An Infant with Blended Phenotype of Zellweger Spectrum Disorder and Congenital Muscular Dystrophy

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Abstract

We report a newborn born to a consanguineous couple with antenatally detected dilatation of third ventricle, unilateral talipes, and intra uterine growth retardation. On examination, there was facial dysmorphism, hypotonia, encephalopathy, joint laxity and muscle hypertrophy in addition to left foot talipes. On evaluation, there were renal cortical cysts, rhizomelia, chondrodysplasia punctata and elevated muscle enzymes, along with a dilated third ventricle. As the phenotype was not consistent with any of the muscular dystrophies or the peroxisomal disorders, an exome sequencing was requested. It revealed a combination of Zellweger syndrome and Ullrich congenital muscular dystrophy type 1.

Keywords: Collagenopathy, consanguinity, dysmorphism, exome sequencing, peroxisomal disorder

Introduction

Consanguinity is a common custom in various parts of India. When a dysmorphic neonate is born to such a couple, possibility of autosomal recessively acquired genetic disorders is very likely. However, in some neonates the dysmorphism may not be diagnostic and in some cases, the features may overlap with another disorder. Hence, a multi-disciplinary evaluation by neonatologist, geneticist and allied sub specialities may be necessary in establishing a diagnosis.

Case History

A 37-weeks male neonate was born by normal vaginal delivery. The baby did not cry after birth, requiring positive pressure ventilation for 30 seconds. Apgar scores were 4, 7 and 7 at 1, 5 and 10 minutes, respectively and cord blood gas was normal. The baby was admitted to neonatal intensive care unit (NICU) because of respiratory distress and dysmorphism. The baby weighed 2,140 grams (2 percentile), with a length of 48 cm (38 percentile) and head circumference of 32 cm (14 percentile). There was facial dysmorphism with wide-open anterior and posterior fontanelle, overlapping sutures, short forehead, broad nose, epicanthal folds and telecanthus [Figure 1a]. In addition, we noted narrow thorax, rhizomelia, right varus deformity, left CTEV, laxity in all the joints and sacral dimple [Figure 1b]. Neurological examination revealed lethargy, poor state to state variability, weak cry, decreased spontaneous activity and peak arousability, poor quality of movements, generalised hypotonia, muscle hypertrophy of upper and lower limbs [Figure 1b] with diminished deep tendon reflexes. The primitive reflexes (rooting, sucking, grasp and Moros) were decreased. We noted nystagmoid movements of eyes.

The mother was a 24-year-old, primigravida with normal first-trimester screening. The pre-conceptional history was insignificant, except for a third-degree consanguinity. Anomaly scan at 20 weeks revealed prominence of third ventricles and unilateral talipes. Genetics opinion was sought, amniocentesis followed by microarray analysis was done, both of which were normal. The growth scans at 25 and 28 weeks showed similar findings and appropriate growth. Growth restriction was noted in the 36 weeks scan. There was no history fever in first trimester, polyhydramnios, decreased fetal movements or antenatal exposure to drugs like sedatives and narcotics. In NICU, baby was started on nasal prong oxygen. Complete blood counts and blood culture were not suggestive of infection. Ultrasonography of abdomen showed bilateral echogenic kidneys with renal cortical cysts, while spine was normal. Neurosonogram confirmed prominent third ventricle and Blake pouch cyst [Figure 1c]. Infantogram showed bilateral short humerus, stippled calcification of hip and knee (chondrodysplasia punctata), bell-shaped thorax, metaphyseal flaring with dislocation of bilateral hip and knee joints [Figure 1d]. Ophthalmologic evaluation was suggestive of intraretinal hemorrhage. Creatine phosphokinase and lactate dehydrogenase were elevated (1171 U/L and 1698 U/L, respectively). Expanded metabolic screen, liver function tests, blood ammonia lactate, echocardiography and serum creatinine were normal.

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However, the presence of Peroxisome biogenesis disorders in the Zellweger spectrum: PEX genes encode gene results in deficiency of functional peroxisomes impairing formation, peroxisomal protein import or both. Mutations in PEX genes result in deficiency of functional peroxisomes impairing fatty acid metabolism, and leading to accumulation of very long chain fatty acids (VLCFAs), phytanic- and pristanic acid, C27-bile acid intermediates and pipeolic acid in plasma and have deficiency of plasmalogens in erythrocytes. Accumulation of all these metabolites leads to multi-organ dysfunction like neurodevelopmental delay, liver dysfunction, adrenocortical dysfunction, hearing and vision impairment. Facial profile is characteristic in early phase of infancy. The long term outlook for infants with Zellweger syndrome is very poor. Most infants do not survive past the first 6 months of life and usually succumb to respiratory distress, gastrointestinal bleeding or liver failure.

COL6A1 gene mutations result in autosomal dominant and recessive forms of myopathies with a spectrum ranging from milder Bethlem myopathy 1 to severe Ullrich congenital muscular dystrophy1.[4] They are collectively known as type VI Collagenopathies. They are hybrid disorders characterised by clinical features attributable to both muscle and connective tissue. The characteristic features include weakness, hypotonia, striking hyperlaxity in distal joints, contractures and club foot. This presentation of Zellweger Syndrome with muscular dystrophy has not been described in literature. In this case, diagnosis could be only confirmed through exome sequencing.

Confirming the diagnosis in a dysmorphic neonate requires good clinical examination, laboratory evaluation and multi-disciplinary collaboration. In those with a Mendelian inheritance pattern, other family members should be screened for carrier status so that future pregnancies can be planned and managed accordingly. Clinical exome sequencing plays a key role in the diagnosis where the presentation is atypical.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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