Unusual cerebellar ataxia: "worm wobble" revisited

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We present an unusual case of cerebellar ataxia in a 2-year-old girl several days after treatment with piperazine citrate for suspected worm infestation. This is the first reported case of delayed onset neurotoxicity following the therapeutic administration of piperazine in a previously well child.

A previously well 23-month-old girl was brought to the accident and emergency (A&E) with drowsiness, unsteadiness, and falls. This rapidly progressed to an inability to stand or sit unsupported and a loss of head control. While in A&E she had a brief episode of limb shaking with rolling back of her eyes and was not able to recognise her parents. Five minutes later she had recovered completely, regained her balance, and was playing as usual.

The family had been to Zambia to visit relatives and returned six days previously. Antimalarial prophylaxis was not taken. The child was covered in mosquito bites but was apyrexial, and apart from an episode of diarrhoea had remained perfectly well. The parents denied any drug ingestion, either in the form of prescribed medications or local remedies in Zambia.

Following admission she had numerous episodes of unsteadiness and rolling of her eyes; each lasted for only a few seconds and was followed by complete recovery. During an episode she was hypotonic and hyporeflexic. Dysmetria was evident as she tried to reach out for toys. At these times she was unable to sit or stand unsupported and would fall over to one or the other side, but sometimes she managed to walk with a broad based gait. Horizontal nystagmus (described by the parents as "eye rolling") accompanied these episodes. In the interval between episodes she was completely well and asymptomatic. Her vital signs were normal as was the rest of the systemic examination. She was the only child of a non-consanguineous marriage following a normal pregnancy and delivery. Her development was age appropriate. There was no past or family history of similar episodes, epilepsy, or any significant illnesses.

Blood investigations, including biochemistry, and a contrast enhanced computed tomography scan were normal. Lumbar puncture showed no white cells; bacterial and viral cultures were sterile. CSF protein was within the normal range. An electroencephalogram, which included an episode of unsteadiness, was normal. Urine for toxicology was clear. A magnetic resonance imaging scan was scheduled for the following day, but not carried out in view of further developments to the case and a spontaneous recovery.

At this stage the child's mother reported an unusual story which changed our outlook on the case. While playing unsupervised in Zambia the child had chewed on their pet dog's bone. The mother, concerned that the child may get worms, obtained piperazine citrate from a local pharmacy and gave it in the recommended dose (65 mg/kg/day) for seven days. The medication was discontinued eight days ago, prior to her initial symptoms.

Over the next 48 hours on the ward her symptoms gradually settled—the episodes were fewer and now lasted only seconds. She made a complete recovery five days later.

DISCUSSION

Several differential diagnoses came to mind when this little girl presented with possible fits and fluctuating cerebellar signs, especially in relation to her recent return from Zambia. Could this have been cerebral malaria, viral encephalitis, or some post-infectious demyelinating process? The transient and fluctuating nature of her symptoms, normal imaging, and blood results made all these unlikely. Piperazine, however, is known to be neurotoxic and cause all of the above symptoms.

We are aware of only two cases in the literature, both of previously well adults, who developed ataxia as a late side effect of piperazine treatment. 1 2

Piperazine is one of several medications that can induce ataxia, yet it is a safe and relatively non-toxic vermifugal agent that has been used for over 50 years in children. 3 Neurotoxicity from piperazine, although rare, 4 includes headaches, confusion, irritability, incoordination, and generalised tonic-clonic, atonic, and myoclonic seizures, even leading to status epilepticus. 5 Both de novo seizures and an increased seizure frequency in epileptics have been described. 6

Although the exact mechanism of piperazine neurotoxicity is not understood, various theories have been put forward to explain its widespread neurotoxic effects. These include postsynaptic neuromuscular blockade, 7 a lowering of the pH with ionic shifts across the cell membrane, 8 and an idiosyncratic demyelinating process, probably a hypersensitivity reaction predisposed to by the presence of the parasite. 1 2 The latter appears to be the most plausible explanation for delayed neurotoxicity.

Side effects of piperazine have most commonly been reported in the setting of drug overdose or renal insufficiency; piperazine is excreted by the kidney. 9 1 However, previously well children have also developed ataxia following administration of the drug in therapeutic doses. The neurotoxic effects are usually seen after the initial doses, and resolution of symptoms is rapid and complete within 24–48 hours of discontinuing treatment. 4 Unfortunately for our patient, facilities for detection of the drug in blood, urine, or CSF were not available, and a further trial of piperazine would have been unethical.

Mebendazole is the preferred treatment for worm infestations in Europe—it has fewer side effects and requires only single dose treatment for most conditions, therefore ensuring better patient compliance. However, mebendazole is not recommended for use in children under two years of age. Piperazine, being relatively cheaper, is favoured in the developing world and can be used at all ages.

In summary, we believe that this is a case of delayed onset piperazine neurotoxicity. When piperazine is prescribed, the possibility of neurological side effects must be explained to...
parents, and they should be advised to discontinue treatment and report to a doctor should these occur.

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REFERENCES

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Graves’ ophthalmopathy

The ocular complications of Graves’ disease in adults are well described but there is a relative poverty of information about children. Ophthalmologists in Hong Kong (W Chan and colleagues. British Journal of Ophthalmology 2002;86:740–2) have described their findings in 83 children with Graves’ disease. There were 72 girls and 11 boys all under 16 years. The mean age of onset of Graves’ disease was 9.5 years and mean duration of follow up at the time of ophthalmic examination 51 months. All patients were treated with oral antithyroid medication. Sixteen children had a first degree family history of thyrotoxicosis.

Twelve of the 83 children had eye symptoms which included pain, sensation of a foreign body, photosensitivity, epiphora, and diplopia. Fifty-two (63%) had signs of ophthalmopathy although it was never severe enough to threaten vision and no child had debilitating ocular myopathy. Thirty-two children had lower lid retraction. Other signs included mild proptosis (10) lagophthalmos (8), lid lag (5), lid oedema (5), and upper lid retraction (4). Four had diffuse conjunctival injection. Only one patient had limited extraocular motility in extreme gaze. Eleven patients had punctate corneal epithelial erosions shown by fluorescein staining.

This is the largest series so far described of children with Graves’ disease and ocular complications. Although two thirds of patients had signs of eye disease they were usually mild.
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