Case Report

Phelan McDermid Syndrome : A Case Report

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ABSTRACT

Background: Phelan McDermid syndrome (chromosome 22q13.3 deletion) is a neurodevelopmental disorder presenting with global developmental delay (GDD)/Intellectual Disability (ID) and autism spectrum disorder (ASD) with multisystemic involvement of varying severity.

Aims: By highlighting this case we would like to increase awareness among general pediatricians of this underreported condition from/within a specific/limited cohort of children with GDD/ID and ASD.

Clinical Description: Our case is a 7 year child who presented to our neurodevelopmental center with GDD, facial dysmorphism, unilateral multicystic dysplastic kidney, limb swelling, behavioral concerns and MRI Brain findings, He was diagnosed with chromosome 22q13.3 deletion on karyotyping and interphase FISH and given multidisciplinary care focusing on all comorbidities.

Conclusion: This case highlights the role of comprehensive testing and evaluation in a child with neurodevelopmental concerns for establishing a diagnosis for prognostication.

Keywords: Phelan McDermid syndrome, 22q13.3 deletion, SHANK3, GDD, ID, ASD, MCDK, dysmorphism, lymphedema

INTRODUCTION

Phelan McDermid syndrome (PMS) is a neurodevelopmental disorder characterized by global developmental delay (GDD), intellectual disability (ID) and autism spectrum disorder (ASD) with mild nonspecific dysmorphic features and several comorbidities. It is a result of terminal deletion of chromosome 22q13.3 leading to SHANK3 gene haploinsufficiency. It is estimated to be a frequently recurring monogenic form of ASD and ID in 0.5% and 2% of cases respectively (1,2). However, it has been under-reported perhaps due to lack of awareness. We present a classic case of PMS, who reported at our multidisciplinary neurodevelopmental clinic for developmental and behavioural concerns. We would like to increase the awareness of this condition among general paediatricians by highlighting its classic diagnostic features to allow for its timely diagnosis and better follow-up.

CLINICAL DESCRIPTION

Our patient, a 7year boy, presented to our center with complaints of GDD, delayed and deviant social communication and behavioral concerns.

He was first born to a non-consanguineous marriage. Antenatally, fetal antenatal ultrasound was suggestive of right multi-cystic dysplastic kidney (MCDK). He was delivered at term by emergency caesarian section in view of meconium stained liquor with birth weight 3 kg, did not cry at birth, received resuscitation and was admitted in NICU for 4 days. However, he did not require invasive ventilation, but received phototherapy for neonatal hyperbilirubinemia.

Parents noticed him to be floppy since early infancy with difficulty in swallowing and drooling of saliva. He had developmental delay in all domains. He had neck holding by 10 months, rolling by 1 year, sitting without support by 18 months, crawling by 2 years, standing with support by 2.5 years, walking without support by 3.5 years. In fine motor skills, he started reaching out for objects by 1 year, developed pincer grasp after 2 years, and at 7 years started scribbling and undressing. In language development, he started cooing by 6 months, babbling by a year and had no meaningful words by 7 years of age. He achieved social smile at 4 months and started recognizing mother by 6 months. At 7 years, he still needed assistance with activities of daily living, was not toilet trained, had difficulty blowing. Parents reported deficits in social communication and interaction like fleeting eye contact, delayed response to name call, absence of pointing. He was hyperactive, restless and had sensory concerns.

Parents also reported presence of a painless swelling over left foot since infancy, progressively increasing to currently reaching the knees, causing him to drag foot while walking.

He had no history of seizures, dystonia, tremor or tics, abnormal body odor, skin or hair changes, echolalia, repetitive behavior, aggression, self- harm. No family history of similar illness, developmental delay, seizures, early death, genetic or metabolic disorders.

On examination, he displayed facial dysmorphism in terms of a long face, dysplastic ears, prominent forehead, bulbous nose, conical teeth, pointed chin with large hands, broad fingers and flat feet. A soft, pitting nontender swelling over left feet and leg with overlying skin normal. He had normal spine, genitalia and no neurocutaneous markers. His head circumference (52 cm), height (124 cm), weight (26.1 kg), BMI (16.7) were within normal limits.

He had mild spasticity in lower limbs and ataxic gait. Except for left exotropia, rest of cranial nerve examination was normal. Cardiovascular, respiratory and gastrointestinal system examinations were within normal limits.

He was under evaluation since 9 months of age for multisystemic involvement i.e. hypotonia, GDD, dysmorphism and renal involvement with leg swelling. CT Scan Brain showed left temporal arachnoid cyst and right parietal subgaleal hematoma. MRI brain at 18 months revealed hyperintense signal on T2 in bilateral temporal white matter region suggestive of delayed myelination for age, small area of gliosis in right periventricular (peri-trigonal) region, with altered signal intensity in cerebellum, brainstem and a 3.4*2.3*1.7 cm arachnoid cyst anterior to left temporal pole. BERA was normal. Refractive errors were identified on ophthalmology evaluation. Metabolic workup {blood Tandem mass spectroscopy (TMS) and urine gas

chromatography - mass spectroscopy (GCMS)} were normal, muscular involvement ruled out by normal CPK and 2D ECHO ruled out cardiac involvement. Repeated ultrasound KUB revealed a small right kidney with 4 cysts with left kidney showing compensatory hypertrophy. Karyotype revealed a 46, XY chromosome complement with derivative chromosome 22 {46, XY, der(22)t(?;22)}. Interphase fluorescence in situ hybridization (FISH) showed heterozygous deletion of 22q13 (99% cells in interphase) which clinched the diagnosis of Phelan McDermid Syndrome.

The child presented to our centre for specialised holistic care for motor and speech delay, hyperactivity and inattention, problems in visuo-motor coordination, perceptual and sensory concerns. He was evaluated by the developmental paediatrician and assessed on psychometric tests. He did not meet the DSM-5 criteria for ASD or ADHD.

Accordingly, he was started on an individualised intervention program targeting development in all domains inclusive of weekly sessions of occupational therapy, physiotherapy and speech therapy and monthly parental counselling. He was prescribed oral risperidone, fluoxetine and methylphenidate subsequently for his behavioural and sensory concerns. He continued independent follow up with a paediatric neurologist and nephrologist.

DISCUSSION

Phelan McDermid syndrome, a 22q13 deletion syndrome presents with multiple comorbidities affecting various systems with varying severity.

Kolevzon, et al, highlighted presence of dolichocephaly or macrocephaly with normal growth in majority with dysmorphic features including periorbital fullness, long eyelash, wide nasal bridge, bulbous nose, malformed ears, pointed chin, large fleshy hands and flat feet, all of which were manifest in our case(1,3). Other features include, hypoplastic/ dysplastic nails, syndactyly of toes, ptosis, epicanthal folds (1).

Our case did not meet the DSM-5 criteria for ASD upon presentation to us, but had sensory and behavioral concerns with motor and speech delays. However, a high prevalence of ASD (up to 84%) is reported in these patients (4).

There is high prevalence of hypotonia with feeding difficulties, delayed motor development, and abnormal gait like high steppage gait, toe walking or broad-based ataxic gait, as in our case (1,4). Further, there is also an increased risk of scoliosis and macrocephaly with raised ICP with increasing age (1).

Hearing and vision problems including strabismus, myopia and retinitis pigmentosa are common (1,5,6).

Brain abnormalities are evident in 73% of cases including corpus callosum thinning, delayed myelination, generalized white matter atrophy, and nonspecific white matter hyperintensities, ventricular dilatation and interventricular, cerebellar, or temporal sylvian arachnoid cysts many of which were present in our patient (1,4,7). Seizure disorders occur in up to 31% cases being highly debilitating and associated with regression(1,7).

Our patient was diagnosed with right MCDK antenatally. Renal abnormalities are relatively common in PMS (38%) and include vesicoureteral reflux, hydronephrosis, renal agenesis, horseshoe kidneys, pyelectasis, polycystic kidney, duplicate kidney, MCDK and Wilms' tumor (1).

Our patient had a progressive swelling of left lower limb since early infancy. Lymphedema has been reported in about 24% cases and represents an especially troubling symptom with risk of cellulitis (1,6).

Other organ involvements include congenital heart defects (25%) like tricuspid valve regurgitation, atrial septal defect, patent ductus arteriosus, and total anomalous pulmonary return (1,3). Gastrointestinal symptoms include gastroesophageal reflux disease, constipation, cyclic vomiting, dental malocclusions (1,6). Pica associated in 50% cases requires behavioral therapy. Children are also prone to immune system dysfunction, including recurring ear and upper respiratory tract infections, seasonal and food allergies and asthma (1,6).

Our patient was diagnosed with karyotype (G banding) showing a derivative chromosome 22 and interphase FISH (using Vysis LSI DiGeorge/VCFS Spectrum Orange/ LSI ARSA Spectrum Green probe) revealing terminal deletion on chromosome 22q13. Deletions 22q13 occurs de novo in majority but in 20% cases, a parent carries a balanced rearrangement leading to significant risk of recurrence in families (1,8). Hence, karyotyping should be performed even with a positive CMA to rule out ring chromosome and translocations along with FISH for biological parents (8,9). Finally, Sanger or next generation sequencing can test for SHANK3 mutations if CMA and karyotyping are unrevealing in a suspected case. SHANK3 gene, a scaffolding brain protein which regulates postsynaptic density of glutamatergic synapses and is identified as the critical gene for its neurological features (10).

The natural history is complicated by comorbidities and associated ASD, ID and behavioral problems, it is imperative to have the child evaluated early by a developmental pediatrician with early and intensive delivery of individualized intervention. Appropriate referrals to orthopedics and physical therapist for neuromotor deficits and regular monitoring for progressive scoliosis or raised ICP with increasing age is warranted. There should be a low threshold for EEG with signs of behavioral changes or regression. Other aspects include early referrals to pediatric audiology, ophthalmology, nephrology and cardiology. Routine management for lymphedema with preventive measures for infections is necessary (6).

CONCLUSION

PMS, a 22q13 deletion syndrome, is not as rare as assumed. Early diagnosis and intervention has prognostic implications. Further, we would like to reinforce the benefits of extensive testing for establishing a diagnosis in view of the holistic care that could be provided to the individual based on the spectrum of comorbidities involved.

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