CASE REPORT

An 8-year-old female child from the suburbs of Chennai, born of non-consanguineous marriage, was brought with history of first episode of right focal motor seizures involving right upper arm, without any concurrent precipitating illness. She was globally delayed in development and was found to be moderately intellectually disabled (DSM5 code: 318.0) and deaf-mute. Her 3-year-old younger sister was normal and there was no family history of any intellectual disability, seizures, congenital defects or genetic disorders. Born through meconium, at term, she had neonatal seizures on day one itself, which was attributed to perinatal asphyxia and was on phenobarbitone for one month and was seizures free till 4½ y. She was diagnosed to have Global developmental delay with a developmental age of 5 mnth at 1 y (DQ-50%) and 1 y at 3 y (DQ-30%). Since then she has improved considerably following regular physiotherapy. She was able to move around freely, though deaf mute. On examination she was conscious, afebrile. She was small built with height and weight, both well below the respective 3rd centiles. There were no neurocutaneous markers, but she had microcephaly with a head circumference < 3rd centile and dysmorphic features like low set ears with mild dysplasia of the right one, high forehead, pointed nose, prominent alae-nasi, mild hypertelorism, epicanthal folds, long philtrum, and large lower lips [Table/Fig-1]. Her fingernails were dystrophic; especially the thumb and abnormal dermatoglyphics were seen in the form of arches in fingertips of her both hands [Table/Fig-2]. There was total absence of nails (anonychia) in her both great toes and all other nails in her toes were also hypo plastic. Her central nervous system examination revealed...
that she was moderate intellectually disabled (IQ= 47 by sequin foam board test (SFT)), with deaf-mutism, horizontal nystagmus bilaterally and a normal fundus. Her tone, power and deep tendon reflexes were normal with equivocal plantar reflexes and normal pain and temperature perception. Her other systems were normal. Her CBC, Serum electrolytes, Calcium, Magnesium, LFT, RFT and urine were normal. USG abdomen, CT and MRI brain were normal. X-ray of limbs showed mild hypoplasia of the terminal phalanges of both fingers and toes, such that soft tissue shadows at end of phalanges were seen more prominent [Table/Fig-3]. Behavioural Observation Audiometry (BOA) showed no observable response, following which BERA was done which showed severe sensorineural hearing loss in the right ear and moderate sensorineural hearing loss in her left ear. EEG taken 20 days later showed generalized epileptiform activity. Routine metabolic screening revealed normal blood glucose, lactate levels. 2-oxaloacetate levels were not done, as it was not available locally. Her seizures were controlled with phenytoin; hearing aid was suggested. Though both her parents and her blood samples were sent to Department of molecular and human genetics, Bayler’s College of medicine, Houston, USA, for genetic analysis as part of an ongoing study to identify the genetic basis, we couldn’t get any positive results from these blood samples. After 4 y she was reassessed at the age of 8 and was found to be at the same level of intellectual disability by SFT, but seizures have become generalized tonic clonic, no change in hearing by BERA, or in peripheral nervous system and no signs of optic atrophy. Her seizures were subsequently controlled with Valproic acid; hearing aid and speech therapy was suggested and is on rehabilitation now.

DISCUSSION

Door syndrome (OMIM220500) is an extremely rare genetic condition with just over 40 cases reported till date since its first description in 1961 [1]. It is inherited as autosomal recessive disorder. The acronym DOOR syndrome was coined by Cantwell (1975) due to the association of Deafness, Onychodystrophy, Osteodystrophy and Retardation (mental), often associated with seizures [2]. Deafness is congenital—both partial and complete sensorineural deafness has been reported. Onychodystrophy manifests in the form of anonychia, hypoplasia or rudimentary nails, discoloured with abnormal structure, shape or texture in one or all the nails. Osteodystrophies can be in the form of absent or dysplastic distal phalanges, triphalangeal thumb or great toe [3]. Intellectual disability may be mild to profound, often associated with seizures and EEG abnormalities. Many of these children go into a progressive deterioration in neurological status with increasing intellectual disability, peripheral nervous system involvement and optic atrophy [4]. But on follow up though there was no optic atrophy/ peripheral nervous system involvement or increase in deafness, we could see a change in seizure pattern becoming generalized tonic clonic. Autosomal recessive forms, frequently called as type 1 form, with high levels of 2-oxaloacetate in blood and urine, are found to have profound intellectual disability with multiple refractory seizures and relatively quick downhill course [5]. Type 2, having milder presentation and quite often normal values of 2-oxaloacetate, usually have better prognosis [6].

Additional features like arch patterns and other abnormal dermatoglyphics, microcephaly, high arch palate; long philtrum, antimongoloid slant, cataract, myopia, astigmatism, progressive optic atrophy and asymmetric face may be seen in many [4]. Mutation in a gene connected with oxidative phosphorylation resulting in defective 1-alpha Ketoglutarate activity in TCA cycle, has been found to be the cause of this syndrome. This results in abnormally high 2-oxaloacetic acid levels in both blood and urine, which can be used to confirm the diagnosis. However, many with type 2 have been reported with normal values of the same, such that the metabolite levels may not always be needed in all typical cases [7].

It has been found in a recent study that TBC1D24 mutations in 16p13.3 were associated with many patients with DOORS syndrome; we couldn’t get any positive results. Whole-exome sequencing was done until a candidate gene was identified, and Sanger sequencing done to confirm mutations. This study in which this child participated possibly shows the genetic heterogeneity in which many patients with most of the phenotypic features may or may not have specific TBC1D24 mutations [8]. Compared to children with both typical clinical features and mutations, heterogeneity may probably be the reason why steady neurological deterioration is not noted in this child at a four year follow-up.

CONCLUSION

Dysmorphic features can be a direction towards possibility of a particular syndrome; however it needs support of Molecular diagnostics for further understanding the pathological pathways underlying unexplained forms of the phenotype. The implementation of the new technologies will allow the analysis of whole-genomes, transcriptomes and interactomes which could lead to detect single base mutations and structural variations, further broadening the possibility of diagnosis in idiopathic cases.

COMPETING INTERESTS

The author(s) declare that they have no competing interests. The cost of sending blood samples and genetic analysis was born by Department of Molecular and Human Genetics, Baylor’s College of medicine, Houston, USA.

ABBREVIATIONS

TCA- Tricarboxylic acid cycle
CBC- Complete blood count
LFT- Liver function tests
RFT- Renal function tests
USG- Ultra sonogram
CT- Computerized tomogram
MRI- Magnetic resonance imaging
BERA- Brain stem Evoked response Audiometry
BOA- Behavioral Observation Audiometry
SFT- Sequin foam board test

ACKNOWLEDGEMENT

We acknowledge and appreciate the timely help rendered by Dr. Phillippee M. Campeau et al., of Department of Molecular and Human Genetics, Baylor’s College of Medicine, Houston for making arrangements for sending blood samples and for doing the genetic analysis. We acknowledge the support of the Chancellor and Dean of the Saveetha Medical College without whose support the management of this patient would have not been possible.

REFERENCES

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FINANCIAL OR OTHER COMPETING INTERESTS: None.