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Neurodevelopmental profile at 5 years of a boy with Dravet syndrome–like phenotype: Does SCN1A gene have something in common?

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ABSTRACT

A boy with Dravet-lile syndrome (DS) was examined with a neurodevelopmental test at 5 years of age and the most affected developmental domains were found to be coordination and perception. Two main hypothesis (channalopathy vs. epileptic encephalopathy) as pathogenetic factors for the developmental impairment are discussed with the first one being more applicable in this case.

KEYWORDS
Dravet-like syndrome, channalopathy, neurodevelopment

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INTRODUCTION

Dravet syndrome (DS) (OMIM 607208) is a distinct epileptic encephalopathy recognized by Charlotte Dravet in 1978 and also known as Severe Myoclonic Epilepsy of Infancy (SMEI). It is a rare disease with an estimated incidence less than 1 per 40 000 [1]. It accounts for about 3% of epilepsy patients in the first year of life [2]. DS was classified as epileptic encephalopathy by the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) in 2001. That classification was later confirmed in the 2010 revision of the ILAE terminology [3].

In the typical clinical presentation healthy developmentally normal infants experience first seizure at around 6 months of age, which is commonly a convulsive status epilepticus. Seizures may be triggered by fever, illness or vaccination. Between 1 and 4 years other seizure types develop including myoclonic, absence and focal seizures. Early development is normal but it slows in the second year of life. EEG studies are normal initially, but after age 2 years generalized spike-wave and polyspike-wave activity with multifocal discharges and photosensitivity are commonly observed [4].

DS is associated with mutations of the gene encoding the alpha-1 subunit of the neuronal sodium channel, SCN1A, in >70% of patients. Mutations of that gene are found also in patients with a common familial epilepsy syndrome named Generalized Epilepsy with Febrile Seizures plus (GEFS+). A small percentage of SCN1A mutation-negative female patients with DS-like phenotype might carry PCDH19 mutations. Pathogenic mutations have also been identified in the GABARG2 and SCN1B genes [5].

In DS, outcome is generally poor, with intellectual disability in most patients and ongoing seizures [6]. The term "borderline" severe myoclonic epilepsy of infancy (SMEIB) is designed for patients without myoclonic seizures or generalized spike and wave activity. It has also been used loosely to indicate milder forms of DS. Nowadays it is acknowledged that the outcome of patients with SMEIB is as bad as that of the core DS [7], an observation that doubts epilepsy is the single cause of the intellectual deficit. Atypical cases with multifocal but not generalized seizures and later cognitive decline have also been described. Most of the patients but not all with borderline and atypical cases were found to have SCN1A mutations [8].

DEVELOPMENTAL IMPAIRMENT IN DS

Although the onset of seizures occurs in the first year of life, the interictal EEG generally does not show any abnormalities. Cognitive and behavioral impairment appears during second year of life or later. More profound studies on neurodevelopment during the first years of life show that visual functions, including cerebral visual processing, are affected before the onset of cognitive decline, which may provide useful prognostic information [9]. Widely reported in the literature are deficits in visuo-constructive abilities [10]. Language development, even though less involved than visuomotor abilities, is also typically affected in patients with DS. Phonetic and phonological disorders like omissions, distortions, substitutions or altered sequencing of phonemes, sometimes leading to almost incomprehensible words are observed in the great majority of cases in the first few years of life, whereas receptive language skills are only slightly below normal [11]. Thus, the main cognitive deficits in patients with DS are in (a) expressive language with relatively spared comprehension, (b) visual-spatial organization, (c) executive function, (d) behaviour (mainly ADHD) which some authors describe as cerebellar-like pattern of cognitive decline [12].

CASE PRESENTATION

A male 7 years old patient of with Dravet-like syndrome is presented. He is the first offspring of healthy parents of Bulgarian ethnic origin. Pregnancy was uneventful. Family history was positive - a father's aunt had three simple febrile seizures during infancy. The onset of DS was at 8 months when the boy presented with a short afebrile generalized tonic-clonic seizure (GTC) which was followed in the next 6 months by 4 recurrent short afebrile and febrile GTC seizures with varying lateralization. Treatment with valproic acid 22mg/kg/d was initiated after the second seizure at 9 months. There were only 2 short seizure relapses at ages 11 months and 25 months, but after 3 years of age seizure frequency increased to 2-5 diurnal and nocturnal GTCS per year despite the increase of valproate to 30mg/kg/d (serum level of 82 mg/l) at 3 years of age. Topiramate 5mg/kg/d was added at the age 5 years and the child became seizure-free until present. No myoclonic or other seizure types were recorded. More than 16 EEG recordings were performed, both awake and asleep, and 4 of them long-term with light and deep sleep included. Most of the EEG's were normal and few showed right- or left sided spike-and-wave activity with secondary generalization. No photosensitivity was found.

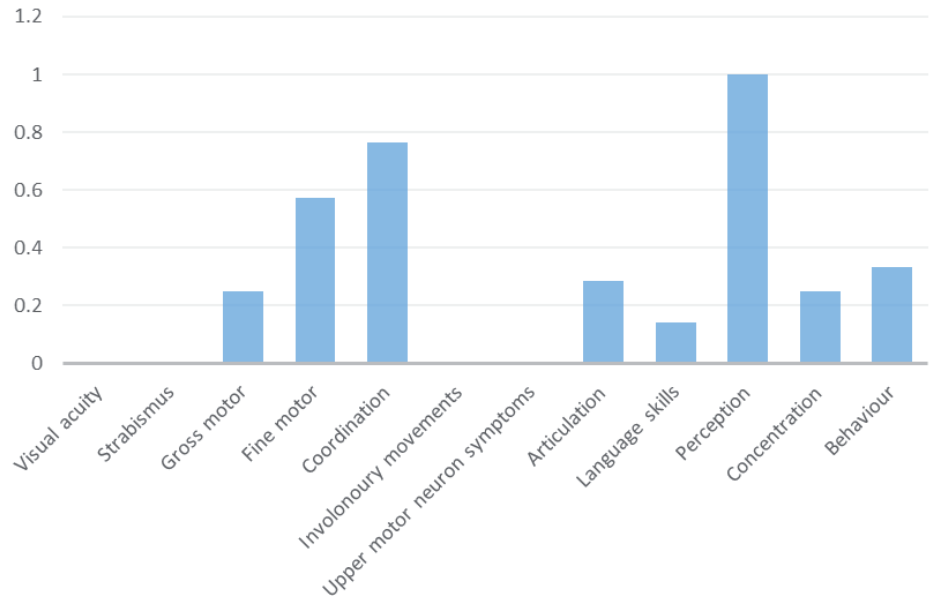
Neurodevelopmental assessment at the onset was in the normal range. Decline in motor and language development was noted in the second year of life. At 5 years the developmental quotient of the child assessed with the Manova-Tomova scale for Bulgarian children showed mild developmental delay (DQ – 55%**).** The most severely affected developmental domains were expressive language and fine motor skills.

Brain MRI at the age 4 years was normal. Somatic and neurological status, blood counts and biochemical work-up, including tandem mass spectrometry (MS/MS) of organic and aminoacids and acylcarnitines were all normal. Genetic testing found only a mutation in intron 8 of the SCN1A gene - rs372840031 (c.1171-9delTT). The mutation was considered as polymorphism, with no proven pathogenic effect. However, family segregation is planned to be performed.

At 5 years a neurodevelopmental examination was performed using the methodology of K. Michelsson and A.Ylinen (1987). A wide range of neurodevelopmental abilities were tested including visual acuity, strabismus, gross motor skills, fine motor skills,

coordination/balance, involuntary movements, upper motor neuron symptoms, articulation, language, perception, concentration and behavior [13]. Sixty items grouped in the 12 afore-mentioned domains were assessed and points are given for unsatisfactory performance [13]. The cut-off value for the Bulgarian population was found to be 26 points [unpublished data of the first author]. The child received 92 points proving neurodevelopmental impairment. The affected developmental domains were gross motor skills, fine motor skills, coordination/balance, perception, articulation, language skills, concentration and behavior (fig. 1). The most affected domains were coordination/balance and perception.

Figure 1. Neurodevelopmental profile at 5 years (the height of each bar reflects the proportion of the worst possible result for the domain)



DISCUSSION

The presented case displays some of the core characteristics of DS – the onset of seizures is before one year; the patient is healthy initially; seizures are febrile and afebrile GTC; familial history is positive for febrile seizures; there is developmental decline with onset in second year of life; topiramate stops seizures. Even more, the neurodevelopmental profile with visuo-constructive and cerebellar impairment is consistent with that of DS [10]. However, the presented phenotype does not fulfill the strict criteria for the core DS - his seizures are not intractable and prolonged, he does not have myoclonic and atypical absences. The presence of pathogenic mutation in the SCN1A gene is not mandatory for the diagnosis neither of the core DS, nor of the borderline or atypical DS (about 30% of the cases do not have the mutation) [7, 8].

DS is classified as epileptic encephalopathy, which implies that clinical and subclinical epileptiform activity is the major factor for cognitive and behavioral impairment [14]. The present case argues this assumption: observed seizures were rare (no more than 5 per year) and short (no more than 3 minutes); no non-convulsive epileptic seizures like absences or complex partial seizures were found; myoclonias were also absent; no epileptic status was documented; no electric status epilepticus was found during the EEG's (although intentionally searched for). The anticonvulsive treatment cannot also be accused for the neurodevelopmental impairment as it was monotherapy in the therapeutic range of a drug that rarely affects postnatal neurodevelopment [15]. Thus the concept of epileptic encephalopathy cannot be attributed to this case unarguably.

The hypothesis of primary effect of chanelopathy on cognition provides an alternative explanation of the presented case. The onset of the neurodevelopmental impairment in the second year with a history of only 3 short preceding GTCS and the following persistence of the impairment despite rarity of seizure suggests its independence from epilepsy. No accusable factors for the impairment were found in the history, clinical, imaging and biochemical examination of the patient. Other authors also support the influence of genetic factors on cognition in DS [16]. Numerous genotype/phenotype associations in a large series were reported [17], but functional studies fail so far to show some consistent relationship between changes to channel properties and neurodevelopmental phenotype.

Since the polymorphism found in the SCN1A mutation in our patient may be benign other causes for the developmental decline distinct form epilepsy and form SCN1A gene may be discussed. Further investigations are needed to clarify the etiological factors including segregation in the family of the SCN1A gene.

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