings revealed an inflammatory giant sigmoid diverticulum.

GCD = giant colonic diverticulum

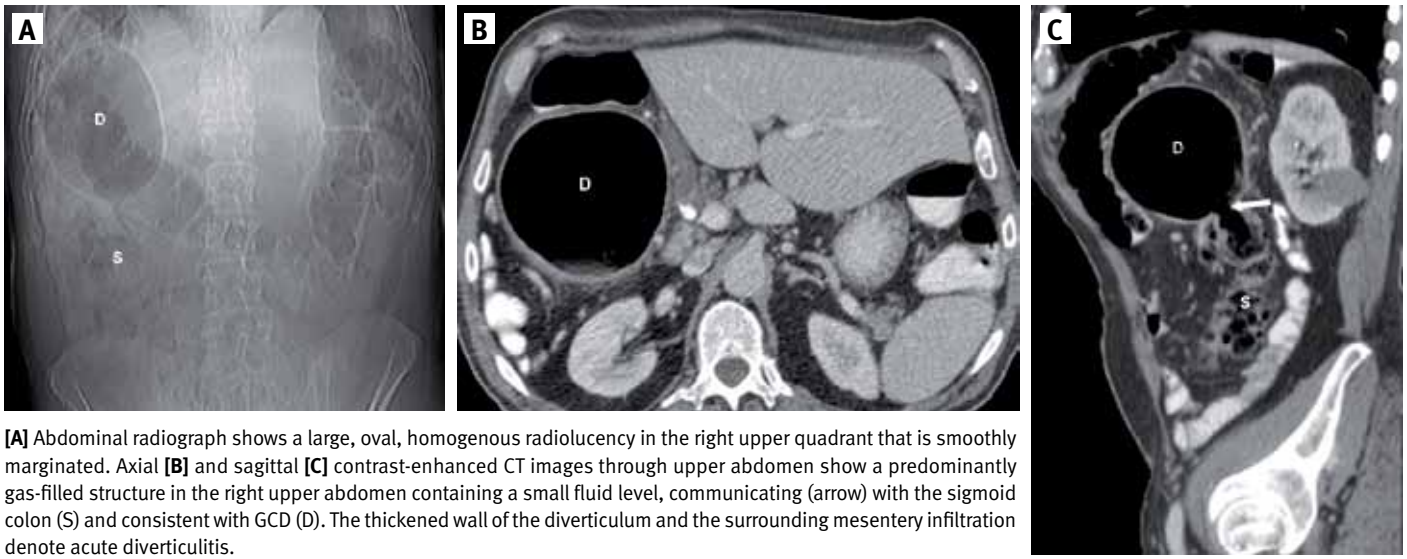
COMMENT

GCD has been reported in different parts of the colon, but up to 90% of cases occur in the sigmoid colon. The mean age of presentation is between 60 and 79 years, and the most frequently reported size of the diverticulum ranges from 4 to 30 cm [2]. The pathogenesis of GCD is still obscure, although associated colonic diverticulitis has been reported in over 90% of cases [2].

There are three histological types of GCD: a) true congenital diverticulum with a normal colonic structural wall, b) pseudo-diverticulum with a mainly mucosal wall, and c) inflammatory GCD with a reactive scar tissue wall that occurs as a result of previous perforation of the small diverticulum. In the last type of GCD there is a ball-valve mechanism, which has been suggested by Nano et al. [4] to be the cause of a gradual increase in the size of the diverticulum culminating in GCD. Depending on the colonic lumen pressure, the air passes through the communicating tract, leading to an intermittently prominent abdominal mass or phantom tumor.

Palpable abdominal mass is present in 60% of the cases and is the most common finding on clinical examination [2]. Complicated GCD may present with acute abdomen due to diverticulitis (as in our case), perforation, focal intestinal ischemia or bowel obstruction – a scenario with a mortality rate of up to 5%.

Plain supine abdominal radiography, a simple and available diagnostic tool, can be used as the first-line investigation. Usually, a large air-filled structure with or without air fluid levels can be seen in close proximity to the sigmoid colon. Barium enema is useful in showing a communication with the bowel in about two-thirds of reported cases; however, it may complicate with perforation, ending with emergency



[A] Abdominal radiograph shows a large, oval, homogenous radiolucency in the right upper quadrant that is smoothly marginated. Axial **[B]** and sagittal **[C]** contrast-enhanced CT images through upper abdomen show a predominantly gas-filled structure in the right upper abdomen containing a small fluid level, communicating (arrow) with the sigmoid colon (S) and consistent with GCD (D). The thickened wall of the diverticulum and the surrounding mesentery infiltration denote acute diverticulitis.

surgery. MDCT with multiplanar reformation and three-dimensional imaging could emerge as an ideal non-invasive technique that offers a unique opportunity to evaluate the presence of GCD, its size, exact location, contents and wall thickness, as well as the surrounding mesentery and accompanying complications. On CT, the GCD usually appears as a predominantly gas-filled structure containing a small amount of fluid and communicating with the colon. The thickened wall of the diverticulum and the surrounding mesentery infiltration represent acute diverticulitis and localized peritonitis [5]. CT scan of the abdomen provides valuable anatomic information that can be very useful in the differential diagnosis of GCD.

The treatment approach for GCD depends on the severity of the clinical presentation, age and the physiological reservoir of the patient. Elderly and high risk patients with asymptomatic GCD can be managed conservatively. Surgery is the recommended treatment for symptomatic non-complicated GCD in the low risk patient. Colostomy with primary end-to-end anastomosis is the preferred procedure. For complicated cases, emergent two-stage bowel resection with colostomy (Hartmann's procedure) is recommended. In the GCD, the inflammatory process can result from increased intra-diverticular pressure, causing venous congestion and edema of the diverticular wall and, consequently, strangulation and microperforation. In these patients, conservative treatment with intravenous antibiotics, fasting, and intravenous fluid maintenance is recommended.

In conclusion, although GCD is rare, physicians and surgeons should consider it in any patient with acute abdominal pain and the finding of a large gas-filled structure in close proximity to the colon on plain film or CT scan. The presenting clinical symptoms are usually non-specific. Knowledge of the imaging appearances and an understanding of the clinical significance of this rare condition are essential for making the correct diagnosis, reducing possible complications and planning patient treatment.

MDCT = multi-detector computed tomography

Corresponding author:
Dr. A.R. Zeina
Dept. of Radiology, Hillel Yaffe Medical Center, P.O. Box 169, Hadera 38100, Israel
Phone: (972-4) 630-4621
Fax: (972-4) 630-4884
email: raufzeina3@hotmail.com
raufzeina@yahoo.com

References

1. Levi DM, Levi JU, Bergau DK, et al. Giant colonic diverticulum: an unusual manifestation of a common disease. *Am J Gastroenterol* 1993; 88: 139-42.
2. Steenvoorde P, Vogelaar FJ, Oskam J, et al. Giant colonic diverticula. Review of diagnostic and therapeutic options. *Dig Surg* 2004; 21: 1-6.
3. Bonvin MMP, Bonte G. Diverticules giants due sigmoide. *Arch Mal Appar Dig Mal Nutr* 1946; 35: 353-5.
4. Nano M, De Simone M, Lanfranco G. Giant sigmoid diverticulum. *Panminerva Med* 1995; 37: 44-8.
5. Portnoy O, Gayer G, Onaca N, Heldenberg E, Apter S. Abdominal computerized tomography in the diagnosis of Meckel's diverticulitis in the adult. *IMAJ Isr Med Assoc J* 2001; 3: 982-3.

"The greatest of faults, I should say, is to be conscious of none"

Thomas Carlyle (1795-1881), Scottish satirical writer, essayist, historian and teacher

"People see God every day. They just don't recognize him"

Pearl Bailey (1918-1990), African-American actress and singer

Absence of Mannose-Binding Lectin in a Female with Relapsing-Remitting Multiple Sclerosis

Gautam K. Malhotra MS[1], Roger Kobayashi MD[2] and Jill A. Poole MD[1]

[1]Pulmonary, Critical Care, Sleep and Allergy Division, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, USA
[2]Immunology and Allergy Division, Department of Pediatrics, University of California Los Angeles School of Medicine, Los Angeles, CA, USA

KEY WORDS: mannose, mannan, multiple sclerosis, complement, autoimmunity

IMAJ 2012; 14: 333–334

Mannose-binding lectin (also known as mannan-binding lectin) is a component of the innate immune system which recognizes repetitive sugar groups on the surface of bacteria and viruses leading to activation of the complement system [1]. While deficiency of the MBL protein can be present in up to 10% of the general population, the majority of individuals with MBL deficiency are asymptomatic due to redundancies in the immune system [1]. However, clinical manifestations of MBL deficiency have been associated with conditions that result in immune suppression and, interestingly, MBL deficiency has recently been associated with autoimmune diseases including systemic lupus erythematosus and rheumatoid arthritis [2]. Its role in other autoimmune disease, if any, has not been well studied, and to the best of our knowledge there are no reports of MBL deficiency associated with multiple sclerosis. We report here on a young adult with relapsing-remitting multiple sclerosis in whom MBL levels were undetectable.

PATIENT DESCRIPTION

We present the case of a 27 year old woman with relapsing-remitting MS in whom MBL levels were undetectable. She was first diagnosed with MS 4 years earlier, after she manifested symptoms of ataxia, vertigo, urinary incontinence, and vision changes consistent with optic neuritis. Episodes of optic neuritis and visual changes responded well to systemic corticosteroids. She continued to suffer from progressive lower extremity weakness and unsteady gait associated with frequent falling. Magnetic resonance imaging of brain revealed new 3 mm left middle frontal gyrus enhancement foci compatible with active demyelination, but otherwise stable multifocal cerebral white matter and corpus callosum T2 hyper-intensities in 2009. The most recent (2010) brain scan showed minimal progressive non-specific white matter changes with a solitary enhancing lesion, and 4 mm inferior tonsillar ectopia with mild crowding at the foramen magnum. Magnetic resonance imaging of the cervical spine in 2009 demonstrated mild degenerative changes with mild kyphosis of the mid-cervical spine, smudgy signal changes with the spinal cord at C6-C7, with features consistent with a demyelinating process. In 2010, cervical spine scan showed minimal degenerative changes. Since the time of her diagnosis, she had attempted several treatment regimens including glatiramer acetate, interferon beta-1a, and interferon beta-1b, but discontinued each due to worsening depression and anxiety. Natalizumab, the humanized monoclonal antibody against the cellular adhesion molecule α4-integrin, was being considered as the next potential therapeutic approach. Her neurologist also recommended consultation with an allergologist/immunologist in view of her history of chronic sinus infections, allergic rhinitis, skin folliculitis, and recurrent urinary tract infections with an approximate frequency of six urinary tract infections per year.

The patient also reported depression, anxiety, migraines, and polycystic ovary syndrome. Her current medications included: ethinyl estradiol and norethindrone, duloxetine, buspirone, aripiprazole, alprazolam, dicyclomine, ranitidine, omeprazole, acetaminophen, butalbital, baclofen, darifenacinhydrobromide, meclizine, diazepam, and fexofenadine. Her most recent MS relapse occurred 1 month earlier, and she was treated with systemic corticorticosteroids. The patient is a current smoker at 10 cigarettes per day for approximately 7 years. She rarely consumes alcohol beverages. She is married, without children, and has two cats in her home. Her biological parents had hypercholesterolemia, and no history of autoimmune disease or recurrent infection.

During her allergy and immunology evaluation, physical examination was essentially unremarkable apart from the fact that the patient was noted to be obese with a body mass index of 46.8 and weight of 110 kg. Skin folliculitis on the chest was also noted. Laboratory testing revealed an MBL level of 0 ng/ml (reference range ≥ 50 ng/ml), which was subsequently confirmed 2 months later by an independent laboratory. Other pertinent laboratory testing revealed elevated levels of C3 (186 mg/dl, range 90–180 mg/dl), complement CH50 (209 CAE units, range 60–144 units), C-reactive protein (23.0 mg/L, range 0.0–5.0 mg/L), and C1Q binding (4.6 µgE/ml, range 0.0–3.9 µgE/ml, standard reference value for the Raji cell immune complex assay). C4

MBL = mannose-binding lectin
MS = multiple sclerosis

level was normal at 25 mg/dl (10–40 mg/dl). Quantitative immunoglobulins were essentially normal with a total IgG of 1082 mg/dl (676–1512 mg/dl), IgA 130 mg/dl (60–378 mg/dl) and IgM 232 mg/dl (46–211 mg/dl). Following vaccination, laboratory tests demonstrated adequate titer responses to diphtheria and tetanus toxoid (protein-conjugated vaccines) as well as Streptococcus pneumococcal vaccination (polysaccharide vaccine). Antinuclear antibody panel, celiac disease panel, antimitochondrial antibody, rheumatoid factor, human immunodeficiency virus, and thyroid function tests were normal. Allergy skin prick test demonstrated significant sensitization to house dust mite and cat dander.

COMMENT

This case is unique due to the complete absence of MBL protein within the context of a young adult with multiple sclerosis. MS is a chronic demyelinating disease of the central nervous system and is generally considered to be an inflammatory autoimmune reaction against CNS antigens, resulting in tissue damage and significant neurological disability [3]. The etiology of MS is not well defined, but it is believed that complex genetic and environmental components contribute to disease susceptibility [3]. Infectious agents such as human herpes viruses and human endogenous retroviruses have been implicated, but no causal bacterial or viral agent has been unequivocally demonstrated in MS [3]. In addition, the pathogenesis of MS encompasses multiple inflammatory and apoptotic processes. The adaptive immune system is well recognized as playing a major role in the pathogenesis of MS, but recently the role of innate immunity has gained significant attention [3]. The complement system is important in innate immunity, which functions in host defense against pathogens, clearance of immune complexes and apoptotic cells, and interfacing between innate and adaptive immunity [1]. In general, the complement system has been implicated in MS pathogenesis, in part, because of the presence of complement components in demyelinating plaques and in the serum and cerebrospinal fluid of MS patients [3]. There are three pathways through which complement can be activated: classical, alternative, and lectin. All pathways converge, resulting in the generation of opsonins and anaphylatoxins as well as the formation of the membrane-attack complex that lyses cells [2]. Thus, it is possible that dysfunction or dysregulation of the MBL pathway could play a role in the pathogenesis of MS.

Of the studies investigating the role of MBL deficiency and autoimmunity, particular focus has been on SLE [2]. Namely, several studies show significant association with MBL deficiencies and SLE (with a nearly twofold increase in susceptibility), even across several ethnic backgrounds [2]. Moreover, reduced levels of MBL have been associated with juvenile-onset SLE and an increased risk for cardiopulmonary complications and cutaneous manifestations [2]. To the best of our knowledge no study has shown a correlation between MBL deficiency and MS severity; however, there are reports demonstrating that higher levels of MBL in patients with MS are associated with low disease activity, suggesting a protective effect of MBL [4].

Despite the potential correlation between MBL deficiency and autoimmune diseases, its exact role is not well defined. However, it is believed that MBL may act as a disease modifier by priming or promoting inappropriate immune and inflammatory responses. Notably, MBL is known to facilitate the clearance of apoptotic cells by binding to and initiating their uptake by macrophages [5]. Loss of this function would lead to an accumulation of cellular debris that could serve as a source of autoantigens. Alternatively, loss of MBL may render the patient more susceptible to other pathogens, particularly viruses, which may have a role in autoimmune disease progression. In our case, the patient did demonstrate evidence for increased infection susceptibility marked by recurrent sinus infections, folliculitis, and urinary tract infections. Interestingly, she also demonstrated a potential compensatory response for the apparent lack of MBL by increased activation of the complement cascade (CH50), C3, and C1q binding proteins.

Considering the integral role of MBL in the innate immune system and its established association with certain autoimmune diseases, it may be beneficial to assay for MBL levels in patients with MS where the relationship may not be as well characterized. This may be particularly important for MS patients with recurrent infections or when determining potential therapies that may result in further immune suppression. Finally, further studies may also be warranted to determine the potential role of MBL and MS as there might be a possibility of providing replacement MBL in the future.

Ig = immunoglobulin
CNS = central nervous system
SLE = systemic lupus erythematosus

Corresponding author:
Dr. J.A. Poole
Pulmonary, Critical Care, Sleep & Allergy Division, Dept.of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, USA 68198-5300
Phone: (1-402) 559-4087
Fax: (1-402) 559-8210
email: japoole@unmc.edu

References

1. Thiel S, Frederiksen PD, Jensenius JC. Clinical manifestations of mannan-binding lectin deficiency. *Mol Immunol* 2006; 43 (1-2): 86-96.
2. Pettigrew HD, Teuber SS, Gershwin ME. Clinical significance of complement deficiencies. *Ann N Y Acad Sci* 2009; 1173: 108-23.
3. Fernandez M, Montalban X, Comabella M. Orchestrating innate immune responses in multiple sclerosis: molecular players. *J Neuroimmunol* 2010; 225 (1-2): 5-12.
4. Petersen T, Moller-Larsen A, Thiel S, Brudek T, Hansen TK, Christensen T. Effects of interferon-beta therapy on innate and adaptive immune responses to the human endogenous retroviruses HERV-H and HERV-W, cytokine production, and the lectin complement activation pathway in multiple sclerosis. *J Neuroimmunol* 2009; 215 (1-2): 108-16.
5. Nauta AJ, Castellano G, Xu W, et al. Opsonization with C1q and mannose-binding lectin targets apoptotic cells to dendritic cells. *J Immunol* 2004; 173 (5): 3044-50.

Spinal Fractures Caused by Hypoglycemic Convolution: Beware of the Distracted Injury

Josh E. Schroeder MD[1], Leon Kaplan MD[1], Roy Eldor MD[2], Amir Hasharoni MD PhD[1], Nurit Hiller MD[3] and Yair Barzilay MD[1]

[1]Spine Unit, Department of Orthopedic Surgery, [2]Diabetic Unit, and [3]Department of Radiology, Hadassah-Hebrew University Medical Center (Ein Kerem Campus), Jerusalem, Israel

KEY WORDS: spinal fracture, hypoglycemic seizure, decompression, cement augmentation, kyphoplasty, osteoporosis

IMAJ 2012; 14: 335–336

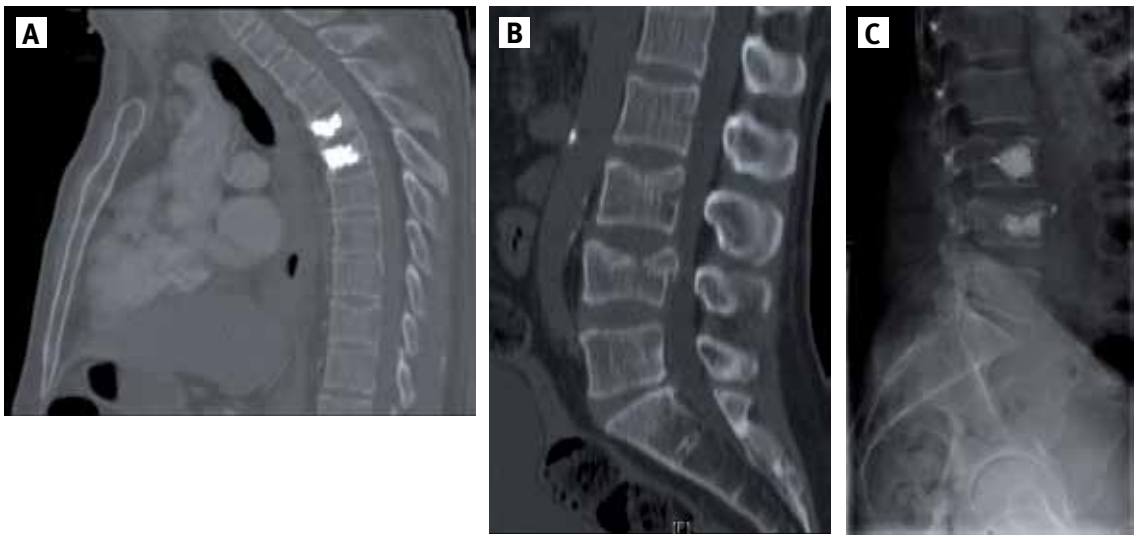
Convolutions are known to dislocate joints and can cause fractures from falls or due to the thrust caused by seizures. Vertebral compression fractures have been described in tetanus and epilepsy [1]. Only a few cases of convulsion-induced vertebral fractures after hypoglycemic attacks in diabetes mellitus have been reported. We present the case of a patient who suffered a hypoglycemic convulsion causing non-contiguous vertebral fractures. These fractures presented gradually, causing neurological symptoms, and led to two surgical interventions.

PATIENT DESCRIPTION

A 53 year old healthy, well-controlled insulin-dependent diabetic man was brought to the emergency department after his wife found him in bed convulsing. His initial glucose levels were 15 mg/dl. An intravenous line was inserted and he was treated with a solution of 25% dextrose until normoglycemia returned.

Upon regaining consciousness, the patient complained of pain in his upper thoracic back and right shoulder. On physical examination, tenderness over the upper thoracic midline was noted and he had a limited range of motion of his right shoulder without any neurological deficit. He was able to walk and had no other complaints. A thoracic computed tomography scan demonstrated vertebral compression fractures of D5 and D6 vertebrae and a fracture of the right scapula. The patient was placed in a body brace; however, the pain continued and robotic guided kyphoplasty of D5 and D6 was performed [Figure A]. The next day the patient's upper back pain disappeared, but he started to complain of radicular pain in his left leg according to the L4 dermatome and could not walk. A CT scan of the lumbar spine demonstrated two previously undiagnosed fractures – a burst fracture of L4 and a compression fracture L3 [Figure B].

In the attempt to avoid another surgical intervention, an epidural catheter was placed remitting the patient's pain. When it was removed, the pain recurred and the patient lost ambulation. He underwent decompression of the left L4 nerve root and cement augmentation of L3 and L4 vertebras [Figure C]. He returned to work and daily activities 3 weeks later. All pain medications were discontinued within 3 months. A diagnosis of primary osteoporosis was made after a full metabolic



[A] Sagittal reconstruction of the CT after kyphoplasty of D5 and D6. We can see the cement is contained in the body of the vertebrae, with full reconstruction of the vertebral height

[B] Sagittal reconstruction of the CT scan showing a burst fracture of L4 and a compression fracture L3

[C] Lateral X-ray after decompression of the left L4 nerve root and cement augmentation of L3 and L4 vertebrae

bone workup, and the patient was put on bisphosphonates, calcium and vitamin D.

COMMENT

Seizures are a known cause of fractures. The most common bones to break are vertebrae, distal radius, and proximal femurs. Interestingly, as in the case presented here, seizures during sleep cause more fractures, indicating that the muscle spasm is strong enough to cause fractures. Most of the vertebral fractures are compression fractures that respond to non-operative treatment (analgesia, rest, bracing). However, burst fractures have also been documented, narrowing the spinal canal, causing neurological symptoms requiring urgent surgical decompression [2].

Hypoglycemia (defined as a measured blood sugar below 70 mg/dl) is a known cause of seizures. When blood glucose levels drop the brain does not receive the basal amounts of glucose needed for normal function, eventually leading to confusion, disorientation, seizures, coma and death. Insulin-dependent diabetic patients suffer from hypoglycemia 10% of the time, and 62–170 episodes of severe hypoglycemia per 100 patient years were reported to occur [3]. Insulin-dependent diabetes has been associated with low bone density. The Nord-Trondelag Health Survey showed a significant increase in hip fracture rates among female diabetic patients compared to non-diabetic female patients [4]. The longer the patient has diabetes, the higher the chances of suffering a fracture. The exact cause of higher fracture risk is not known; however, animal models suggested a deleterious effect of insulin-like growth factors and other cytokines on diabetic bone metabolism. In addition, the fact that the disease usually starts at a young age, when bones are still growing, may influence maximal bone density and bone mineralization. There is an association between diabetes and celiac disease, gastropathy and neurogenic bowel syndrome – all factors that lead to osteomalacia and osteoporosis and increase the risk of fractures.

Despite the high prevalence of osteopenia and hypoglycemic events in diabetic patients, there are singular reports in the English literature of vertebral fractures caused by hypoglycemia-induced epileptic seizures in diabetic patients. In his article, Nabarro [5] states that in his long career as a diabetologist he encountered only four cases of vertebral fractures caused by hypoglycemia, and that these fractures are most likely missed, indicating the need for a thorough evaluation of diabetic patients complaining of back ache after suffering from a nocturnal hypoglycemic event.

The incidence of concomitant vertebral fractures is as high as 10% in traumatic and osteoporotic fractures. The fractures can be in adjacent levels or skipping vertebrae. These fractures can be easily missed, as the patient refers to the primary cause of pain and the second injury may be masked at that time. As in the case presented here, only after undergoing treatment for the T5-T6 fractures did the patient begin to suffer from the lumbar burst fracture. In trauma cases, ATLS (Advanced Life Trauma Life Support) recommends a whole-body CT scan to avoid missing injuries in stable patients as part of the secondary survey. The case described here raises the question whether convulsion-induced trauma should be managed in the same way. These fractures need to be sought with a high index of suspicion when the patient complains of sensorineural changes after the initial diagnosis.

In conclusion, vertebral fractures are an elusive complication and should be looked for in patients suffering backache after hypoglycemic convulsions. If a fracture is noted, a complete survey of the spine is recommended to rule out other vertebral lesions. These patients must be treated for their acute injuries followed by a full evaluation and treatment of their metabolic bone disease.

Corresponding author:
Dr. J.E. Schroeder
Dept. of Orthopedic Surgery, Hadassah-Hebrew University Medical Center (Ein Kerem Campus), P.O. Box 12000, Jerusalem 91200, Israel
Fax: (972-2) 677-8052
email: Schroeder.josh@gmail.com

References

1. Mattson RH, Gidal BE. Fractures, epilepsy, and antiepileptic drugs. *Epilepsy Behav* 2004; 5 (Suppl 2): S36-40.
2. Roohi F, Fox A. Burst fracture of the first lumbar vertebra and conus-cauda syndrome complicating a single convulsive seizure: a challenge of diagnosis in the Emergency Department. *J Emerg Med* 2006; 31 (4): 381-5.
3. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2009; 94 (3): 709-28.
4. Forsen L, Meyer HE, Midthjell K. Edna TH. Diabetes mellitus and the incidence of hip fracture: results from the Nord-Trondelag Health Survey. *Diabetologia* 1999; 42 (8): 920-5.
5. Nabarro JD. Compression fractures of the dorsal spine in hypoglycaemic fits in diabetes. *Br Med J (Clin Res Ed)* 1985; 291 (6505): 1320.

Capsule

The mechanisms of protein aggregation

Amyloid fibrils are insoluble protein aggregates that play a role in various degenerative diseases. Recent experiments have provided insight into fibrillar structures; however, the mechanisms of aggregation remain unclear. Neudecker et al. describe the structure of a transient folding intermediate in a protein SH3 domain known to undergo aggregation. The intermediate is stabilized by non-native interactions and exposes an aggregation-prone β strand. Thus, for this protein, folding from the intermediate state will compete with aggregation.

Science 2012; 336: 362

Eitan Israeli