MEDICAL MEMORANDA

Piperazine Neurotoxicity: "Worm Wobble"

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It is well known in both adult and paediatric medicine that an admission diagnosis of "head injury" can be the presenting feature of another disorder, and unless a clear history of the incident can be obtained from an eye-witness it can be extremely difficult to be sure of the sequence of events leading to admission.

The following case illustrates this point and also serves to remind us of the occasional role of commonly used drugs in producing unexplained symptoms.

Case Report

A 2½-year-old girl was found lying on the floor of her bedroom by her parents. As she was subsequently noticed to be drowsy and unsteady on her feet she was assumed to have fallen out of bed and possibly to have hit her head. She was admitted to the accident department of the local hospital for observation of a possible head injury. No signs of external injury and no abnormal neurological signs were noted, and a skull *x*-ray film showed no bony injury. The nursing staff noticed that she was a little unsteady on her feet but by the following day no abnormal signs were obvious, and as she had previously been a normal healthy child she was allowed home without further investigations.

Three days later her parents brought her back to the hospital, having again noticed unsteadiness when walking, falling about, and episodes in which she became vacant and limp. She was admitted for observation and investigation. In the ward she had attacks during which she would stare vacantly, lose muscle tone, and fall to the ground without warning. There were no convulsive movements and only momentary losses of awareness. At other times she was found to be incoordinated in the use of her hands and also in gait. Apart from an ataxia of cerebellar type formal neurological examination disclosed nothing abnormal. There was no pyrexia or other evidence of infection and no abnormal signs outside the central nervous system. A more detailed history showed a normal pregnancy, birth, and early development.

W.B.C., plasma viscosity, urea and electrolytes, blood sugar, serum calcium, skull and chest *x*-ray appearances, and lumbar puncture were normal but an E.E.G. showed the presence of high amplitude slow activity in all areas with occasional short bursts of high amplitude, rhythmic delta waves at 3 c/s: an abnormal but non-specific record.

After 48 hours in the ward her symptoms gradually settled and she once more seemed normal. At this point we were unsure of the diagnosis, but on further questioning the mother volunteered the information that the child had started a course of a preparation containing piperazine citrate for a threadworm infestation, that the course had been interrupted by the first admission, and that on each occasion administration of the drug had preceded symptoms by about 48 hours. Dosage had been appropriate to her age and size (5 ml or 750 mg daily). On the basis of this information it was decided to use the preparation under supervision, and after three doses the same symptoms of incoordination and absences reappeared. We therefore felt that an aetiological association was established.

The symptoms subsided rapidly on withdrawal of the drug and she was discharged home fit and well, her mother having been advised not to give piperazine again. An E.E.G. six weeks later was normal.

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Comment

Piperazine has been in use since the 1880s as a treatment for gout and "rheumatism," and since Mouriquand *et al.* (1951) first described its use as a vermifuge many thousands of doses must have been prescribed for oxyuriasis or for ascariasis. As a vermifuge piperazine is felt to be a safe and non-toxic drug, and the sparcity of reports of adverse reactions in the English literature supports this idea.

Standen and White (1953) first reported side effects, and as a result of this and subsequent reports three types of side effect are now recognized—gastrointestinal, allergic, and neurological. Of the last, ataxia of a cerebellar type resulting in incoordination and muscular hypnotonia is the most common (hence "worm wobble"). Neurological side effects are seen after accidental or deliberate overdosage, when renal insufficiency delays excretion (Miller and Carpenter, 1967), and more rarely after normal therapeutic dosage, as shown in this case.

The following hypotheses have been suggested to explain the neurological effects of the piperazines. (*a*) Neuromuscular blockade, probably in a post-synaptic position, since acetylcholine release is not prevented (Beani *et al.*, 1964). It seems logical that the widespread central effects could also be mediated via synaptic blockade. (*b*) Possible biochemical causes include a lowering of the pH and ionic shifts across cell membranes. (*c*) Hypersensitivity, which may be predisposed to by the presence of parasites, could produce symptoms by causing vasomotor changes or acute demyelination. This latter suggestion does not fit the known transient nature of the symptoms but one case has been reported in which symptoms persisted for 12 months (Cusmano and De Langlade, 1963). (*d*) The more soluble the salt of piperazine the greater the incidence of side effects. This may partly explain the greater incidence in Europe, where the small molecule hexahydrate is commonly used.

Though the exact mechanism of piperazine neurotoxicity remains incompletely understood it is possible that such effects may occur more frequently than is at present realized, and it may be possible to assess the true incidence with foreknowledge and closer observation. The symptoms may be very mild and disappear quickly on withdrawal of the drug. When piperazine is prescribed, however, the possibility of neurological effects should be explained to the parents and they should be advised to discontinue the drug and report to a doctor if they occur. Accuracy of dosage should be stressed and the use of standard 5-ml spoons encouraged.

Any previous history of neurological conditions, especially epilepsy, should be taken as a contraindication to the use of piperazine. Viprynium embonate seems to be an equally effective alternative.

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References

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