Wolcott-Rallison Syndrome Affecting Three Consecutive Conceptions of a Consanguineous Couple

Permanent neonatal diabetes mellitus (NDM) is a debilitating condition. In couples with consanguineous marriage, and especially with multiple children being affected, a strong possibility of genetic causes should be kept and evaluated appropiately. Wolcott-Rallison syndrome is one such syndrome, now being more commonly diagnosed in Indian families. A couple presented to the fetal medicine unit for genetic counselling at a gestational age of 9 weeks, because of two previous babies being affected with early onset type 1 diabetes mellitus. There was a 3rd degree consanguinity. The elder child was 6 year-8 month-old girl, with hyperglycemia detected at 1 month of age. She was evaluated by the pediatrician. She had history of multiple episodes of seizures, unconsciousness and developmental delay in all fields, with a motor age of 2 years and social and language age of 4 years. Parents were not compliant with either regular insulin administration or home blood glucose monitoring. On examination, she was stunted (height 86 cm, <3rd centile), underweight (weight 11.4 kg, <3rd centile) and had microcephaly (head circumference 43 cm, <3rd centile). The child had a chubby look, round facies, delayed dentition, dental caries and short stubby fingers. There was firm hepatomegaly with liver span of 12 cm. We evaluated for hypothyroidism, celiac disease, polyendocrinopathies and genetic syndromes causing type 1 diabetes mellitus. There were no clinical features suggestive of exocrine pancreatic insufficiency. The younger sibling was a female child who was diagnosed as type 1 diabetes mellitus at 1 month of life and succumbed the following month. Medical records were unavailable. A detailed three-generation pedigree did not reveal any other family member with similar manifestations.

The skeletal survey revealed a bone age >4 years, with small carpals, hypo-mineralized metacarpals, and notching of anterior vertebrae, suggestive of skeletal dysplasia (**Fig. 1**). The laboratory evaluation did not reveal any abnormalities in hemoglobin, leucocyte counts, thyroid function tests and liver enzymes. Blood urea nitrogen was 15.3 mmol/L, creatinine was 61.9 µmol/L, and glycosylated hemoglobin was 12.7%. A genetic panel for causes of PNDM and maturity-onset diabetes of the young (MODY) was done. It revealed a homozygous non-sense variation in exon 17 of the *EIF2AK3* gene (chr2:g. 88857412G>A), consistent with Wolcott-Rallison syndrome. Subsequently, we carried out sanger variant analysis for the same gene in the fetus by chorionic villus sampling at 14 weeks of gestation. It also revealed homozygosity for chr2:g. 88857412G>A and c.3193C>T. The couple were advised termination of pregnancy and were counseled regarding recurrence risk and need for antenatal diagnosis. The importance of home blood glucose monitoring and insulin administration was explained for the older child and management plan with concerned specialist was arranged.

Neonatal diabetes mellitus is a rare form of type 1 diabetes mellitus, with onset in first 6 months of life and an incidence of 1 in 90,000 to 1,60,000 live births [1]. Most NDMs are monogenic, and can be either transient or permanent. The most common mutations causing NDM worldwide are related to defects in potassium channel subunit genes, namely *KCNJ11* and *ABCC8* [2]. Similarly, in India, most published literature shows that the commonest mutations are related to potassium channel mutations [3]. In the setting of parental consanguinity, most common causes related to an autosomal recessive inheritance. These include mutations in *EIF2AK3, GCK, GLIS3, RFX6, IER31P1* and *MNX1* genes. Except GCK1, the remaining mentioned mutations result in syndromic forms of type 1 diabetes mellitus, with extra-pancreatic involvement [1,4]. Thus, it becomes important to get focused evaluation for autosomal recessive conditions in such a scenario. Wolcott-Rallison syndrome is being recognized as an important cause of syndromic permanent NDM in Indian subcontinent [5,6]. This syndrome has high mortality and several associated morbidities including skeletal dysplasia, episodic liver failure, renal dysfunction, exocrine pancreas insufficiency and developmental delay. The frequency of extra-pancreatic manifestations increases with increasing age, with initial appearance of skeletal abnormalities, followed by liver and renal dysfunction. In the index child, we could note developmental delay and skeletal dysplasia.

Evaluation for monogenic causes should be done in all cases of permanent NDM. When associated with consanguinity and extra-pancreatic manifestations, syndromic neonatal diabetes mellitus with autosomal recessive inheritence is most likely. Timely genetic diagnosis and prenatal confirmation can avert birth of an affected progeny.

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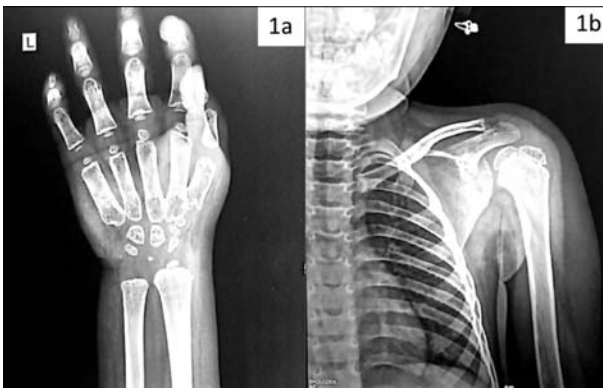

Fig. 1 (a) *X*-ray wrist anteroposterior view of the index child, and (b) *X*-ray showing thoracic spine, ribs and humerus.

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Glossopharyngeal and Vagus Nerve Palsy in a Child With Scrub Typhus Meningitis

Scrub Typhus is an acute febrile illness caused by *Orientia tsutsugamushi,* an obligate intracellular Gram negative bacterium. The disease is endemic in Southeast Asia and Pacific Islands, and is prevalent in the Shivalik ranges from Kashmir to Assam, the Eastern and Western Ghats and the Vindhyachal and Satpura ranges in Central India [1]. The usual clinical features include fever, myalgia, headache, an eschar, regional or generalized lymphadenopathy and hepatosplenomegaly [1].

A five-year-old boy, from North 24 Parganas district of West Bengal, was referred with high grade fever for eleven days and severe headache and myalgia. On examination, he was haemodynamically stable and had generalized lymphadenopathy and hepatosplenomegaly. Other system examinations were normal. He was given supportive management with antipyretics.

A few hours after admission, he developed nasal intonation of voice with nasal regurgitation of food. Deviation of the uvula to the left and weakness of right palatal muscles was noted on examination, signifying palsy of right sided glossopharyngeal nerve and pharyngeal branch of vagus nerve. The possibility of involvement of other vagal branches was ruled out in the absence of dysphonia. Other cranial nerves and rest of the neurological examination were normal.

Complete blood counts showed a high (90%) neutrophilic differential leukocyte count. Acute inflammatory markers were raised but liver and renal function tests were normal. Work-up for etiology of fever was positive for scrub typhus IgM antibody (ELISA) which showed a five-fold rise subsequently. Cerebrospinal fluid revealed mononuclear pleocytosis with elevated protein but negative cultures. MRI brain was normal. He was started on oral azithromycin prescribed at 10 mg/kg once a day for 7 days. Child was afebrile within 30 hrs of the first dose. Physiotherapy of pharyngeal muscles was demonstrated and he was discharged with the advice to continue the same. There was no residual nerve palsy on follow-up after 4 weeks.

Glossopharyngeal and vagus nerve palsy have been associated with Varicella Zoster, Enterovirus and other pathogens [2]. However, palsy of these nerves due to *O. tsutsugamushi* has not been described earlier in the paediatric age group.

[1]The disease process is initiated by the bite of the mite. The pathogen multiplies at the bite site, forming an eschar, followed by proliferation of the organism in the endothelial cells of small vessels with perivascular infiltration of lymphocytes causing focal or disseminated vasculitis. The eschar is considered pathognomic but may be found in 7% to 80% of the patients [3]. Central nervous system involvement commonly manifests with altered sensorium due to aseptic meningitis or acute encephalomyelitis. Occasionally, seizures, intracerebral haemorrhage, cerebellitis, and rarely acute transverse myelitis, neuroleptic malignant syndrome, Gullain Barre syndrome or nerve palsy may be noted [4].

Cranial nerve involvement in scrub typhus may result from direct invasion of central nervous system by the bacteria leading to acute vasculitis or secondary immune reaction leading to vasculitis of vasa vasorum of nerve. There have been four earlier reported cases of abducens nerve palsy in scrub typhus, causing diplopia [3-5]. Multiple cranial nerve involvement, viz. 3rd, 7th, 9th, 10th and 12th have been earlier described in a case of scrub typhus meningitis and cerebellitis [6]. There were no residual deficits in any of the above cases.

The index case developed glossopharyngeal and vagus nerve (pharyngeal branch) palsy at the summit of symptoms. Although doxycycline is the recommended drug for treatment, he was treated with azithromycin, as use of doxycycline below 8 years of age is controversial. In an endemic country like India, scrub typhus should be kept as a differential in fever for more than 7 days with neurological deficits. Timely diagnosis and intervention can have complete resolution of neurological deficits.

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