Official Journal of the European Paediatric Neurology Society

Case study

Rett-like onset in late-infantile neuronal ceroid lipofuscinosis (CLN7) caused by compound heterozygous mutation in the MFSD8 gene and review of the literature data on clinical onset signs

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http://dx.doi.org/10.1016/j.ejpn.2014.07.008

ARTICLE INFO

Article history:
Received 15 July 2014
Received in revised form
16 July 2014
Accepted 27 July 2014

Keywords:
CLN7
MFSD8
Rett like onset
Compound heterozygous
Ataxia
Blindness
IRDA

ABSTRACT

Background: We present clinical and molecular findings of a patient with ceroid-lipofuscinosis CLN7, with a compound heterozygous mutation of the MFSD8 gene, with Rett syndrome clinical signs onset and a later development of full picture of vLINCL.
Case presentation: A 7 years-old female patient with normal development until the age 12 months, developed Rett like clinical picture (psychomotor regression, microcephaly, stereotypic hands movements in the midline, hyperventilation episodes) present at the onset of her condition (age 18 months), features still present at the initial evaluation in our clinic at age 5 years.
Results: MECP2 (methyl CpG binding protein 2) gene mutation was negative. At age 6 years she was readmitted for severe ataxia and blindness, seizures, and severe developmental regression leading to NCL (neuronal ceroid lipofuscinosis) suspicion. EEG showed slow background with IRDA (intermittent rhythmic delta activity). A conjunctive biopsy showed abnormal curvilinear and fingerprint lysosomal deposits, and genetic analysis revealed two heterozygous mutations of MFSD8 gene (c.881C > A p.Thr294Lys and c.754 + 2T > A) each inherited from carrier parents and a heterozygous variant (c.470A>C p.Asp157Ala) of CLN5 gene.
Conclusion: NCL should be suspected and MFSD8 genetic testing should also be considered in patients with Rett like phenotype at onset and negative MECP2 mutation. Such cases should be carefully and frequently re-evaluated in order to avoid delayed diagnosis and offer proper genetic advice to the family. In our knowledge, this might be the first case of CLN7 disease with Rett like onset described in the literature, which developed typical vLINCL clinical phenotype after age 5.5 years. A short review of the literature showing NCL onset modalities is presented.

1. Introduction

The neuronal ceroid-lipofuscinoses (NCLs) are a group of neurodegenerative inherited lysosomal storage disorders characterized by progressive cognitive and motor deterioration, ataxia, visual loss, seizures, and early death. The present proposal for classification, underlying the genetic and clinical heterogeneity, takes into account the responsible gene, precise genetic defect, clinical characteristics (age at onset, presenting symptoms, disease progression), biochemical phenotype and ultrastructural features, functionality and other remarks (additional disabilities, etc.), structured in 7 diagnostic axes, the last 3 being optional.[1] 13 mutated genes have been described so far[2–4] as responsible for the classically described NCL phenotypes: congenital, infantile, late-infantile, juvenile, adult. Variant late-infantile NCL (vLINCL) is genetically heterogeneous, with 5 major underlying genes identified so far. CLN7 disease, produced by MFSD8 gene mutations has a rather homogenous phenotype[5] with 10–15% patients with an atypical onset or course[4,6]; onset typically occurs between 2 and 11 years of age (mean onset 5 years) with a late-infantile clinical picture showing motor and cognitive decline, seizures, visual loss, ataxia. A Rett-like onset have been described in the infantile CLN1 disease,[7,8] but not in CLN7 (one male patient with Turkish variant NCL have been described having stereotyped hand movements associated to an autistic behaviour in the evolution of his disease, but not at the onset).[8] Both Rett syndrome and NCLs may have apparently normal development until age 9–24 months with subsequent progressive loss of cognitive and motor skills, progressive microcephaly and development of seizures and different neurological signs, including ataxia. We here present clinical and molecular findings in a patient with a compound heterozygous mutation of the MFSD8 gene, having a relative early onset age, as for the infantile form, and clinical signs from both infantile and late infantile forms. Our case has an atypical onset for the CLN7 disease phenotype, with Rett syndrome clinical signs around age 18 months and a later development of full picture of vLINCL (around age 5.5 years).

2. Case presentation

We present a 7 years old female patient, first admitted in our clinic at 5 years old, for evaluation of a global regression. She has had unremarkable perinatal and family history. Both parents are reported as Caucasian and unrelated. Head circumference at birth is not known. She had an under average developmental milestones achievement, but within normal range until age 12 months (head lift at 5 months, sitting acquired at 7 months and she was able to stand around 12 months of age when she made the first steps with aid), independent walking at 16 months. Voluntary grasping was normally developed until age 10–12 months. She produced syllables at age 5 months and she was able to say 3 meaningful words at age 12 months. She subsequently gradually lost cognitive and motor abilities and had difficulties in