Infections and glycosphingolipids

A recent case report in the journal described a Gaucher's disease patient, dangerously infected with salmonella that responded poorly to antibiotic treatment. However, use of enzyme replacement with glucosylceramidase lowered tissue levels of glucosylceramide (GlcCer), and produced a slow but dramatic improvement. The article points out that infection is an important aspect of the genetic disorder. I would like to mention important observations that explain this unfortunate complication and their significance for many patients with infections.

Many research studies have shown that a wide variety of bacterial and viral infections involve binding of the organism to a glucosphingolipid in the cell surface. Patients with Gaucher's disease accumulate not only GlcCer, but also some of the more complex glucosylphosphatidyl inositol and glucosylceramides. This second order distortion explains why these patients are susceptible to infection. In the case of salmonella, the organism binds to GlcCer and acidic glucosylphosphatidyl inositol.

It follows then that depleting glucosphingolipids in people should reduce the number of binding sites for infectious agents and, possibly, prevent the development of new infections. If the glucosylphosphatidyl inositol already bound to infectious particles are in a reversible equilibrium, one can expect that a decrease in the body's total glucosylphosphatidyl inositol content will force the infectious particles to leave the body, one way or another. This, basically, is why enzyme replacement helped the Gaucher's patient.

Lowering cellular glucosylphosphatidyl inositol has indeed been shown to reduce adhesion of pathogens.1,2 Mouse depleted of their glucosylphosphatidyl inositol resisted colonization of the urinary tract. Interference with HIV-1 progression by glucosylphosphatidyl inositol depletion is also established.3,4 Studies of this sort utilised inhibitors of GlcCer synthase. Other approaches can also achieve reductions in cellular glucosylphosphatidyl inositol. Caloric restriction long been known to extend life, slowing the appearance of infections, cancer, atherosclerosis, and other serious illnesses. Brief fasting or caloric restriction might prove helpful in fighting a current illness. This approach should also be helpful for micro-organisms that bind primarily to glycoproteins.

Other means of slowing glucosylphosphatidyl inositol synthesis have been described.5 These include the use of chlorpromazine, tamoxifen, verapamil, RU-486 (mifepristone), androgens, all-trans retinoic acid, and cyclosporine. Glucosamine, widely used to prevent joint pain, should compete against glucose, lowering the level of uridine diphosphoglucone.

Biosynthesis of the GlcCer precursor, ceramide, can be slowed by inhibiting sphingomyelin hydrolysis. This can be done by avoiding arachidonic acid, a stimulator of the enzyme. Dietary fats should therefore be restricted to olive and canola oil. Glutathione, the major thiol in cells, slows sphingomyelin hydrolysis and should be maintained at a high level by eating a glutathione precursor, N-acetyl cysteine. 3-O-Methyl sphenoglycan is a direct inhibitor of the hydrolase. Supplementing the diet with modest amounts of antioxidants will protect glutathione against oxidation. Carnitine, available as a food supplement, helps lower tissue fatty acids by speeding their oxidation. (Since ceramide is formed from two molecules of fatty acid, general fat depletion will not work. ) The level of ceramide can also be lowered by stimulating its conversion to sphingomylins by reaction with lecithin; ergo, eat extra lecithin. GlcCer, the simplest glucosylphosphatidyl inositol, is normally degraded by hydrolysis, which can be speeded by phosphatidylserine, available as a food supplement.

Shree proposes some explanations for his patients' complaints about their lymph glands, but surprisingly fails to mention adrenal insufficiency as a possible cause of those symptoms. Enlargement of lymph nodes is one of the many clinical features of CFS shares with primary adrenal insufficiency.5 As a consequence of their common adrenal abnormalities, CFS and Addison's disease6 also share an additional feature, namely, impaired production of dehydroepiandrosterone sulphate, which is secreted from the adrenal glands.7

Shree points out that general and neurologically examination and other investigations were normal in all patients with CFS. His article, however, does not specify whether those investigations also included an assessment of adrenal function. As such, the diagnostic criteria for Addison's disease is not met in his patients. In view of the 42 clinical features that CFS shares with Addison's disease, I believe that the careful evaluation of the adrenal function of patients with CFS would have enlightened Shree more than did all other investigations combined.

Phantom lymphadenopathy. An association with chronic fatigue syndrome

Shee reports an association between chronic fatigue syndrome (CFS) and what he regards as a “phantom lymphadenopathy”. However, his failure to observe “true lymphadenopathy” in patients with CFS complaining of swollen lymph glands, because he did not compare their dimensions with the ones that were measurable before the appearance of patients’ complaints.

As someone who suffered from CFS and reported on its dramatic resolution thanks to old and new drugs for Addison's disease,8 I clearly remember that my lymph nodes, just a few days after the abrupt onset of CFS, became mildly painful and began to swell gradually. This slow process of enlargement lasted approximately one month. However, even when my lymph glands stopped swelling further (but continued to be mildly painful), their dimensions were still clinically within normal limits. This may indirectly explain why Shee found that “careful examination did not confirm lymphadenopathy” in CFS patients with “self diagnosed enlarged lymph glands”.

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References

BOOK REVIEWS

The reviewers have been asked to rate these books in terms of four items: readability, how up-to-date they are, accuracy and reliability, and value for money, using simple four point scales. From their opinions we have derived an overall “star” rating: * = poor, ** = reasonable, *** = good, **** = excellent.

Narrative-based Primary Care: a practical guide.


The progressive decline in GPs’ morale has resulted not only from an increasing workload, but also from awareness that patients, R Baschetti
Retired Medical Inspector of the Italian State Railways, CP 67, 06001–970 Fortaleza (CE), Brazil; baschetti@baydenet.com.br

References
How To Survive in Anaesthesia, 2nd Edition


This is aimed at trainees in their first year of anaesthesia. The book’s light-hearted, easy reading style cleverly passes the tips and tactics that experienced anaesthetists use to avoid the disasters that lurk around every operating theatre corner. The 2nd edition of the book has been reduced in physical size to operate theatre corner. The 2nd edition of the book has been reduced in physical size to 631186 ISBN 0-7279-1683-1.

Teaching medicine is an art, constantly undergoing change, with mechanisms for imparting knowledge being continuously challenged and criticised. Certain aspects of medicine, and in particular surgery, will always need to be didactic and some of my best memories from medical school emanate from forcefully delivered lectures which left no room for lateral thinking, a far cry from today’s problem orientated learning processes.

The editors and authors have combined both styles and have sought to provide a comprehensive textbook covering all aspects of surgery, both core general surgery and relevant subspecialties. The book seeks to provide a “roadmap” for common symptoms and signs and has been divided up into non-emergencies and emergencies. The style and arrangement of the book are different from other textbooks of surgery. The focus is on symptoms and signs which the surgical trainee is likely to encounter, and works backwards to show how one can identify which of several possible diseases produced that clinical picture. I have to say that I found this quite difficult and rather unstimulating, though this probably represents my own medical training in a more traditional didactic environment. The book suffers from a minimum of colour, presumably for economic reasons, but also how and when, and to become more reflective and honest (both intellectually and emotionally). Putting this into practice involves repeatedly testing ideas or beliefs (I was struck by the analogy to the approach of Popper) without undermining expertise, and then acting within “currently accepted systems of thought”, which will change over time. Open minded and reflective GPs, particularly those involved in teaching, will find this excellent book both thought provoking and useful. Already, I have changed my own greeting to “What would you like to tell me about?”

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Pathways in Surgery. 3rd Ed.


Statistics in Clinical Practice. 2nd Ed.


This book starts by describing how statistics are used to summarise data in numerical and graphical form. Particular topics included are different forms of data, measures of central tendency and dispersion, and the normal distribution. Further chapters deal with probability and how statistics can be used in interpreting clinical data and drawing conclusions. Topics described here are sensitivity, specificity, p values, confidence intervals, standard error, and statistical power. The final chapters deal with statistical modelling including linear regression and assessment of bias.

The text is clearly and concisely written with many worked examples and questions to explain the concepts. I would highly recommend the book to both qualified health professionals and students in training who want a basic understanding of statistics and how they can be used to interpret clinical papers. It will also be of value to those wanting an introduction to research methodology. The book is reasonably priced at £14.95.

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Warwick University Short Course

7–10 July 2003: Techniques and applications of molecular biology: a course for medical practitioners. A four day residential course for those in the medical profession wishing to improve their understanding of the principles and applications of genetic engineering techniques. Details: Dr Charlotte Moorman, Department of Biological Sciences, University of Warwick, Coventry CV4 7AL, UK. (tel: 04 0214 7652 3540; fax 04 0214 7652 3701; email Charlotte.Moorman@warwick.ac.uk).