J. Paediatr. Child Health (2005) **41**, 218–220

Hepatic failure in a child with anti-epileptic hypersensitivity syndrome

Albert M Li, Edmund AS Nelson, Ellis KL Hon, Frankie WT Cheng, Dorothy FY Chan, Ngai Chuen Sin, Kwok Chiu Ma, Kam Lau Cheung and Tai Fai Fok

Department of Paediatrics, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong

Abstract: An 11-year-old boy developed severe hypersensitivity reaction to phenobarbitone resulted in fulminant hepatic failure. During the course of illness, he developed clinical features compatible with severe acute respiratory syndrome (SARS) that may have complicated the recovery of his underlying hypersensitivity reaction, which was subsequently controlled with intravenous immune globulin and corticosteroids.

Key words: anti-epileptic hypersensitivity syndrome; hepatic failure; SARS.

CASE REPORT

An 11-year-old boy with an idiopathic seizure disorder since the age of 6 years was put on phenobarbitone (5 mg/kg per day) 2 weeks prior to his first admission. He had a previous history of mild skin rash to carbamazepine. There was no other significant past medical or family history.

He had developed flu-like symptoms a few days prior to admission, for which he was given antibiotics by a general practitioner. On admission, he had fever and an itchy generalized urticarial skin rash and was treated as a case of antibiotic-induced allergic reaction. He was given a 3-day course of prednisolone (1 mg/kg per day) and the rash and fever responded rapidly. Routine blood tests including liver function were normal. His seizures became more frequent and phenobarbitone was recommenced prior to discharge.

He returned 2 days later with worsening skin rash and fever. On this occasion, the phenobarbitone was considered the likely cause of the reaction. Examination revealed generalized lymphadenopathy and a widespread itchy erythematous maculopapular rash. Baseline blood investigations showed a haemoglobin level of 11.7 g/dL, total white cell count of 7.9×10^9/L of which 3% was eosinophils (0.2×10^9/L) and 7% was lymphocytes (0.6×10^9/L) and a platelet count of 104×10^9/L. Liver function was normal. Chest radiograph did not reveal any pneumonic changes. He remained febrile and a repeat liver function on day 4 showed evidence of hepatitis with a raised alanine aminotransferase (ALT) of 1361 IU/L and an international normalized ratio (INR) of 2.12. The clinical picture was compatible with anti-epileptic hypersensitivity syndrome (AHS). Prednisolone (1 mg/kg per day) was restarted on day 5 and associated with improvement allowing discharge 10 days after admission. The ALT at the time of discharge was 1066 IU/L and INR was normal. During this admission, he stayed on the same isolation ward, but in a different cubicle to two patients with severe acute respiratory syndrome (SARS).

He was re-admitted 2 days later with a high swinging fever (up to 40°C), malaise, myalgia, dry cough and worsening of his skin rash. On examination, the chest was clear and the liver was enlarged to 4 cm below the right costal margin. Chest radiograph showed bilateral basal haziness. A possible diagnosis of SARS was suspected and he was managed according to our local guidelines at the time that included ribavirin. ALT on admission was 1142 IU/L, INR was 1.5 and blood glucose and ammonia levels were normal. Over the next 3 days, his temperature started to subside and there was no progression of the pneumonic changes on serial chest radiographs. Preliminary viral screen on nasopharyngeal aspirate sample, using rapid test polymerase chain reaction (RT-PCR) was negative for coronavirus and ribavirin was stopped. His fever pattern (Fig. 1) once again became unsettled and his condition further deteriorated 3 days later when he became more tired, jaundiced and less responsive. Urgent cranial computed tomography (CT) and ultrasound scan of the abdomen were unremarkable. INR subsequently went up to 4.94 and the highest ammonia level was 137, while the ALT has dropped to 433 IU/L. It was considered that this dramatic deterioration could be related to AHS and a dose of intravenous immune globulin (IVIG, 1 g/kg) was given prior to transfer to the regional liver unit for possible liver transplant. The work-up for other possible causes of liver failure was unrevealing. His level of consciousness deteriorated further and he was intubated and ventilated. However, over the next 24 h, while being prepared for a living-related liver transplant, his condition improved with the INR dropping to 2.7 and the ammonia level trending downward. He was extubated after 48 h, but developed thrombocytopaenia requiring platelet transfusion. In view of the possibility of this being related to ongoing AHS a further dose of IVIG (1 g/kg) was given with a significant improvement in the platelet count. Five days after the second dose of IVIG he developed high fever and increasing rash over the extremities. A third dose of IVIG (1 g/kg) and prednisolone (2 mg/kg/day) were given and associated with a dramatic drop in temperature and improvement in the rash and general condition within 24 h.

DISCUSSION

Anti-epileptic hypersensitivity syndrome (AHS) may be underrecognized and is potentially fatal. The course of recovery can be fluctuating and long, even in mild cases.[1] We described a child with severe AHS whose presentation was complicated by symptoms and signs that were compatible with the diagnosis of SARS. His subsequent response to IVIG and steroid may suggest an underlying autoimmune type of pathogenesis.

Correspondence: Dr Albert Martin Li, Department of Paediatrics, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong. Fax: 852 2636 0020; email: albertmli@cuhk.edu.hk

Accepted for publication 9 March 2004.

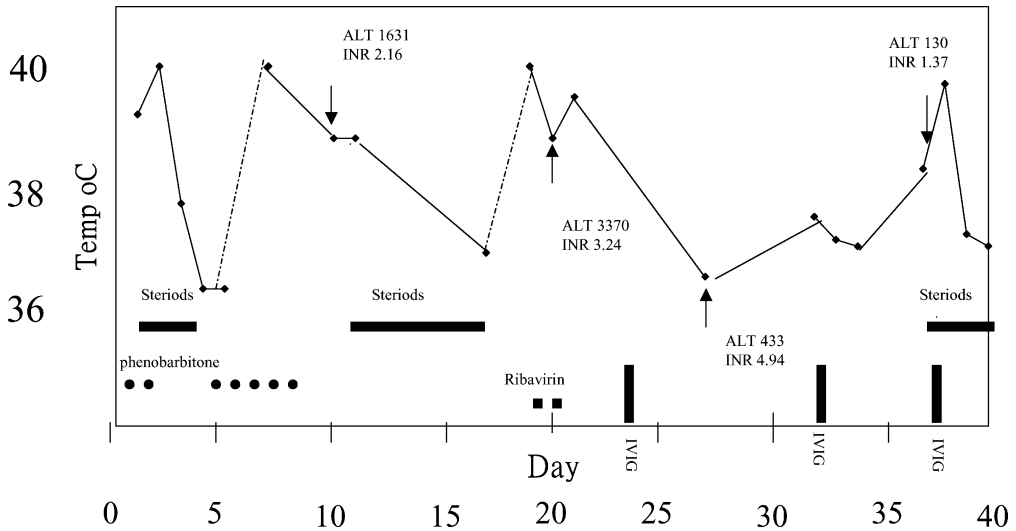

Fig. 1 Temp., temperature (°C); ALT, Alanine aminotransferase (iu/l); INR, international normalized ratio; NH3, Ammonia (umol/l); IVIG, intravenous immune globulin. D1 – first hospital admission, D5 – first hospital discharge, D7 second hospital admission, D19 – third hospital admission, D27 – condition deteriorated, transferred to liver unit.

AHS is an idiosyncratic, non-dose-related adverse reaction reported to occur with anticonvulsants that contain an aromatic ring (carbamazepine, phenobarbital and phenytoin). Our patient had a previous mild reaction to carbamazepine and that could well be the early warning sign that he was prone to AHS. The condition was first described with the use of phenytoin.[2] The true incidence is unknown and has been estimated to be between 1 in 1000 and 1 in 10 000 exposures.[3] In a review by Bessmertny *et al*.[4] 14 cases of AHS were identified over a period of 11 years. Eight patients were taking phenytoin, six carbamazepine and four phenobarbital alone or in combination. The mean age was 10.4 years and the mean time from exposure to development of symptoms was 23 days. The occurrence of AHS has no relationship with the underlying neurological condition for which anti-epileptic treatment was started. In addition to rash and fever (present in all patients by definition), other common features of AHS were lymphocytosis (71.4%), elevated erythrocyte sedimentation rate (64.3%), elevated aminotransferases (64.3%), lymphadenopathy (57.1%), eosinophilia (42.8%), coagulopathy (42.8%), leucocytosis (35.7%), leucopaenia (35.7%), hyperbilirubinaemia (35.7%) and nephritis (7.1%). In Bessmertny's series all children recovered except for one who died from liver failure. This child was taking a combination of phenytoin and carbamazepine, and there was a delay of 2 weeks after the start of symptoms before the medications were stopped.

The underlying pathogenesis of AHS is unknown. There is evidence that the condition is immune mediated with autoimmune hypothyroidism being a recognized late complication following AHS.[1] Others have proposed that AHS is a form of graft-versus-host disease.[5] The use of steroids in this condition is controversial with both positive and negative results being reported in the literature.[6–9] In Bessmertny's series, the clinical outcome was similar between children who received systemic steroid therapy and those who did not.[4] There have been earlier reports on the use of IVIG for AHS,[10–12] improvements in terms of rise in platelet count, alleviation of symptoms of fever, rash, oedema and oral ulcers were seen within 24–48 h after single-dose therapy. In our patient, the fluctuating course of AHS necessitated the use of multiple doses of IVIG and steroid, and on each occasion there was definite clinical and laboratory response. It has been suggested that IVIG blocks CD95, a cell surface receptor on keratinocytes, which plays a role in triggering apoptosis. Antibodies present in IVIG have also been shown to block CD95-mediated keratinocyte death *in vitro* and in patients with toxic epidermal necrolysis and a similar mechanism could be responsible for improvement seen in AHS.[1]

Our patient had multiple exacerbations during the course of the illness, the first episode could be explained by the reintroduction of phenobarbitone. The second episode could be induced by an intercurrent infection. The diagnosis of SARS was suspected when our patient re-presented with high fever, cough, chest radiograph changes, malaise and myalgia. He had been staying in the same isolation ward where SARS cases were being treated. Although no direct contact was likely and strict infection control measures were practiced by medical and nursing staff, it was considered feasible that transmission could have occurred. Early adult experience suggests that patients with an underlying hepatic problem may have a higher risk of morbidity and mortality if affected by SARS.[13] His RT-PCR was negative and we stopped the ribavirin after 48 h. Ribavirin as a possible exacerbating factor for the hepatic damage was considered unlikely. Liver dysfunction associated with its use has never been reported and the drug is a recognized treatment for chronic hepatitis C.[14]

In summary, it is important for clinicians to be aware of the anti-epileptic hypersensitivity reaction and cross-reaction between the various aromatic anti-epileptics is common. Prompt withdrawal of the culprit medication usually results in complete resolution of symptoms in most cases. However, our patient continued to have exacerbations for up to 6 weeks after stopping the treatment. The role of steroids and IVIG in this condition is still unresolved but in our case, their use was temporarily associated with clinical and laboratory improvement. Whether any secondary viral or bacterial infection during the course of the reaction may exacerbate the condition is unknown.

REFERENCES

1 Schlienger RG, Shear NH. Anti-epileptic drug hypersensitivity syndrome. *Epilepsia* 1998; **39**: S3–7.
2 Saltzstein S, Ackerman L. Lymphadenopathy induced by anticonvulsant drugs and mimicking clinically and pathologically malignant lymphomas. *Cancer* 1959; **12**:164–82.

3 Gennis MA, Vemuri R, Burns EA, Hill JV, Miller MA, Speilberg SP. Familial occurrence of hypersensitivity to phenytoin. *Am. J. Med*. 1991; **91**:631–4.
4 Bessmertny O, Hatton RC, Gonzalez-Peralta RP. Anti-epileptic hypersensitivity syndrome in children. *Ann. Pharmacother.* 2001; **35**: 533–8.
5 Gleichmann H. Studies on the mechanism of drug sensitization: T-cell dependent popliteal lymph node reaction to diphenylhydantoin. *Clin. Immunol. Immunopathol*. 1981; **18**: 203–11.
6 Vick NA. Suppression of carbamazepine-induced skin rash with prednisone. *N. Engl. J. Med*. 1983; **309**: 1193–4.
7 Chopra S, Levell NJ, Cowley G, Gilkes JJ. Systemic corticosteroids in the phenytoin hypersensitivity syndrome. *Br. J. Dermatol*. 1996; **134**: 1109–12.
8 Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): An update. *Dermatology* 2003; **206**: 353–6.
9 Hampton KK, Bramley PN, Feely M. Failure of prednisolone to suppress carbamazepine hypersensitivity. *N. Engl. J. Med*. 1985; **313**: 959.
10 Salzman MB, Smith EM. Phenytoin-induced thrombocytopenia treated with intravenous immune globulin. *J. Pediatr. Hematol. Oncol*. 1998; **20**: 152–3.
11 Scheuerman O, Nofech-Moses Y, Rachmel A, Ashkenazi S. Successful treatment of antiepileptic drug hypersensitivity syndrome with intravenous immune globulin. *Pediatrics* 2001; **107**: e14.
12 Straussberg R, Harel L, Ben-Amitai D, Cohen D, Amir J. Carbamazepine-induced Stevens-Johnson syndrome treated with IV steroids and IVIG. *Pediatr. Neurol*. 2000; **22**: 231–3.
13 Lee N, Hui D, Wu A *et al*. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N. Engl. J. Med*. 2003; 348.
14 Lawrence SP. Advances in the treatment of hepatitis C. *Adv. Int. Med*. 2000; **45**:65–105.