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 glucosylceramide glucosidase lowered tissue levels of glucosylceramide (GlCer), 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 GlCer, but also some of the more complex glucosphingolipids formed from GlCer. This second order accumulation explains why these patients are susceptible to infection. In the case of salmonella, the organism binds to GlCer and acidic glucosphingolipids.

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 glucosphingolipids already bound to infectious particles are in a reversible equilibrium, one can expect that a decrease in the body's total glucosphingolipid 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 glucosphingolipids has indeed been shown to reduce adhesion of partner cells. Mice depleted of their glucosphingolipids resisted colonization of the urinary tract. Interference with HIV-1 progression by glucosphingolipid depletion is especially promising. Studies of this sort utilised inhibitors of GlCer synthase. Other approaches can also achieve reductions in cellular glucosphingolipids. Caloric restriction has 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 infection. This approach should also be helpful for micro-organisms that bind primarily to glycoproteins.

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

GlCer precursor, ceramide, can be slowed by inhibiting sphingomyelin hydrolisis. 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 sphingomyelin 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 is not helpful.) The level of ceramide can also be lowered by stimulating its conversion to sphingomyelin by reaction with lecitin; ergo, eat extra lecitin. GlCer, the simplest glucosphingolipid, is normally degraded by hydrolysis, which can be speeded by phosphatidylserine, available as a food supplement.

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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 lymphadenopa-thy” in patients with CFS complaining of swollen lymph glands does not exclude a real, albeit subclinical enlargement of those 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, 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”.

Shee 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 of clinical features that CFS shares with primary adrenal insufficiency. As a consequence of their common adrenal abnormalities, CFS and Addison's disease also share an additional feature, namely, impaired production of dehydroepiandrosterone sulphate, which is secreted from the adrenal glands.

Shee points out that general and neurological 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. Hypoadrenalism, despite being present in CFS (as well as in Addison's disease), is not mentioned in Shee's article as a possible explanation for the symptoms of his patients with CFS and, therefore, he probably omitted to measure their cortisol levels.

In view of the 42 clinical features that CFS shares with Addison's disease, I believe that a careful evaluation of the adrenal function of patients with CFS would have enlightened Shee more than did all other investigations combined.

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References

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,
How To Survive in Anaesthesia. 2nd Edition


This is aimed at trainees in their first year of anaesthesia. The book’s lighthearted, easy reading style cleverly passes on 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 make it even more portable. This probably represents my own medical picture. I have to say that I found this quite difficult and rather unstimulating, though it is also an excellent introduction to research methodology. 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.

Teaching and learning in clinical contexts: a resource for health professionals

A new web based learning programme for clinical teachers has been launched (www.clinicalteaching.nhs.uk). It has been developed as part of a London Deanery initiative to develop web based educational packages to support training of doctors and other health professionals. The project has been led by Dr Shelley Head, Dean of Postgraduate Medicine at the London Deanery and managed by Judy McKinnon, Head of Curriculum Development at Imperial College School of Medicine. The Steering Group is chaired by Dr Diana Wood, Deputy Dean for Education at Bart’s and the Royal London Medical School; membership includes representatives from each of the London medical schools and from the Faculty of Health and Social Care Sciences at King’s University.

For further information contact: Carol Jollic, Project Officer (tel: 020 8995, email: carol@jollic.fsword.co.uk).

NHS Education for Scotland e-Library

Readers who work for the NHS in Scotland might like to know of a new initiative launched by NHS Education for Scotland. The Scotland e-Library is a virtual collection of healthcare information resources designed to encourage delivery of high quality healthcare services focusing on evidence based care and best practice (www.elib.scot.nhs.uk).

For further information contact: Dr Ann Wales, NHS Scotland Library Service Development Coordinator (tel: 0141 223 1551; fax: 0141 223 1403; email: ann.wales@nes.scot.nhs.uk) or Nicola Carlyle, Communications Officer (tel: 0141 247 6602; fax: 0141 225 9970; email: nicola.carlyle@nes.scot.nhs.uk).

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 include 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.
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