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Review article

Outlining a core neuropsychological phenotype for Dravet syndrome

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ABSTRACT

An up-to-date review on neuropsychological phenotypes in Dravet syndrome is reported. After recalling the results of various though not numerous studies in the literature, primarily retrospectively, the hypothesis of an original neuropsychological phenotype in Dravet syndrome is presented, consisting of a defect in sensorimotor integration, especially of visuoconstructive abilities. That is particularly evident in the less impaired patients and in the first several years of life. This core phenotype is eventually considered inside the analysis of the etiological multifactorial origin of the cognitive decline, which is especially expressed by the encephalopathy/channelopathy controversy.

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Introduction

Attention devoted to the pathophysiologic mechanisms underlying cognitive and behavior impairment in Dravet syndrome (DS), one of the traditional primary examples of infantile epileptic encephalopathy, has been increasing in the scientific community. DS is an early onset epileptic syndrome that begins in the first year of life with prolonged febrile or afebrile generalized clonic or preferably hemiclonic seizures. Other key epileptic signs are hyperthermia-induced seizures and frequent episodes of status epilepticus. Subsequently, other types of seizures occur, such as atypical absences, myoclonic and focal seizures, and are generally refractory to antiepileptic medication. Reflex seizures and photosensitivity are other possible findings. EEG in the first year of life may be normal. Only with the onset of afebrile seizures do focal or generalized spike and polyspike waves generally appear with a slowing of the background. From the second year of life, a cognitive decline and frequent behavioral disorders, as well as neurological impairment (myoclonias, cerebellar or pyramidal disorders), become evident (Dravet et al., 1992).

A mutation in the voltage-gated sodium channel type I alpha subunit gene (*SCN1A*), generally de novo, is observed in 70% to 80% of DS cases. Hundreds of *SCN1A* mutations have been identified to date, but in *SCN1A* non-mutated patients, other types of mutations may occur (*PCDH19*, *SCN1B*, *SCN2A*) (Catarino et al., 2011). Other mutations in regulatory regions of the gene outside the coding sequences may impair or prevent channel expression

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(Catterall et al., 2010). *SCN1A* mutations have been observed in a spectrum of epileptic syndromes, ranging from benign forms (*GEFS+*) with normal or mildly impaired cognitive development to catastrophic epilepsies (Harkin et al., 2007; Marini et al., 2009). The genetic mutation is expressed with a reduced function of $Na_v1.1$ sodium channels widely scattered in the brain. Impaired GABAergic firing in the hippocampal interneurons lowers the seizure threshold and impaired GABAergic firing in the cerebellar Purkinje cells accounts for neurological (ataxia) abnormalities. Moreover, mutations may play a role in determining neuropsychological disorders (Catterall et al., 2010). Phenotypes of DS patients are extremely varied, including both epileptic and neurological/neuropsychological signs. Neuropsychological phenotypes in particular range from exceptional normal competence (Buoni et al., 2006) or specific partial defects up to severe global involvement of all abilities.

DS was classified among the epileptic encephalopathies by the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) in 2001 (Engel, 2001) and was confirmed in the 2010 revision of the ILAE terminology. It was specified that in epileptic encephalopathies, "the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone and that these can worsen over time." However, "we must recognize that the source of an apparent encephalopathy is usually unknown; it may be the product of the underlying cause, the result of an epileptic process, or a combination of both" (Berg et al., 2010). No case is more paradigmatic of such a problematic condition than DS.

Developmental impairment in DS is progressive

Although the onset of seizures occurs in the first year of life, the interictal EEG generally does not show any abnormality. Cognitive and behavioral impairment apparently begins to appear during the second year of life or later, as shown by reports of different neuropsychological studies on early ages (Wolf et al., 2006; Ragona et al., 2010, 2011; Chieffo et al., 2011a, 2011b; Nabbout et al., 2013). As reported in Table 1, there are only three prospective longitudinal

Table 1
General data of neuropsychological studies.

Authors	Case number	Age range	Study type	Assessment techniques	Longitudinal data	Overall DQ/IQ outcome
Chieffo et al. (2011a)	5	0.6–4 years	Prospective longitudinal	Visual function, Griffiths	***At onset***. normal ***Outcome***: normal 2, borderline 2, MMR 1	
Wolf et al. (2006)	20	0.11–16 years	Retrospective, partially longitudinal	observation, Brunet–Lézine	***In 14 cases (0.11-13 years)*** ***1-3 y*** no**rmal→60** ***4–6 y*** lower ***Over 6 y*** less than 40	***over 6 y*** less than 40
Ragona et al. (2010)	37	0.6–28 years	Retrospective, partially longitudinal	observation, Griffiths, Wechsler	***In 8 cases (0.6–10 years)*** Developmental steep falling curve in the first 4 years	***0.6–6 y*** normal 5, MMR 5, MoMR 3, sevMR 2 ***7–10 y*** MMR 3, MoMR 2, SevMR 1 ***Over10*** MMR 2, MoMR 2, SevMR 12
Ragona et al. (2011)	26	0.4 m–8 yeas	Retrospective, partially longitudinal	Griffiths, Brunet-Lézine	***Study at 1 and five years*** Group 1 (19 cases): steep falling (mean, 39 points) Group 2 (7 cas) mild falling (mean 12 points)	***At first examin. (mean 11 m)***: all but two normal ***Slowing from the second year of life***
Chieffo et al. (2011b)	12	0.9–10 years	Retrospective, partially longitudinal	Griffiths, Wechsler	***Decline from the third year of life*** ***Milder falling from the fourth year***	***At first assessment*** (6–84 m): normal 6, mildly delayed 8 ***At outcome (4-10 y)***: normal 1, borderline 6, MMR 5
Ricci et al. (2015)	5	3–6/8 years	Prospective longitudinal	Visual function, Griffiths, Wechsler, Specific skills	***At first assessment***: MMR 4, MoMR 1 ***At outcome***: MMR 1, MoMR 4	
Nabbout et al. (2013)	67	Last follow up 1.1–23.9 (mean 6.4)	Prospective, partially longitudinal	Brunet–Lézine, Wechsler, observation	First evaluation: at a mean age of 34 months (SD = 22, range 9–91), significantly higher than at second evaluation Second evaluation: at a mean age of 66 months (SD = 43, range 15–175), severe cognitive decline (around or below 40) except 2 cases.	Significant lower DQ or IQ with increasing age, stronger after 3 y
Battaglia et al. (2013)	9	4.6–13	Retrospective	Griffiths, Wechsler		MMR 7 Mo MR 2
Vileneuve et al. (2014)	21	6–10 years	Prospective	Wechsler, VABS		MMR 3 MoMR 12 NT 6
Akiyama et al. (2010)	31	18–43 years	Retrospective	Interview and/or questionnaire		Generally, severe mental retardation.
Genton et al. (2011)	24	20–50 years	Retrospective	No specific quantitative assessment		Moderate to severe mental retardation.
Takayama et al. (2014)	64	19–45 y	Retrospective	"Clinical assessment"		Intellectual disability was found in all patients; especially, severe

MMR: mild mental retardation; MoMR: moderate mental retardation; SevMR: severe mental retardation.