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PSEUDO-TORCH- A RARE MUTATION CAUSING GLOBAL DEVELOPMENT DELAY, MICROCEPHALY AND EXTENSIVE BAND LIKE BRAIN CALCIFICATION

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ABSTRACT:
Pseudo-TORCH 1 syndrome is an inherited autosomal recessive disorder that clinically and radiologically mimic congenital TORCH infection. We report a case of three and half years old child who presented with early infantile seizures, progressive microcephaly, facial dysmorphism and global developmental delay. There were symmetrical band like intra-parenchymal calcification as well as in pons and thalami. Serological testing for infectious agents was negative. His Whole exome sequencing revealed OCLN gene mutation consistent with Pseudo-TORCH syndrome-1.

KEY WORDS:
Calcifications, Microcephaly, Pseudo-TORCH, Whole exome sequencing.

INTRODUCTION:

Pseudo-TORCH syndrome (PTS) is an inherited autosomal recessive disorder with homozygous or compound heterozygous mutation in the gene encoding occludin (OCLN) on chromosome 5q13 (OMIM # 251290). PTS is characterized by the presence of early onset infantile seizures, developmental delay, spasticity, microcephaly and intracranial calcifications which can be seen at birth even in almost all cases. This clinical course simulates the disease manifested after intrauterine infection with Toxoplasma gondii, Rubella, Cytomegalovirus, Herpes simplex (TORCH syndrome), hence the name pseudo-TORCH.Features like neonatal jaundice, thrombocytopenia, and visceromegaly affect less than half of these patients.In PTS, despite repeated testing, serology for TORCH comes negative.[1] Apart from extensive brain calcifications, brain malformation has also been seen as an associated feature, including dandy walker malformation, polymicrogyria, hypogenesis of corpus callosum and marked white matter loss.[2,3]

CASE REPORT

3.5 years old boy, product of consanguineous marriage, 6th in order of 6 siblings with three sibling deaths in early neonatal period, delivered full term at 38 weeks with uneventful birth. His anthropometric measurement at birth showed OFC-30 cm (<3rd centile), length-49cm (25th centile) and weight-2.6kg (10th centile). He required neonatal admission owing to respiratory difficulty and considering small head size and previous siblings' deaths, his neonatal metabolic screening was done that came negative for aminoacidopathies, organic acidemia and fatty acid oxidation defects. He was treated as pneumonia and was discharged at 9th day of life.

He had first seizure at the age of 3 months, which started with subtle seizures and apneic episodes followed by tonic seizures and later developed myoclonic jerks during the course. Seizures were refractory to treatment with only partial control with polytherapy. (Levetiracetam, carbamazepine, valproic acid, clonazepam, steroids, vigabatrin and ketogenic diet). There was global developmental arrest with partial neck holding only and speech confined to cooing only. Though there was no cataract but his vision was affected and was only able to fix gaze. At 1 year examination, he had marked microcephaly with OFC of 33.5 cm (3rd centile), prominent sutures with tower shaped skull, high-arched palate, low-set ears, and sloping foreheadand signs of spasticity. CT brain done at 6 months of age showed mild hydrocephalus with symmetrical bilateral calcification involving thalami as well as pons. Considering microcephaly, brain calcification, previous neonatal deaths, extensive workup for TORCH done. Systemic examination and investigation showed no visceromegaly, heart defect, cataract or thrombocytopenia.

INVESTIGATION	FINDINGS
TORCH serology	Negative
Neonatal metabolic screening	Negative for aminoacidopathies/ organic acidema/ fatty acid oxidation defect, hypothyroidism
Ammonia, Lactate, Anion gap Bone profile (Calcium, Magnesium) Electroencephalography	Normal Normal Multifocal epileptiform discharges
Opthalmological examination	No cataract or disc changes
Cardiac screen	Normal
Whole exom sequencing	Homozygous mutation in OCLN gene, ENST00000355237.6:c.1324G>T, ENSP00000347379.2:p.Glu442Ter consistent with pseudo-TORCH syndrome 1.

MRI Brain showed malformation in term of pachygyria and agenesis of corpus callosum. Child had intractable seizures despite being on multiple anti-epileptic drugs with frequent episodes of status epilepticus. Unfortunately, child expired at 3.5 years of age. Genetic counselling of family has been done.

Figure 1: MRI Brain T1W images showing pachygyria (orange arrow), lissencephaly (yellow arrow) and agenesis of corpus callosum (green arrow) with calcification involving periventricular areas, bilateral thalami and midbrain(red arrow)

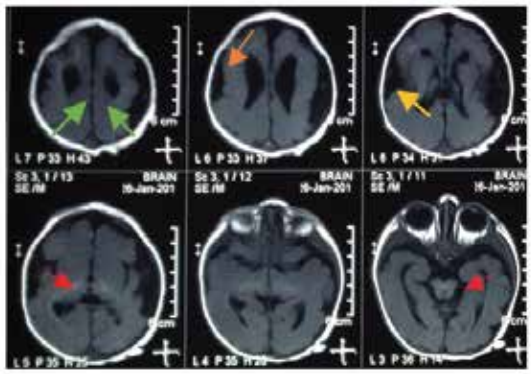
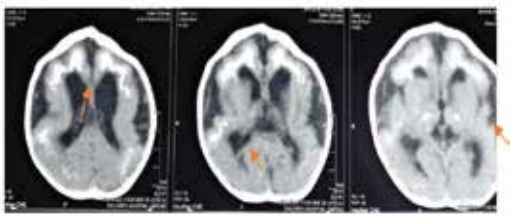


Figure 2: CT Brain showed extensive parenchymal, thalamic calcification with atrophic changes (orange arrow)



DISCUSSION

Pseudo-TORCH syndrome-1 is an inherited autosomal recessive disorder caused by mutation in the OCLN gene that clinically and radiologically mimics congenital TORCH infection.The OCLN gene encodes occludin, an integral part of tight junctions in cerebral blood vessels. Itmaintains the blood vessel integrity and thus the blood brain barrier. Mutation leads to ischemic and vascular insults in utero leading to cortical malformations which is unique to PTS contrary to TORCH.[4] The prevalence rate of PTS is <1/1000000 and approximately only 40 cases has been reported in literature. First described in 1985 in 2 brothers with microcephaly, spasticity, intellectual disability and brain calcification,[5] the disease continued to evolve in terms of new imaging findings of extensive calcification in deep brain structures including thalami, basal ganglia and brainstem like our index case as well as associated brain malformation.[6] Various brain malformation including Dandy Walker, polymicrogyria, hypogenesis of corpus callosum and marked white matter loss has been commonly seen but rare ones including hydranencephaly and lissencephaly has also been described in literature like our index case.[7,8] Crow et al described a phenotypic overlap of Pseudo-TORCH with Aicardi-Goutieres syndrome (AGS) due to similar clinical picture and extensive brain calcification but the

genetic basis are different and the genetic analysis of OCLN mutation in our case excluded the diagnosis of other related syndromes including AGS and Cockayne syndrome.[9] The life expectancy of children born with this rare disorder varies between neonatal age to around 4 years of age as per available case reports.[5,6.]

The importance of this case report is to create an awareness about the early diagnosis of this genetic disorder which mimics TORCH. Considering the high prevalence of cytomegalovirus and toxoplasmosis in our part of the world, a high index of suspicion should be kept particularly if serological tests for TORCH come negative. Our index family had 4 deaths including the index patient. This emphasizes that a genetic diagnosis is mandatory in such cases through carrier testing and antenatal screening in subsequent pregnancies which can prevent further morbidity and mortality.

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Author's contribution:
Javeria Raza Alvi; data collection, data analysis, manuscript writing, manuscript review
Saher Gul Ahdi; data collection, data analysis, manuscript writing, manuscript review
Mahrukh Sultan; concept, data analysis, manuscript review
Tipu Sultan; concept, data analysis, manuscript review

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