

From the coalface of clinical paediatric neurology: Menkes disease – a lesson not to be forgotten

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The differential diagnosis of child abuse or non-accidental injury is extensive and includes rare metabolic disorders. We report a case in which child abuse was wrongly diagnosed. Fortunately the correct diagnosis could be made in time to re-unite the child with his parents.

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As medical practitioners we spend our days making decisions. Some are easy, some more difficult. Many have profound effects on the lives of the families we work with. Although we strive towards perfection, we all make mistakes. We report a case of Menkes disease that illustrates the devastating effect of wrongfully labelling a case as one of child abuse. It also highlights the importance of reconsidering a diagnosis once new clinical features are noted. Making the correct diagnosis of a rare and tragic condition becomes even more important when a confirmatory genetic test is available. This can prevent families like our patient's from having another child with the same condition.

Case report

A male infant aged 3.5 months was referred to our paediatric neurology unit from another tertiary hospital, where he had been taken 2 weeks earlier because of convulsions. Before this he had been thought to be a completely normal little baby boy. Initial work-up by the referring paediatric neurology team included a search for perinatal infections (all negative), a metabolic screen (normal) and a lumbar puncture (normal). A magnetic resonance imaging (MRI) study revealed mildly increased subdural spaces without abnormal signal as well as periventricular leucomalacia (mild) and a small area of gliosis in the right paraventricular region thought to be caused by an old infarct (Fig. 1a). The rest of the brain appeared to be structurally normal. He was discharged on a combination of three anti-epileptic drugs. On clinical examination at our centre it

was apparent that his skull sutures were already overriding despite a normal head circumference of 40.5 cm. He had sustained ankle clonus and was fisting. Visual fixation was absent. His epilepsy remained uncontrolled with up to 15 seizures a day, which ranged from eye twitching to possible infantile spasms. At each follow-up visit he continued to be hypotonic and appeared excessively sleepy. He never made eye contact. The upper motor neuron signs remained. His parents reported that his feeding was deteriorating.

A follow-up EEG was performed at the age of 4 months. This revealed persistent lateralising epileptiform discharges (PLEDs) on the left and raised the possibility of a structural abnormality. It was decided to do a repeat MRI scan (Figs 1b and c). This unexpectedly revealed even larger subdural spaces with clear evidence of subdural bleeds of different ages. The reporting radiologist sounded an alert, suggesting that these findings were consistent with non-accidental injury (NAI), and from then on the patient's condition was labelled as such. He was admitted to hospital. Radiographs of all the long bones were performed (Fig. 2). Multiple old rib fractures and 'bucket handle' fractures of the metaphyses of both humeri were seen. A bone scintigram (Fig. 3) revealed focal uptake on the right side of the chest where old rib fractures were seen on plain radiographs. There was no scintigraphic evidence of multiple areas of trauma. This radiological appearance was reported as in keeping with NAI and was reviewed by a senior radiologist. The case was reported to the authorities (July 2008).

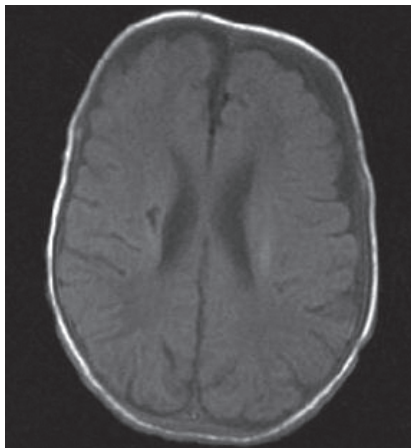


Fig. 1a. MRI scan at 3 months of age.

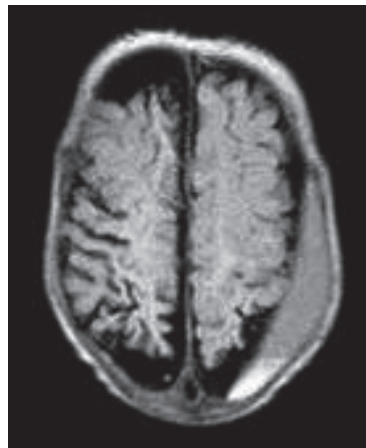


Fig. 1b. T2 flair image at 4.5 months of age demonstrating subdural bleeds of different ages and severe cortical atrophy.

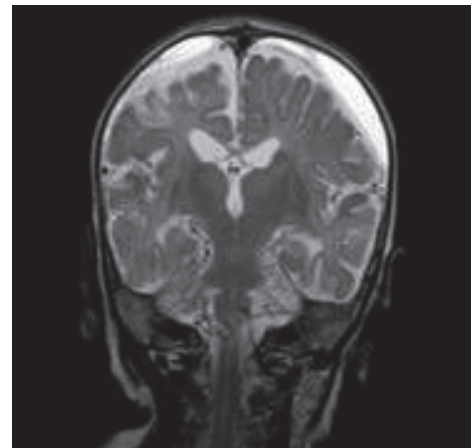


Fig. 1c. T2 coronal image demonstrating bilateral subdural haematomas.

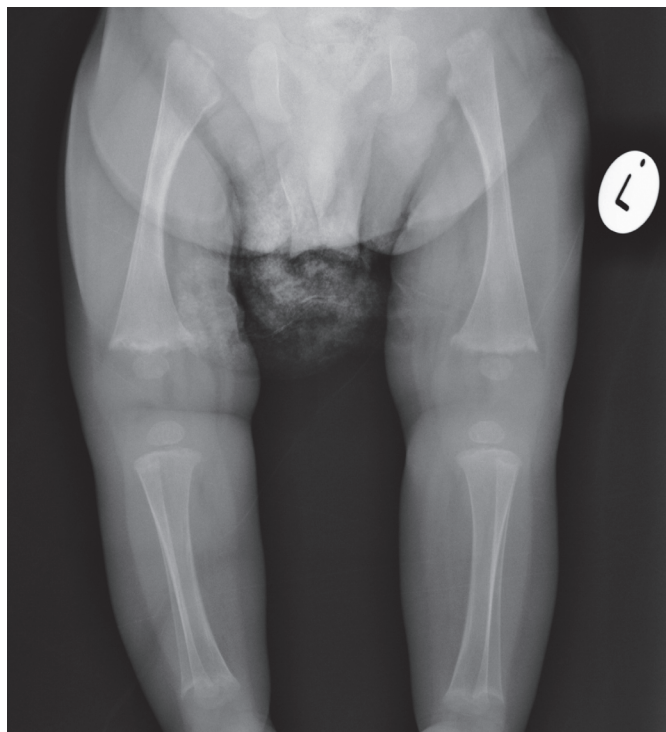


Fig. 2. Radiographs of lower extremities. There are metaphyseal irregularities throughout the distal aspects of both femurs. The differential diagnosis for this appearance was given as *NAI*, vitamin C deficiency, vitamin D deficiency and syphilis.

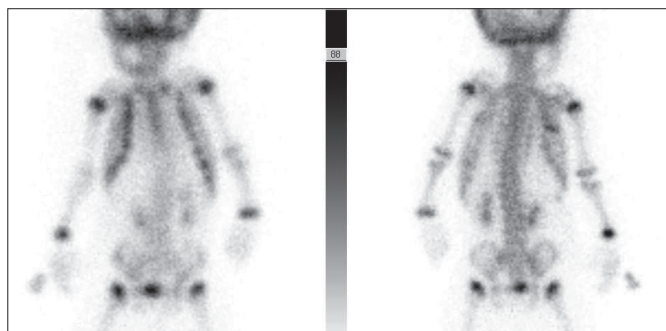


Fig. 3. Bone scintigram – apart from expected increased uptake at growth plates, there is also focal uptake at the right side of the chest.

Investigations for possible underlying clotting disorders, metabolic disorders and nutritional bone diseases were all negative. Testing for congenital syphilis was negative. On clinical examination the patient's hair was thought to be normal at that time. The neurosurgical team was consulted regarding the subdural haematomas. It was decided to drain these, as his convulsions remained extremely difficult to control. In theatre he bled profusely during the procedure and was given copious amounts of blood and plasma. This episode triggered a second round of extensive haematological investigations to exclude causes of a bleeding tendency.

Throughout this 2-month period the patient's concerned parents remained at his bedside. Despite the support of both sets of grandparents this was an enormous ordeal for them, and they even experienced animosity from other members of their families. Meetings were held with the family, their legal representative, the doctors and the social workers. The possibility of child abuse was upheld because of the combination of findings of subdural bleeds of various ages and the radiological findings. He was then discharged to a place of safety nearer to his parents' home, where they continued to visit him every day. His parents describe their feelings at this time as 'unreal'; 'we kept thinking that this can't be true'.



Fig. 4. The patient at follow-up. Note typical facial appearance with heavy jowls and gingival hyperplasia. His hair and eyebrows are wiry and straight. (Photograph placed with permission from his parents.)

During a follow-up visit 3 months after discharge the attending physician noted the wiry appearance of the patient's new hair growth (Fig. 4). Blood was sent away for analysis of serum copper and caeruloplasmin. Both levels were reported as zero (below detection limits), and a repeat sample was requested to confirm the findings. The serum copper level was once again below detection limits and the serum caeruloplasmin level was 0.0398 g/l (normal 0.2 - 0.6 g/l). A diagnosis of Menkes disease was made on the basis of this analysis. On review the clinical presentation fitted this diagnosis perfectly. A meeting with the parents, the social worker involved and the clinical geneticist was arranged within a few days of the results becoming available. The condition was explained and discussed. The patient was released into his parents' custody the same day. He continued to be followed up at our clinic for the next 2 years. Control of seizures was always a challenge, and he required placement of a gastrostomy tube for feeding. He was lovingly cared for by his dedicated parents until he died in his sleep in June 2010 aged 2 years and 4 months.

The patient was the first and only child of parents who were in their mid-20s at the time. His DNA was analysed by the genetic laboratory of the University of Chicago, which confirmed a deletion of exons 2 - 23 of the *ATP7A* gene. Recently the mother was confirmed as a carrier of this deletion, which enables the family to exclude Menkes disease prenatally in future pregnancies.

Discussion

Menkes disease or 'kinky hair disease' was first described in 1962 by John Menkes and co-workers.¹ It is an X-linked recessive genetic disorder of copper transport leading to a maldistribution of copper in the body. The pathophysiological underpinnings were described in 1972 by Danks *et al.*² It is a fascinating piece of medical history

that the finding of abnormal wool in copper-deficient sheep led to investigations of copper metabolism in patients with a suspected diagnosis of Menkes disease.² The unavailability of copper for the synthesis of various copper-dependent enzymes, including some needed for the formation of keratin, elastin and collagen, explains the abnormalities of both the hair and the vascular walls.^{2,3} Gliosis and cystic degeneration found on autopsy in the brains of known cases are thought to be the result of vascular insufficiency, while the inherent weakness of the arterial walls would explain the frequency of intracranial haemorrhages.²

The genetic basis of the disorder, namely that it is caused by mutations in the copper-transporting ATPase gene (*ATP7A*), has been known for almost 20 years.⁴ Testing is clinically available⁵ at various overseas laboratories, but unfortunately not in South Africa. Milder variants associated with ATPase deficiency have been described,⁵ but description of these is beyond the scope of this article. A clear correlation between the severity of the disease and the genotype has been demonstrated.⁵

The expected course of the disorder is one of relentless neurodegeneration and death by 3 years of age.^{5,6} Knowledge of the pathophysiology led to trials of both oral and parenteral copper administration. Oral treatment is ineffective owing to patients' inability to absorb copper from the gut. Subcutaneous injections of copper histidine or copper chloride, which have to be given in the first 10 days of life (well in advance of any clinical abnormalities becoming apparent), appear to be of benefit. Outcome has been variable, with normalisation of developmental outcome in some cases while others have shown no or little improvement despite early treatment.^{5,6} The reason for this appears to be linked to the *ATP7A* genotype; some mutations permit residual copper transport and predict a more favourable response to treatment.⁶ Making the diagnosis early enough for treatment to be attempted is a challenge in itself. Reliable prenatal diagnosis is limited to genetic testing for a known mutation (the *ATP7A* gene is large and the mutation types are diverse) and implies that there would already have been an affected child in the family. Measurement of placental copper (expected to be elevated in affected cases) presents unique challenges as chorionic villus samples can be contaminated by copper from the maternal deciduum or from instrumentation.⁷ Low serum copper and ceruloplasmin levels in healthy term newborns precludes their use for early neonatal diagnosis.^{6,7} Serum copper levels only reach adult levels by 1 - 2 months of life,^{6,7} while low ceruloplasmin levels at birth reach a nadir by 2 - 3 months.⁷ Kaler *et al.* have demonstrated that plasma levels of the catecholamines dihydroxyphenylacetic acid, dopamine, norepinephrine and dihydroxyphenolglycol as well as the ratios between some of these differ significantly between affected and unaffected infants.⁶ This may provide an alternative method for early biochemical diagnosis in infants at risk. Measurement of norepinephrine and dopamine is possible in South Africa (the specimen needs to reach the laboratory within 30 minutes on ice, or to be centrifuged and frozen – personal communication – M Funk, March 2012), but measurement of plasma levels of dihydroxyphenylacetic acid and dihydroxyphenolglycol cannot currently be done here (personal communication – C Vorster, March 2012). Hope remains that detection of some of the above by tandem mass spectroscopy may become a viable method for neonatal screening in future.⁷

Menkes disease is characterised clinically by the following features in its classic form:^{2,3,5}

- Infants appearing healthy for the first 2 - 3 months of life.
- Thereafter hypotonia (floppy infants), seizures, loss of milestones and failure to thrive are noted.
- Hypothermia/instability of temperature control.
- Characteristic hair changes: very coarse, wiry and often lightly pigmented.

- Facies described as 'jowly' with gingival hypertrophy and delayed eruption of teeth.
- The clinical course is one of relentless neurological deterioration. Death usually occurs by 3 years of age.

With special investigations the following can be seen:^{2,3,5,8}

- Radiography of the long bones: metaphyseal spurring; periosteal reaction in the diaphysis similar to the changes seen in scurvy.
- Microscopy of the hair: twisted hair (pili torti) with fractures of the hair shafts (trichorrhexis nodosa). These changes may not necessarily be present from the outset;^{2,6,8} neither are they unique to Menkes disease.⁶
- Neuroimaging: cerebral atrophy, bilateral ischaemic lesions in the deep gray matter of the cortex due to vascular infarctions; subdural haematomas (almost invariable).
- MR angiography: tortuosity of intracranial vessels. (With conventional angiography this has also been demonstrated in systemic vessels but would hardly be regarded as a routine investigation.²)
- EEG: multifocal paroxysmal discharges or hypsarrhythmia.
- Visual evoked responses: low amplitude or absent.
- Serum copper and serum ceruloplasmin: very low values are characteristic and can be regarded as diagnostic beyond the first 3 months of life.⁶

The combination of the subdural bleeds with the radiological appearance of the long bones can very easily be confused with NAI. Metaphyseal fractures, also known as 'bucket handle fractures', are described in radiological textbooks as 'highly characteristic of and specific' for NAI in young children under 18 months.⁹ Subdural haematomas, especially if bilateral and of different ages, are also regarded as being highly specific for NAI.⁹

As our case shows very clearly, exclusion of alternative causes for the pathologies found is of the utmost importance. The differential diagnosis of child abuse or NAI is extensive and includes rare and generally unknown metabolic disorders (Table 1). The challenge for the clinician lies in recognising the features of these disorders and thus avoiding a wrongful assumption that the patient is a victim of abuse. In an infant boy with seizures, subdural bleeds and bony abnormalities, the typical facial appearance and peculiar hair are important pointers to the possibility of Menkes disease and should prompt the clinician to test serum copper and ceruloplasmin levels, both readily available in South Africa.

Recommendations and conclusion

In South Africa the Children's Act stipulates that failure of a medical practitioner to report a suspected case of child abuse constitutes an offence that may be punished by a fine or jail sentence. The Act also protects the practitioner, as any report made in good faith cannot be held against him or her (personal communication – T Geldenhuys,

Table 1. Examples of metabolic disorders that may be misdiagnosed as child abuse

Osteogenesis imperfecta ¹⁰
Ehlers-Danlos syndrome type IV ¹¹
Menkes disease ¹²
Glutaric aciduria I ¹³
Secondary hyperparathyroidism ¹⁴
X-linked hypophosphataemia ¹³
Epidermolysis bullosa ¹⁵
Methylmalonic academia ¹³
Fatty acid oxidation disorders ¹²

December 2011). Even so, a doctor is sometimes placed in a difficult situation with the law on the one hand and his or her intuition (right or wrong) on the other. Final decisions have to be guided by what is in the best interests of the child, although even this may not turn out to be the best option in the end. In our case, dedicated and loving parents were forcibly kept apart from their child. The most valuable lesson may be that communication lines between parents and doctor have to be kept open and prejudicial statements kept to a minimum. More often than not, it is only in retrospect that the correct diagnosis appears obvious!

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