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J Walsh, W Reardon

Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Ireland

Correspondence to:
Dr William Reardon, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Ireland; enquiries@williereardon.com

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ABSTRACT

Awareness of the rare condition of Job syndrome is low among both paediatricians and geneticists. Consequently, observation of the recurrent fractures in the majority of such cases can result in misdiagnosis of non-accidental injury in young children who have the syndrome. The case we report here represents an example of this diagnostic pitfall, which deserves wide recognition due to the serious consequences for children, families and paediatricians acting as experts in legal actions in such circumstances.

Statistics show that there were 26 400 children on child protection registers in England in March 2006¹ and that 7% of children experience serious physical abuse at the hands of their parents or carers during childhood.² Fundamental to a diagnosis of child abuse is the active exclusion of conditions with physical findings suggestive of non-accidental injury (NAI). It is estimated that approximately 7% of children whose signs indicate abuse actually have an underlying medical condition causing their injuries.³ The conditions generally cited in this respect include the phenotypes of osteogenesis imperfecta, the Ehlers-Danlos spectrum of disorders and glutaric acidemia type 1,³ which can, respectively, be characterised by recurrent fractures, excessive bruising and subdural haematomas.

Job syndrome (hyperimmunoglobulinaemia E/hyper-IgE) is a rare primary immunodeficiency disorder associated with recurrent staphylococcal skin abscesses, chronic eczematoid dermatitis and a predisposition to mucocutaneous candidiasis. Rarely diagnosed in early childhood, the hallmark of the condition is an extremely raised IgE level. Recurrent fractures have been documented in children with Job syndrome, but most such patients have been adults.⁴ Osteoporosis has been a feature in some of these individuals. However, the condition is not widely recognised, and, indeed, a recent authoritative article on unexplained fractures in infancy omitted any mention of the disorder.⁵ A case is detailed in which recurrent fractures in a 16-month old girl with Job syndrome were misinterpreted as being caused by non-accidental injury.

CASE REPORT

The patient was referred to us aged 16 months by a solicitor seeking an expert opinion with respect to legal proceedings for NAI. The child was born at term to non-consanguineous parents of normal family history and her birth weight of 2.8 kg was on the ninth centile. At neonatal evaluation, a large anterior fontanelle and heart murmur were noted.

Subsequent assessment by a cardiologist confirmed mild valvular pulmonary stenosis. When she was 3 weeks old, the infant was referred to hospital by her GP because of the large anterior fontanelle.

When she was re-examined at age 7 weeks, eczema was noted to be covering her trunk and face. She was failing to thrive and a skeletal survey was performed. The eczema remained poorly controlled despite active management and she required admission to hospital when she was 4 months of age (fig 1). While an inpatient she was reviewed by a clinical geneticist and was noted to have skull asymmetry, a large anterior fontanelle, dysplastic ears, hypertelorism and down-slanting palpebral fissures. Her karyotype was normal and FISH analysis for 22q11 and 1p36 deletions was normal.

When the child was 6 months old, she was readmitted to hospital with a severe exacerbation of eczema, thought to be due to poor compliance with treatment. A deep laceration was noted on the right wrist, attributed to a pressure injury from an elastic band which was holding a mitten in place to minimise scratching. A well-demarcated swelling was noted on the anterior surface of the right shin. *x* Rays revealed a transverse fracture of the right tibia and fibula with callus formation. Her mother recalled that she heard a crack when she was changing her nappy. A skeletal survey showed healing fractures at the angles of the sixth and seventh ribs on the left side not present on an *x* ray taken 6 weeks previously. Ophthalmological assessment showed no retinal haemorrhages and CT scan of the brain was normal. Radiological review established that there had been at least five fractures, including a re-fracture of the initial tibial and, possibly, fibular fracture, in addition to the rib fractures (fig 2A,B).

The child was placed in foster care but problems with weight gain and eczema persisted. Her foster mother reported that her skull shape changed following sleep. When the child was 1 year of age, a left posterior auricular swelling required incision and drainage. Culture confirmed *Staphylococcus aureus* infection.

Expert reports from specialists in paediatrics, orthopaedics and radiology suggested a probable diagnosis of NAI in the absence of an alternative explanation for the injuries. The eczema was, in these circumstances assumed to be atopic and unrelated. However, review by a geneticist led to recognition of Job syndrome, which also explained the clinical features of the case. Serum IgE levels of 1615 kU/l (normal <15.2 kU/l) were consistent with this diagnosis.

At 18 months old, the anterior fontanelle remains patent. Eczema continues to require

Case report



Figure 1 The patient with eczema at 4 months of age. Parental/guardian informed consent was obtained for publication of this figure.

intensive management. Molluscum contagiosum has recently been observed in the skin, as commonly arises in Job syndrome. Further fractures have not recurred.

DISCUSSION

An association between Job syndrome and recurrent fractures has been described by several observers. Recurrent fractures of the left tibia, fibula and femur were reported in a 5-year-old girl in whom Job syndrome had been diagnosed when she was 2 years of age. Serial radiographs of this patient revealed progressive anterior bowing of the left femur and osteoporosis of all bony structures.⁶

Likewise, a radiological diagnosis of osteogenesis imperfecta tarda has been reported in a patient with Job syndrome, based on recurrent fractures and reduced bone density.⁷ Further observations include multiple fractures of pharynx, rib and fibula in a 15-year-old boy with Job syndrome⁸ whose bone density was normal. While most reported fractures have been in older children, Grimbacher *et al*⁴ recorded fractures in young children which occurred while their nappies were being changed and observed that some cases had been confused with NAI. The incidence of bone fractures was unknown in Job syndrome until Grimbacher *et al* studied 30 patients and found that 57% of them had had at least three fractures. The fractures had occurred at all ages and were often due to unrecognised or minor trauma. They occurred in long bones, ribs and pelvic bones. In two patients with multiple fractures, femoral, radial and vertebral bone density values were consistently lower than normal; however, in three others, values were normal or near normal. Three of four additional patients without recurrent fractures also had low bone density values.⁴

Syndrome diagnosis, especially in the absence of a confirmatory laboratory test, is often challenging, and requires specialist insights and experience.⁹ However, the syndrome is generally recognised in the second decade of life by which time a fairly full complement of syndrome features may be present, easing the difficulty of diagnosis. In contrast, there is a dearth of information on the early presentation and natural history of the condition in early childhood and consequently the profile of the syndrome currently presented in the literature may be misleading with respect to small children. For instance, some authors describe dysmorphic features, claiming there is a "typical face"¹⁰ comprising prominence of the brow and increased width between the corners of the ala nasi. However,

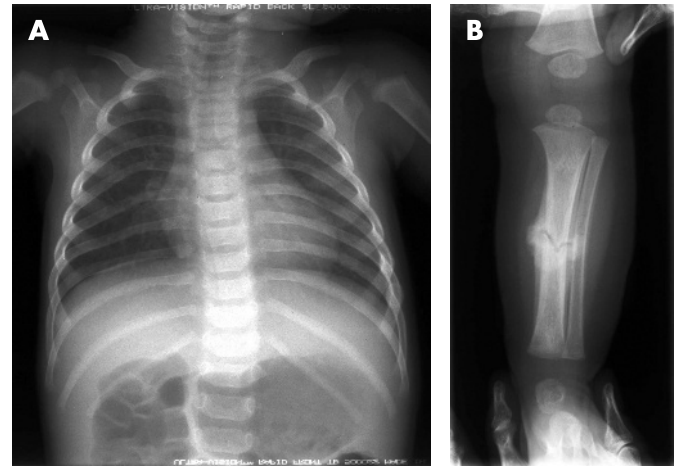


Figure 2 (A, B) x Rays at the age of 5 months show the healing left angular fractures of the sixth and seventh ribs, while the right tibia and fibula demonstrate callus formation and fractures underlying the clinical swelling. Parental/guardian informed consent was obtained for publication of this figure.

while such features are useful as regards adult patients, there is nothing to suggest that they are diagnostically useful in early childhood. As is so often the case with syndromes, where the same condition is described very differently in the literature of different medical subspecialties, Job syndrome is described very differently in immunological and genetics literature.

IgE levels are frequently raised in cases of atopic eczema and can overlap those seen in Job syndrome. While a definitive diagnostic DNA test is not available for Job syndrome, the combination in our case of a raised IgE level (>100 times the normal range), eczema, fractures, a history of cold abscess with positive *S aureus* culture, inappropriately delayed closure of the anterior fontanelle and the extraordinary skull plasticity reported by the foster mother, suggested the true diagnosis of Job syndrome.

The paediatrician should be aware of the possibility of Job syndrome when assessing the child with recurrent fractures. This does present a difficulty in that children with eczema who also have unexplained fractures may have significantly elevated IgE levels associated with the eczema. It will therefore be necessary to consider other features in the history, such as a wide anterior fontanelle, occasionally an actual craniosynostosis (Job syndrome is thought to be synonymous with craniosynostosis with hyper-IgE syndrome),¹¹ skull plasticity, additional dermatological features (such as molluscum contagiosum in our case), cold abscesses with positive *S aureus* culture, etc. Nonetheless, sometimes it may not be possible to distinguish between the child with eczema and associated raised IgE who has been the subject of NAI and the child with Job syndrome where the additional features of the syndrome are yet to declare themselves.

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Parental/guardian informed consent was obtained for publication of the person's details in this report.

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