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Case Study
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Homozygous Mutation of *OCLN* Gene Result in Pseudo-TORCH Syndrome Type I: A Case Reports and Literature Review

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Abstract

Clinical similarities of TORCH syndrome but serological negative findings for infectious agent named it Psuedo-TORCH syndrome, which follows autosomal recessive inheritance but it has genetic heterogeneity. Here we reported a case of 11 month old girl of consanguineous parent with psychomotor retardation, microcephaly and intracranial calcifications but she was serologically negative for TORCH infection and positive for homozygous mutation in the gene encoding occluding (*OCLN*) on chromosome 5.

Introduction

Psuedo-TORCH syndrome is a rare disorder of autosomal recessive inheritance where the patient presented with variable manifestations that resemble congenital intrauterine infection [1]. Intracranial calcification and microcephaly are the important clue to detect TORCH syndrome (toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis) here Psuedo-TORCH syndrome mimic the clinical and neuroradiologic features of TORCH infection in the absence of bacteriological or virological evidence of infection [2]. The name of this disease was first described by Baraister et al. [3] who reported two boys of same family presented with spastic tetraplegia, microcephaly, seizure and intracranial calcifications [3].

Case Study

Baby Afifa a 13 month old girl of consanguineous parent presented with the complaints of recurrent seizure since 3 months of age, in the form of clonic movement of limbs and blinking of eye involving the left half of body occurring 3 to 4 times in a day. Mother also complained that her child unable to stand alone but able to recognize her mother. She was delivered normally at hospital and cried immediately after birth. Her developmental milestone is delayed, she had achieved her neck control at 6 months of age and start to sit unsupported since 10 months of age, and she can speak only baba and dada. Her parents was maternal cousin and there is history of epilepsy among the family member, Her one maternal uncle and one paternal aunt has been suffering from epilepsy since their childhood, both of them were well controlled with antiepileptic drugs. Baby Afifa has been treated with antiepileptic drug phenobarbital for the last 6 months without remission of seizure. On examination her OFC 41 cm, which lies below 3rd centile, no facial dysmorphism except convergent squint on both eyes and has no neurocutaneous markers on skin survey. Vitals were stable during examination. Anthropometrical examination reveals her weight is 8 kg; weight for age lies just above 15th centile, supine length is 65 cm, length for age just on 10th centile. Hypertonia present on four limbs. All deep tendon reflexes are brisk without clonus. Her motor developmental age corresponds 6 months, speech and cognition corresponds 9 months of age. Her vision and hearing is intact.

Investigations

TORCHS screening was negative, S. ammonia, Blood lactate, CBG, S electrolytes, ABG all reports were within normal levels, IMD panel was normal. EEG showed focal epileptiform discharge from left frontoparietal region of brain with poverty of normal activity in background. Hearing assessment refers to no hearing impairment. Eye evaluation reveals normal anterior and posterior chamber. CT scan of brain reveals intracranial calcification with cerebral atrophy. Clinical exome sequencings shown in Table 1 (Figures 1-3).

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Table 1: Clinical exome sequencings.

Gene	Location	Variant	Zygosity	Disease(OMIM)	Inheritance	Classification
OCLN(+)ENST00000355237.6	Exon 3	c.90del p.Gly31GlufsTer34	Homozygous	Pseudo-TORCH syndrome - 1	Autosomal Recessive	Pathogenic
SCN3A(-)ENST00000283254.12	Exon 23	c.4184A>C p.Asn1395Thr	Heterozygous	Developmental and epileptic encephalopathy-62	Autosomal Dominant	Uncertain Significance
PAK1(-)ENST00000278568.8	Exon 4	c.398C>T p.Ser133Leu	Heterozygous	Intellectual developmental disorder with macrocephaly, seizures and speech delay	Autosomal Dominant	Uncertain Significance

Figure 1: Case.

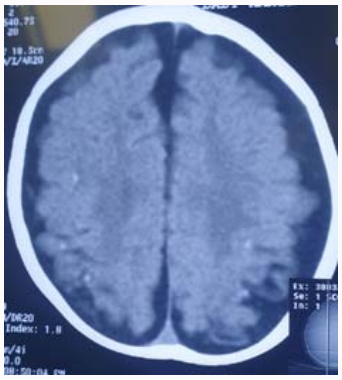

Figure 2: CT scan of brain.

Figure 3: Results of Clinical exome sequencing.

According to the results of next generation sequencing patient was finally diagnosed as a case of epileptic encephalopathy due to Pseudo-TORCH Syndrome-1, we managed the patient by multidisciplinary approach, for seizure oral form of levetiracetam was prescribed and at the same time speech therapy, developmental and occupational therapy was started and now patient is under our supervision with good seizure control and there is progressive improvement of neurocognitive behavior.

Discussion

Pseudo-TORCH syndrome is one of the rare clinical syndromes that mimic the presentation of congenital TORCH infection without sero-positivity and it follows the autosomal recessive inheritance [3]. The common presentations of pseudo-TORCH syndrome are congenital microcephaly, developmental delay, and recurrent seizure, on neuro-radiology intracranial calcification, simplified gyration and polymicrogyria [4]. Here our case Afifa presented with recurrent seizure and delayed developmental milestones with family history of epilepsy. Our patient had no history of perinatal asphyxia. One study reported two patients with Pseudo-TORCH syndrome from a consanguineous family with complex heterogeneous presentation like early onset seizure, severe psychomotor development, visual impairment, chronic renal dysfunction, calcifications in thalami, basal ganglion and subcortical white mater, sanger sequencing identified a homozygous genomic rearrangement involving the *OCLN* gene [5]. O'Driscoll et al. [4] also reported their patient with some renal impairment Reardon et al. [6] have reported patients with hepatosplenomegaly, platelet dysfunction and purpura along with seizure and microcephaly which mimics the presentation of TORCH infection, but in our case we didn't find any renal, hematological or hepatobiliary abnormality. Eye manifestations like nystagmus, cortical visual impairment, corneal clouding, congenital cataract and microphthalmia was documented from different studies, we have only found convergent squint as eye manifestations [7-9]. Facial dysmorphism in the form of hypertelorism, microphthalmia,

micrognathia, high arched palate, low set ears and sloping forehead was observed by Monastiri et al. [9] and Abdel-Salam et al. [10]. Different cases presents with different manifestations with clinicoradiologic findings similar to congenital CMV infections but was negative for serology. One cases of pseudo-TORCH syndrome presented as Dandy-Walker syndrome which is a hind brain deformity with large posterior fossa cyst, this presented was explained in that way that extensive calcium debris from pseudo-TORCH syndrome in cerebrospinal fluid lead to obstruction at fourth ventricle outlet that leads to hydrocephalus and enlargement of posterior fossa cyst with cerebellar compression [3]. So the main difference of DWM from pseudo-TORCH syndrome is the presence of features of raised ICP in the DWM. Aicardi-Goutieres Syndrome (AGS) is another inherited form microcephaly which may mimic the presentation of pseudo-TORCH syndrome, most of the cases it follows autosomal recessive inheritance [11]. Spastic quadriplegia, progressive microcephaly, profound psychomotor retardation with bilateral symmetrical extensive calcifications in the basal ganglion is the prominent features of AGS [12,13]. The identified gene mutation is differ from pseudo-TORCH syndrome, most common gene mutation identified in AGS are *TREX1* gene, *RNASEH2A*, *RNASEH2B* and *RNASEH2C* [14]. Whereas the most common identified genetic mutations are the homozygous or compound heterozygous mutations in the *OCLN* gene located on chromosome 5q13 in pseudo-TORCH syndrome 1, USP18 gene mutation on chromosome 22q11 associated with pseudo-TORCH syndrome 2 and *STAT2* gene on chromosome 12q13 mutation is associated with pseudo-TORCH syndrome 3 [2,4,10]. Along with homozygous mutation of *OCLN* gene there are another two heterozygous mutation occurred in our cases for that reason our patient presented with recurrent seizure. Though the patients showed clinical and radiologic features of congenital CMV infection but she was negative for serology and due to presence of marital consanguinity we went for genetic study and finally patient diagnosed as a case of pseudo-TORCH syndrome. We managed the patient symptomatically by multidisciplinary approach and counseled them about the course of the disease.

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