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TITLE OF CASE

Roifman Syndrome; A Description of Further Immunological and Radiological Features

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SUMMARY

Roifman syndrome is a rare, autosomal recessive inherited syndromic immunodeficiency. We wish to add to the available literature by reporting two brothers with clinical, radiological and immunological features of Roifman syndrome, confirmed on whole exome sequencing. We report an excellent response to subcutaneous immunoglobulin therapy in both brothers, reducing infection burden and hospital admissions. New radiological features are also described here which may assist in the diagnosis of other patients.

BACKGROUND

Roifman syndrome is a rare congenital multisystem disorder characterized by growth retardation, microcephaly, cognitive impairment, spondyloepiphyseal dysplasia and immunodeficiency.[1] Merico *et al.*[2] later established that biallelic mutations in *RNU4ATAC* were causative for this rare syndromic disorder, of which fewer than twenty cases have been described in the published literature.[1-8] Here we describe novel radiological findings in two brothers recently diagnosed with Roifman syndrome. We also wished to report evidence of an excellent response to subcutaneous immunoglobulin in both children, improving their rates of infection and reducing hospital admissions.

CASE PRESENTATION

Patient 1

P1, a dichorionic-diamniotic twin 2, was born at 31+1 weeks gestation with a birthweight of 900g. He had respiratory distress syndrome requiring intubation and ventilation. He also developed *Escherichia coli* sepsis in the neonatal period. Cranial ultrasound showed bilateral ventriculomegaly but no evidence of periventricular leukomalacia. He was noted to be hypotonic and dysmorphic with hypertelorism, a flat nasal bridge, prominent eyes and low-set ears. He had brachydactyly, an abnormal distribution of body fat and mild pectus carinatum (Table 1). He was discharged at term.

P1 had delayed gross motor skills and speech. He walked at 2years and spoke at 2.5 years. He had proptosis and a right-sided strabismus. Ophthalmology noted significant myopic astigmatism but no other abnormalities. MRI brain showed diffuse white matter volume loss.

P1 also demonstrated increased susceptibility to infection, manifest with recurrent otitis media and recurrent lower respiratory tract infections from the age of 4years. He developed severe varicella at 5 and later herpes zoster at 9years of age. Detailed immunological evaluation demonstrated panhypogammaglobulinemia with poor specific antibody titres to tetanus, pneumococcus and *Haemophilus influenzae* type B*,* against which he had been previously vaccinated. He boosted well to repeat vaccination, but his titres fell below protective levels quickly post booster vaccination. Detailed lymphocyte immunophenotyping demonstrated B cell lymphopaenia (154 x 10^6/L) with a relative increase in the proportion of transitional B cells and a decrease in the proportion of class-switched memory B cells. He was also found to have low mannose-binding lectin levels.

P1 was later commenced on immunoglobulin replacement therapy, Hizentra 150mg/kg subcutaneously once a week, with resolution of his recurrent infections and an improvement in weight from the 25th to above the 50th centile. His height remains on the second centile. P1 was noted to have broad metatarsals, small epiphyses, flared metaphyses and flared iliac crests, in keeping with previous reports of Roifman

syndrome (Figures 1- 3). However, this boy was also noted to have bullet-shaped vertebrae with a central beak anteriorly which has not previously been documented in Roifman syndrome (Figures 4 and 5).

Patient 2

P2, the younger brother, again a dichorionic-diamniotic twin, was born at 36+4 weeks gestation with a birthweight of 1.52kg. He was noted to be dysmorphic early in life with bilateral cryptorchidism, hypertelorism, a flat nasal bridge, a short nose and fifth finger clinodactyly. He had three muscular ventricular septal defects (VSDs) on echocardiogram (Table 1). P2 was discharged home well at 1 month of age but re-presented at 12 weeks with adenovirus bronchiolitis leading to respiratory failure, for which he required prolonged mechanical ventilation and a tracheostomy, due in part to severe bilateral tracheobronchomalacia. His tracheostomy was ultimately decannulated at 2 years and 5 months of age. He had postnatal growth failure requiring nasogastric and later percutaneous enteroscopic gastrostomy (PEG) feeding. He developed hypothyroidism for which he was prescribed oral levothyroxine. His height tracked along the 2nd centile despite weight and head circumference on the 50th centile. He demonstrated significant global developmental delay. He started crawling at 3.5 years and walked at 6 years of age. An MRI of the brain showed reduction in white matter volume and slight thinning of the corpus callosum with a lack of posterior pituitary bright spot.

P2 demonstrated increased susceptibility to infection. At 15 months, he developed *Haemophilus influenzae* (serotype F) sepsis and meningitis. He was prone to recurrent perineal candidiasis. He had recurrent episodes of otitis media for which he required grommets. He later developed recurrent lower respiratory tract infections prompting a detailed immunological assessment. This demonstrated normal serum immunoglobulin levels, but poor specific antibody titres to tetanus, pneumococcus and *Haemophilus influenzae* type B against which he had been previously vaccinated. Booster vaccinations did not improve these titres. Lymphocyte immunophenotyping demonstrated marked B-cell lymphopaenia with a total count of 68 x 10^6/L (normal 600-1300 x 10^6/L), with a relative increase in

transitional B cells and reduction in class-switched memory B cells. He was ultimately commenced on immunoglobulin replacement therapy, Hizentra 200mg/kg subcutaneously once a week, which led to a significant reduction in his infection burden. Ophthalmology review noted small optic nerves bilaterally. P2's imaging demonstrated many of the findings previously documented in Roifman syndrome including flared iliac wings, metaphyseal flaring, flared costo-chondral junctions and absent 12th ribs (Figure 6). There was also evidence of kyphoscoliosis and mild platyspondyly. As well as absent ossification of the talus and calcaneus, delayed ossification of the distal phalanges was noted (Figure 7). Vertebral bodies were noted to be pear-shaped or bullous in nature which caused early diagnostic confusion as these have also not been previously described in Roifman syndrome (Figure 8).

INVESTIGATIONS

The diagnosis of Roifman syndrome was ultimately established after duo exome sequencing revealed compound heterozygous mutations in *RNU4ATAC* (n.13C>T;p.? , n.48G>A;p.?) in both P1 and P2, both variants previously described in patients with Roifman syndrome.

Table 1: Summary of patient features

	Patient 1	Patient 2
Dysmorphic Features	Hypertelorism Flat nasal bridge Proptosis Low-set ears Brachydactyly Pectus carinatum	Hypertelorism Flat nasal bridge Short nose Fifth finger clinodactyly Bilateral cryptorchidism
Cardiology		Ventricular Septal Defects (Three muscular)
Development	Gross motor delay Walked age 2 Intellectual disability Hypotonic	Gross motor delay Walked age 6 Intellectual disability Tracheostomy PEG
Immunological Features	Varicella age 5 Herpes zoster age 9 Recurrent respiratory infections Panhypogammaglobulinemia Poor vaccine antibody responses B-cell lymphopaenia Low mannose binding lectin levels	Severe adenoviral bronchiolitis *Haemophilus influenzae* sepsis and meningitis Recurrent respiratory infections Normal immunoglobulin levels Poor vaccine antibody responses B-cell lymphopaenia
Endocrine		Hypothyroid diagnosed at 13 months
Ophthalmology	Myopic astigmatism	Small optic nerves bilaterally
Neurological	Ventriculomegaly Diffuse white matter volume loss	Reduction in white matter and slight thinning of corpus callosum
Radiology	Bullet-shaped vertebrae with central beak anteriorly Metaphyseal flaring Flared iliac crests Small epiphyses	Pear-shaped vertebral bodies Kyphoscoliosis Metaphyseal flaring Flared iliac wings Flared costochondral junctions Absent 12th ribs Absent ossification of talus and calcaneus Delayed ossification of distal phalanges

DIFFERENTIAL DIAGNOSIS

The low incidence of Roifman syndrome means that it is poorly recognised in clinical practice. Here, we describe two children who were 8 and 12 years old before a unifying diagnosis was made despite early suspicions of an underlying syndromic immunodeficiency and skeletal dysplasia. Multiple references were made throughout the notes to features similar to mucopolysaccharidosis both clinically and radiologically, despite negative investigations. In particular, coarse facial features, short stature, recurrent respiratory infections and developmental delay were all thought to be concerning for mucopolysaccharidosis. In addition, bullet-shaped vertebrae with anterior central beaking found in P1 would typically be associated with mucopolysaccharidosis and have not previously been reported in Roifman syndrome.[2] Urinary glycosaminoglycans were negative and although a metabolic consult was sought, this diagnosis was ultimately ruled out. Other diagnoses that were considered included Schimke's immuno-osseous dysplasia. While the short stature and hypothyroidism were in keeping with this condition, our patients did not have the characteristic renal dysfunction, atherosclerosis or cerebral ischaemia commonly associated with this disease. Radiological features were also thought not to be consistent with the flattened vertebral bodies, laterally displaced femurs or shallow acetabular fossae typically seen in Schmike's immuno-osseous dysplasia. This diagnosis was ruled out using DNA sequencing methods.

TREATMENT

We wished to report evidence of an excellent response to subcutaneous immunoglobulin therapy in both brothers, improving their rates of infection. As this can be administered by parents at home, it has significantly reduced the number of hospital visits required for this family. Three patients who have been treated with intravenous immunoglobulin therapy have been reported.[9, 10] The boys were previously

treated with azithromycin prophylaxis with limited success, and this was ceased once immunoglobulin therapy was established. Multidisciplinary team input has been essential for these boys as, while immunoglobulin administration has effectively treated their immunodeficiency, their development remains delayed and they continue to require support.

OUTCOME AND FOLLOW-UP

Today both patients are doing well and have had no recent infections or admissions. With multidisciplinary team input, they continue to make developmental progress. P2 has recently had his PEG removed. He remains on thyroxine replacement.

DISCUSSION

Similar to previous studies, our patients displayed many of the recognised features of Roifman syndrome, including brachydactyly, fifth finger clinodactyly, hypertelorism, narrow nasal bridge, hypoplasia of the corpus callosum, intellectual disability, recurrent otitis media, recurrent pneumonia, intrauterine growth restriction, postnatal growth retardation and short stature.[1, 5] P1 was found to have multiple small muscular VSDs on echocardiogram, a pathology that has also been reported in two previous cases of Roifman syndrome.[6, 7]

We highlight previously undocumented radiological features of Roifman Syndrome. Images from P1 show bullet-shaped vertebrae with anterior central beaking. P2 demonstrates pear-shaped vertebral bodies. As well as absent talar and calcaneal ossification, we report delayed ossification of the distal phalanges in P2. Further to Bogaert *et al.* findings of bilateral agenesis of the 12th ribs, we have also documented 11 ribs in P2.[3] Short ribs with anterior splaying, flared iliac wings and narrow sacrosciatic notches noted in the neonatal period are consistent with the diagnosis and these findings have been reported previously.

Endocrine dysfunction is less well documented and was previously thought not to be a feature.[2] In the case we present, hypothyroidism was diagnosed after the first year of life, requiring thyroxine replacement therapy. Heremans *et al.* reported two patients with subclinical hypothyroidism and a third patient who developed hypothyroidism in adulthood.[8] It is worth considering that endocrine dysfunction may be characteristic of this condition also.

We report two patients with Roifman Syndrome who have been treated successfully with subcutaneous immunoglobulin replacement therapy and have done extremely well, with a significant improvement in their infection burden leading to reduced hospital admissions. As the parents can administer treatment at home this has lead to a significant improvement in their quality of life and in the family's life as a whole.

These patients provide further information on this rare and poorly described condition and serve as a reminder to clinicians of the importance of repeated clinical re-evaluation in patients who do not have a unifying diagnosis as genetic testing continues to advance.

LEARNING POINTS/TAKE HOME MESSAGES

- The low incidence of Roifman syndrome means that it is poorly recognised in clinical practice. Here, we describe two children who were 8 and 12 years old before a unifying diagnosis was made despite early suspicions of an underlying syndromic immunodeficiency and skeletal dysplasia. We report two brothers with clinical, radiological and immunological features of Roifman syndrome, confirmed on whole exome sequencing.
- Both brothers have been successfully treated with subcutaneous immunoglobulin replacement therapy, leading to a reduced infection burden and improved quality of life.
- Bullet-shaped vertebrae have been previously cited, but here we report bullet-shaped vertebrae with anterior central beaking which has not previously been associated with the condition and would typically be found in mucopolysaccharidosis. We also report pear-shaped vertebrae which have not previously been documented in Roifman syndrome.
- Endocrine dysfunction is less well documented and was previously thought not to be a feature. In P2, hypothyroidism was diagnosed after the first year of life, requiring thyroxine replacement therapy. It is worth considering that endocrine dysfunction may be characteristic of this condition also.

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FIGURE/VIDEO CAPTIONS

Figure 1; Bilateral feet X-rays showing broad metatarsals. 9 years 5 months.

Figure 2; Bilateral hand X-rays showing broad metatarsals. 9 years 5 months.

Figure 3; X-ray abdomen and pelvis with small broad femoral capital epiphyses with broad femoral necks. 9 years 5 months.

Figure 4; Lateral lumbar spine X-ray T10-sacrum (9 years 5 months) demonstrating anterior central beaking at T10, T11, T12 vertebral bodies.

Figure 5; Sagittal CT thorax T1-L2 (9 years 3 months) demonstrating anterior central beaking at T10, T11, T12 vertebral bodies.

Figure 6; X-ray chest and abdomen showing short ribs with anterior splaying, absent pubic ossification and narrow sacrosciatic notches. 1 week old.

Figure 7; Left foot X-ray demonstrating absent ossification of talar and calcaneal bones, as well as distal phalanges. 1 month old.

Figure 8; Sagittal CT thorax with pear-shaped vertebrae. 5 years 9 months.

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