Clinical report of Roifman syndrome with vitamin D-dependent rickets – an undocumented association

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Roifman syndrome is a rare genetic disorder with a worldwide prevalence of less than 1 in 1 000 000. It is characterized by growth retardation, abnormal bone formation (spondyloepiphyseal dysplasia), retinal dystrophy with visual defects, cognitive delay, immunodeficiency, and specific phenotypical features such as microcephaly, prominent forehead, long curvy eyelashes, long philtrum, dental abnormalities, and brachydactyly. This syndrome was first reported by Dr Roifman 20 years ago and was initially thought to be X linked owing to its male preponderance. It was identified later to be an autosomal recessive genetic defect in the noncoding parts of the gene *RNU4ATAC* (RNA, U4atac Small Nuclear U12-Dependent Splicing). The common presentations of this syndrome are due to recurrent infections secondary to immunodeficiency. There is no documented association of vitamin D-dependent rickets with this syndrome previously mentioned in the literature. This is a clinical report of a child presenting with refractory hypocalcemia secondary to vitamin D-dependent rickets who was later diagnosed to have Roifman syndrome owing to the distinctive phenotypical features and associated immunodeficiency. This is also the first clinical report of this syndrome from India.

Keywords:
immunodeficiency, *RNU4ATAC* gene, Roifman syndrome, spondyloepiphyseal dysplasia, vitamin D-dependent rickets

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Introduction

Roifman syndrome is a rare genetic disorder identified 20 years ago by Roifman who reported the association of spondyloepiphyseal dysplasia, retinal dystrophy, and immunodeficiency with characteristic phenotypical features as a syndrome which was named after him (Roifman, 1999). It is a rare genetic disorder with both autosomal recessive and X-linked recessive modes of inheritance (Gray *et al.*, 2011; Merico *et al.*, 2015). Roifman syndrome is almost exclusively seen in males. The prevalence is estimated to be less than 1/1 000 000 (Orpha.net, 2020). Typically, this syndrome is diagnosed between the ages of 3 and 5 years when children present with recurrent infections owing to their underlying immunodeficiency. The Roifman syndrome gene was found on the noncoding part of DNA, which could only be identified because of the newer techniques that are available recently that are capable of doing a whole-genome sequencing. This gene also regulates 800 other genes, thus explaining the various other defects that are found to be associated with this syndrome.

The phenotypical features described in Roifman syndrome are long curvy eyelashes, microcephaly, prominent forehead, long philtrum, upturned nose with dysplasia of alae nasi, thin upper lip, downturned corners of the lower lip, and brachydactyly with short stature (Roifman, 1999). Humoral immunodeficiency resulting in recurrent infections is the commonest presentation (Gray *et al.*, 2011). Other symptoms that have been described to be associated with the syndrome are minimal cognitive delay, retinal dysplasia, and visual-spatial orientation defects (Fairchild *et al.*, 2011; Gray *et al.*, 2011). It may be associated with intrauterine and postnatal growth retardation in some children. Excessive trabeculations and intratrabecular recesses in the ventricles of patients with Roifman syndrome termed as a 'spongy myocardium' have been reported (Mandel *et al.*, 2001). MRI had shown partial agenesis of the corpus callosum and hippocampal atrophy in some individuals with the syndrome (Fairchild *et al.*, 2011). Association of hypogonadotropic hypogonadism has also been reported (Robertson *et al.*, 2000).

Apart from the characteristic phenotypical features, complete blood count shows neutropenia, and the immunoglobulin (Ig) levels are low, especially the IgG level, with normal or low levels of other Igs such as IgA, IgE, and IgM. Low antibody titers for polio, tetanus, measles, and rubella are seen. T-cell antibody titers are normal, as it is a predominantly B-cell deficiency. Radiological imaging shows spondyloepiphyseal dysplastic changes in the vertebrae. MRI brain may be

normal or shows partial corpus callosum agenesis and hippocampal atrophy in some children. Confirmatory diagnosis is only done by genetic testing, identifying the *RNU4ATAC* gene defect.

The genetic defect of the *RNU4ATAC* gene responsible for Roifman syndrome was identified by Merico *et al.* (2015). The mutation in the *RNU4ATAC* gene causing Roifman syndrome is biallelic (Merico *et al.*, 2015) which codes for the minor spliceosomal sRNA U4ATAC that forms a base-paired complex with U6atac, and they are required for minor U12-dependent splicing (Shukla *et al.*, 2002). This gene is also implicated in the microcephalic osteodysplastic primordial dwarfism type 1 (MOPD1), which is a different disorder from Roifman syndrome (Jafarifar *et al.*, 2014; Merico *et al.*, 2015). Biallelic *RNU4ATAC* pathogenic variants have been described also in Lowry Wood syndrome (Farach *et al.*, 2018), a rare autosomal recessive type of multiple epiphyseal dysplasia and microcephaly.

The management is only supportive with the treatment of infections, intravenous immunoglobulin infusion if severe immunodeficiency, management of associated skin disorders such as eczema, and developmental support. Prenatal diagnosis and counseling are available for this disorder.

Clinical report

A baby boy was born at full-term gestation of 38 weeks by normal vaginal delivery to a nonconsanguineously married parent. The baby cried immediately after birth with Apgar scores of 9 and 10 at 1 and 5 min, respectively. The baby did not have any neonatal intensive care admission after birth and was roomed in with his mother, initiated on breastfeeds, and was discharged home on the second day. The baby developed seizures on day 3 of life characterized by generalized stiffness of hands and legs with unresponsiveness lasting for less than a minute, for which he was readmitted to the neonatal ICU of the hospital where he was born and was investigated further for the cause of his seizures. All his investigations during that period such as the complete blood count, C-reactive protein, blood and cerebrospinal fluid cultures, blood sugar, and electrolytes along with cranial ultrasound and cerebrospinal fluid analysis were normal except for a low calcium value of 5.4 mg/dl. The seizures were attributed to hypocalcemia and were treated with intravenous calcium followed by oral calcium supplements after a day, and he was discharged home on advice to continue the calcium supplements for a period of 3 months. The calcium supplements were withdrawn at 3 months of age, and the child had a recurrence of seizures with an episode of pneumonia, needing admission to the same hospital. He was treated with intravenous antibiotics for pneumonia and was noted to have hypocalcemia again, which was treated with intravenous calcium, and he was discharged after 5 days with advice to continue his calcium supplements for a period of 6 months this time.

The child had a second episode of pneumonia when he was 2 years of age, which was when he was presented to our center. This episode of pneumonia was severe, leading to multiorgan dysfunction syndrome secondary to infection. The seizures recurred during the illness with persistent hypocalcemia ranging from 5 to 5.5 mg/dl despite intravenous calcium supplementation. The cause of hypocalcemia was evaluated further this time. His lowest level of serum calcium was 5 mg/dl and ionized calcium of 0.5 mmol/l. He also had low phosphate levels of 1.3 mg/dl with high alkaline phosphatase level of 1500 IU/dl. His parathyroid hormone levels were normal at 40 pg/ml, and a workup for renal cause of rickets with urea, creatinine, arterial blood gas, and urine calcium, creatinine ratio was within the normal range. However, he had very low vitamin D levels (<5 ng), suggestive of vitamin D deficiency, which was corrected with intravenous vitamin D followed by an oral correction. Other investigations for seizures such as metabolic screening for inborn errors of metabolism, electroencephalogram, and MRI of the brain were also done, which were normal. His lumbar puncture was not suggestive of a central nervous system infection. Owing to persistent hypocalcemia despite supplementation, low phosphate level, and increased alkaline phosphatase level with low vitamin D level, and negative investigative results for other causes of seizures, this child's seizures were attributed to hypocalcemia secondary to vitamin D deficiency and was treated accordingly. The other significant feature noted in this child was severe eczema unresponsive to emollients, moisturizers, and steroid creams.

Because of recurrent severe pneumonia and severe eczema unresponsive to regular medications, underlying immunodeficiency was suspected, and his Igs profile was checked, which showed a selective IgG deficiency, with IgG levels of 150 mg/dl, which was low for his age. However, his IgM, IgA, and IgE levels were 60, 58, and 47.3 mg/dl, respectively, which were within the normal limits for his age. As the child was noted to have peculiar phenotypical features not seen in both parents, immunodeficiency, and global developmental delay characterized by only sitting at the age of 16 months and babbling, he was further evaluated for genetic disorders associated with immunodeficiency. The characteristic phenotypical

features observed in this child were long and curved eyelashes, prominent and wide forehead, wide-open anterior fontanelle, long philtrum, thin upper lip, short and stubby fingers, and toes with height value on the fifth percentile and head circumference on the 50th percentile. There was no alopecia. He also had severe eczema unresponsive to emollients and steroid creams. The ophthalmological evaluation was normal, and the radiograph skeleton revealed minimal dysplasia of the thoracic vertebrae; however, the long bones and epiphyses were normal as the child was only sitting with support when he presented and had not started to bear weights. His karyotyping revealed a normal XY pattern, and the clinical exome sequencing confirmed Roifman syndrome with the specific genetic defect in the *RNU4ATAC* gene. Interestingly, this child caught up on the gross motor and fine motor milestones once the hypocalcemia and vitamin D deficiency was corrected with daily dosages of calcium and vitamin D supplements within 6 months of treatment. The child started walking independently, running, and speaking two-word sentences, reciting rhymes, and identifying two colors on follow-up within 6 months of therapy with vitamin D correction and daily supplementation, thus catching up with the delays observed earlier during his admission. He was on fortnightly monitoring of calcium and vitamin D levels to determine the optimal therapeutic dosage. When the vitamin D supplement was stopped after completing his initial correction of vitamin D deficiency, it was noticed that his calcium levels and vitamin D levels started to drop again; hence, the levels of active vitamin D (1, 25 dihydroxycholecalciferol) were checked and were found to be low. Therefore, he was started on daily supplementation of 1, 25 cholecalciferol along with 20 mg/kg of elemental calcium, which was later reduced to 10 mg/kg/day of elemental calcium supplementation after 1 month. Since his calcium, phosphorus, and vitamin D levels were well maintained with daily oral supplementation of active vitamin D once a day (minimal dosage) and oral calcium not in high dose along with a normal parathyroid hormone level, clinically a diagnosis of vitamin D-dependent rickets type 1a was made, and he was continued on the same treatment. As type 1b is associated with secondary hyperparathyroidism (Levine, 2020) which was not seen in this child and type 2a is resistant to vitamin D even at high dosage owing to the receptor defect (Levine, 2020), clinically these were excluded. However, genetic testing was not done to confirm the type of vitamin D-dependent ricket. Child is doing well on follow-up. He is also on monthly IgG level monitoring with the administration of intravenous Ig infusions whenever the levels drop significantly below the normal range. There have been no major illnesses needing hospitalization since. The differential diagnosis that was considered in this child before the genetic confirmation were developmental delay owing to vitamin D-deficiency rickets, inborn errors of metabolism causing developmental delay and recurrent infection, and syndromes associated with immunodeficiency.

Discussion

Classically children with Roifman syndrome present between the ages of 3–4 years with recurrent infections owing to underlying immunodeficiency (Gray *et al.*, 2011) and the characteristic phenotypical features (Roifman, 1999) with confirmatory genetic testing clinching the diagnosis. The reported child, on the contrary, presented with seizures owing to hypocalcemia in the neonatal period, which recurred every few months when calcium supplements were discontinued. The cause for hypocalcemia was initially not investigated, as it was thought to be owing to transient hypocalcemia of the neonatal period. As this syndrome is uncommon in India with this child being the first reported case from the country, the typical phenotypical features were not considered significant in the parent hospital where the child was born and readmitted twice with seizure episodes secondary to hypocalcemia. Only when the child presented for the third time with seizures and life-threatening pneumonia to our center, he was further evaluated for causes of hypocalcemia, which was found to be owing to the vitamin D deficiency, and also for underlying immunodeficiency causing his severe pneumonia with unresponsive eczema, which was confirmed by the low IgG levels. The peculiar phenotypical features, developmental delay, and immunodeficiency led us to look for an underlying genetic disorder that is associated with immunodeficiency through genetic testing. It was confirmed by the genetic testing of sequence analysis to be Roifman syndrome caused by the defect in the *RNU4ATAC* gene. As this is the first reported case of Roifman syndrome from the country, the phenotypical features were not linked to the syndrome before the genetic test results were available. The other important feature that was noted in this child was his vitamin D deficiency. Although the phenotypical features noted in this child such as the broad forehead, long curved eyelashes, thin upper lip, long philtrum, brachydactyly, and the minimal dysplasia of the thoracic vertebrae in the chest radiograph have already been described in the literature on Roifman syndrome (Roifman, 1999), it was noted that there was no documented literature about the association of vitamin D-dependent rickets with this syndrome, though there are documented association of renal tubular acidosis, which was excluded in this child (Orpha.net, 2020). Another peculiar feature noted

in this child was his response to vitamin D correction, which resulted in the improvement of his motor milestones and cognition in terms of beginning to walk independently, speak two word sentences, recite rhymes, point to body parts, name two colors all within a period of 6 months. There is no description of improvement in mental or motor capabilities in the literature among the previously reported children or adults with this syndrome. As it is known that the Roifman syndrome gene is present in the noncoding part of the DNA that controls more than 800 other genes, which in turn are responsible for various associated features described with this disorder (Roifman, 1999; Merico *et al*., 2015). This particular association of vitamin D-dependent rickets needs further research to prove whether the occurrence of these two disorders together is a mere coincidence or if any underlying genetic connection could be established between the two. Further research on this association would also help to determine the role of vitamin D supplementation in Roifman syndrome to improve the cognitive and motor delays associated with the syndrome if the two disorders are proven to be associated considering the significant catch-up in the motor and cognitive milestones noted in this child following vitamin D supplementation.

Conclusion

Roifman syndrome is a rare genetic disorder with a defect in the noncoding part of the *RNU4ATAC* gene, which is also responsible for regulating 800 other genes, resulting in various associations seen with this disorder apart from the characteristic phenotypical features. The associations described are minimal cognitive delay with visuospatial orientation defects, intrauterine and postnatal growth retardation, excessive trabeculations, and intratrabecular recesses in the ventricles of patients with this syndrome termed as a spongy ventricle, partial agenesis of the corpus callosum, and hippocampal atrophy. Some other associations reported were hypogonadotropic hypogonadism.

Of all the features of Roifman syndrome reported from multiple countries, there were no reports of any association with vitamin D-dependent rickets mentioned in the literature. As this child mainly presented with recurrent hypocalcemic seizures, secondary to vitamin D-dependent rickets instead of the typical presentation with recurrent infections due to immunodeficiency as described in the literature, we decided to report this unusual association. Considering the fact that vitamin D-dependent rickets is also an autosomal recessive disorder like Roifman syndrome, further research is needed to determine if the two disorders are associated or whether the occurrence of both together in this child is a mere coincidence.

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Conflicts of interest

There are no conflicts of interest.

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