LETTERS

Another case of HBV associated membranous glomerulonephritis resolving on lamivudine

Connor and colleagues’ (see page 446) report rapid resolution of a hepatitis B associated membranous glomerulopathy and nephrotic syndrome after two months of oral lamivudine. We would like to add our experience with lamivudine in a similar case.

A 5 year old female of Vietnamese origin presented with a two week history of periorbital swelling and weight gain. She had 3 plus protein, 10–20 dysmorphic red blood cells, and red blood cell casts in her urine. Serum albumin was low at 19 g/l, cholesterol was 9.8 mmol/l, and serum complement C3 and C4 were reduced (0.61 g/l and <0.1 g/l, respectively). She was hepatitis B surface antigen positive and hepatitis B surface antibody negative. The physician caring for her at that time placed her on prednisone 60 mg/m²/day in three divided doses, and referred her to our service six weeks later, as the nephrotic syndrome was unresponsive to steroids. Her viral load initially was 1090 pg/ml of hepatitis B DNA in peripheral blood, and rose to >2000 pg/ml after four weeks of steroids, when ALT peaked at 72 U/l. A renal biopsy revealed stage II membranous glomerulonephritis. A liver biopsy showed focal lobular and portal inflammation and changes consistent with a mild chronic hepatitis.

She was started on lamivudine at a dose of 50 mg once daily (2.5 mg/kg), with steroids being weaned off over four weeks. Two weeks later the hepatitis B DNA dropped to 1686 pg/ml, decreased to 7 pg/ml two months later, and was undetectable at three months.

She continued to be hepatitis e antigen positive without detectable e antibodies. The patient’s proteinuria was cleared after three months of treatment, and serum albumin remained normal thereafter. She continued to take lamivudine for 13 months without rebound proteinuria. Six months after discontinuing lamivudine, she remained clinically well, her urinalysis showed 0.04 g of protein per 24 hours, and there was microscopic haematuria. Hepatitis B DNA rose to >2000 pg/ml, indicating continued active viral replication.

A repeat renal biopsy showed multiple electron dense deposits which had been incorporated into the lamina densa with fragmentation of the latter, consistent with a membranous glomerulonephritis stage II/III. She has evidence of hyperfiltration with a glomerular filtration rate of 163 ml/min/1.73 m² as determined by Tc DTPA clearance.

The ideal treatment for hepatitis B associated membranous nephropathy in children is yet to be determined. There is one retrospective analysis of six studies comprising a total of 82 children that showed 60% complete remission 12 months after the diagnosis, 7.3% renal failure, 2.4% end stage renal failure, and 30% persistent disease.3 Steroid therapy should not be used as it does not appear to be beneficial, and the steroids may enhance viral replication in mononuclear cells.4 The average duration of proteinuria is 30 months.5 We believe that treatment with lamivudine in this case likely suppressed the virus and resulted in early remission of clinical nephrotic syndrome; however, the subsequent rebound in viral load and renal biopsy results probably indicates loss of viral suppression, leading to the subclinical relapse. It is unknown at this time if the strain of hepatitis B has developed resistance to lamivudine. Effective viridal agents may be needed to prevent relapses of hepatitis B induced membranous glomerulonephritis. Finally, further work is needed to investigate the efficacy of this treatment in a larger cohort and to establish guidelines about the duration of such therapy.

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References

PCD or not PCD
In response to the leading article on primary ciliary dyskinesia (PCD)1 and the commentaries by Dr Andrew Boon, we write as clinicians with an interest in PCD who work in general paediatrics and neonatology. We agree with Dr Boon that the identification of an uncommon medical disorder from the large number of children presenting with common symptoms and signs is a major challenge for the general paediatrician. We also support the view that it is undesirable and certainly impractical to refer every child with recurrent episodes of cough, rhinitis, and sore oritis media for further investigation. However, we believe that the aim of the editorial by Professor C O’Callaghan and Dr A Bush was to provide information on subtle differences in the clinical presentation of PCD to help us differentiate these patients from those with common non-specific childhood respiratory problems. For example, it is uncommon for a term infant to be admitted to a neonatal unit with significant respiratory concerns following a vaginal delivery but common in infants with PCD. We performed an as yet unpublished questionnaire survey of individuals belonging to the PCD support group which identified that 47% had been admitted to a neonatal unit with unexplained respiratory problems following a normal vaginal delivery. Rhinitis is also very rarely seen in normal neonates but is extremely common in patients with PCD. Other subtle clues increasing the likelihood of PCD are the characteristic of the cough and middle ear problems especially the development of persistent otitis media after tympanostomy tubes.

There is of course no doubt that a cheap reliable screening test would significantly help promote early diagnosis of PCD but it is not yet on the horizon. A detailed history especially of the neonatal period will help those working in neonatology or general paediatrics to highlight the patient that should be referred for further investigations including cilia studies.

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Hazards in the epidemiological study of sudden infant death syndrome
The study of Platt and Pharaoh confirms the increased risk of SIDS in twins compared with singletons.3 They point out that a major component of that higher accrued risk is that twins tend to be of low birthweight. Their finding that like-sex twins are at no greater risk than unlike-sex twins adds to the substantial evidence concerning the very limited role of genetic susceptibility for SIDS, and the rarity of recurrence in siblings of victims.1

The authors illustrate the gratifying fall in the number of SIDS during the six years of their 1990s study. As the number of infants categorised each year as SIDS in England and Wales comes nearer to that of 200, so it becomes more important for those involved in epidemiological studies to be sure that the categorisation (i.e. the diagnosis) is correct. I refer to infants who, a few years after they have been categorised as SIDS, have been re-assessed, usually because of a subsequent child being abused or killed, and, in the course of court proceedings, findings are made that...
the previous infant(s) were killed by the parent, rather than dying of natural causes. Currently, there does not seem to be a mechanism for correcting the national childhood mortality statistics when later, correct diagnoses are made. For instance, in the 1990s, I am aware of at least 20 infants who were initially categorised as SIDS, but who in later years, after extensive child protection investigations, were deemed to have been killed, usually by smothering. Colleagues will know of other cases: the true number will be higher. It is unfortunate that the official statistics do not seem to be altered retrospectively, and remain a misleading figure for any researcher. I should add that, since much of the cases of parental killing of which I am aware involves twins, the conclusions of Platt and Pharoah are more likely to have been strengthened rather than weakened by such false diagnosis. Hopefully the number of SIDS continues to fall, it will become ever more difficult for research workers to compare small subgroups of SIDS within national mortality statistics unless the statistics are revised retrospectively in response to later correct diagnosis.

It is appropriate to warn of an additional hazard for research workers in this field. In the same issue of Archives there was an interview of 2 epidemiologists in the UK, partly concerning the possibility of vagal overactivity as a cause of sudden infant death. They referred to a “positive family history of SIDS”. A particular hazard here is that, unless details of that family history are verified in considerable detail, mistakes may be made. In recent years I have been involved with families in which parents who have repeatedly denied that their children were killed by them have provided to paediatricians, genetic counseling services, and to SIDS research workers, a false family history of SIDS—for instance, mother saying that two of her own siblings “died of SIDS”. Such statements invariably are taken at face value and become part of the medical history: they are included in family trees in the hospital notes, and they have been quoted and displayed in published research concerning SIDS, yet subsequent questioning of the relevant grandparent has revealed that no such infant deaths occurred. Presumably, the mother responsible for smothering or killing her child has invented the family history, either to gain more medical attention for herself, or as a cover to distract from her actions.

A second reason for verifying the alleged previous infant deaths in more detail is that, even if a death has occurred, it is necessary to explore the extent of the contemporary investigation and pathological examination. In one of Professor Emery’s studies of infants initially categorised as SIDS, detailed re-assessment pointed to either a definite natural cause, or abuse, in two thirds of cases. 1

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Use of inhaled corticosteroids in children
I read with interest the article Survey of adrenal crisis associated with inhaled corticosteroids in children byeshire of and the accompanying editorial in the December issue of Archives.

In the reported cases, the children had been administered substantially (up to 5 times) higher than the Glaxo SmithKline (GSK) Core Data Sheet recommended Fluticortolone dose of 400 mcg/day and use of fluticasone (FP) at such doses is certainly not endorsed by GSK. Within the recommended doses, there is a wealth of data from controlled clinical trials that Fluticasone is a well tolerated and effective drug in adults and children. There are a number of recent studies in children which identified no cases of adrenal crisis and no effect on growth with fluticasone. In a recent survey, the GSK Core Data Sheet recommended Fluticortolone dose of 400 mcg/day and use of Fludicasone (FP) at such doses is not endorsed by GSK. Within the recommended doses, there is a wealth of data from controlled clinical trials that Fludicasone is a well tolerated and effective drug in adults and children. There are a number of recent studies in children which identified no cases of adrenal crisis and no effect on growth with Fludicasone.

There are also a number of methodological deficiencies in this survey, the most important being that the survey is not case-controlled and it lacks information on true incidence versus the previous infant(s) were killed by the parent, rather than dying of natural causes. Currently, there does not seem to be a mechanism for correcting the national childhood mortality statistics when later, correct diagnoses are made. For instance, in the 1990s, I am aware of at least 20 infants who were initially categorised as SIDS, but who in later years, after extensive child protection investigations, were deemed to have been killed, usually by smothering. Colleagues will know of other cases: the true number will be higher. It is unfortunate that the official statistics do not seem to be altered retrospectively, and remain a misleading figure for any researcher. I should add that, since much of the cases of parental killing of which I am aware involves twins, the conclusions of Platt and Pharoah are more likely to have been strengthened rather than weakened by such false diagnosis. Hopefully the number of SIDS continues to fall, it will become ever more difficult for research workers to compare small subgroups of SIDS within national mortality statistics unless the statistics are revised retrospectively in response to later correct diagnosis.

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