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PCDH19-related epilepsy and Dravet Syndrome: Face-off between two early-onset epilepsies with fever sensitivity

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ABSTRACT

Aim of this study is to compare PCDH19-related epilepsy and Dravet Syndrome (DS) in order to find out differences between these two infantile epilepsies with fever sensitivity.

We retrospectively reviewed the medical records of 15 patients with PCDH19-related epilepsy and 19 with DS. Comparisons were performed with Fisher's exact test or Student's *t*-test.

Females prevailed in PCDH19-related epilepsy. Epilepsy onset was earlier in DS (5.0 + 2.1 *vs* 11.2 + 7.0 months; $p < 0.05$). The second seizure/cluster occurred after a longer latency in PCDH19-related epilepsy rather than in DS (10.1 ± 13.6 *vs* 2.2 ± 2.1 months; $p < 0.05$). Seizures were mainly single and prolonged seizures in DS, and brief and clustered in PCDH19-related epilepsy. Myoclonic and clonic seizures have been found only in DS. Other types of seizures were found in both epilepsies with a prevalence of GTCS and atypical absences in DS, and focal motor and hypomotor seizures in PCDH19-related epilepsy. Seizures with affective symptoms have been confirmed to be typical of PCDH19-related epilepsy. Status Epilepticus equally occurred in both groups. Photosensitivity was detected only in DS. No differences were found about the presence of intellectual disabilities and behavioral disturbances.

We were able to find out some distinctive features, which could address the diagnosis towards DS or PCDH19-related epilepsy, since first manifestation. These considerations suggest to definitively considering *PCDH19* gene as cause of a proper epileptic phenotype.

1. Introduction

Protocadherin19 (PCDH19)-related epilepsy is a recently described epileptic syndrome, with onset in the first three years of life, characterized by clustered and fever induced seizures, often associated with intellectual disability (ID) and autistic traits (Marini et al., 2012). *PCDH19* gene is located on chromosome Xq22, and the condition has an unusual X-linked mode of inheritance affecting only carrier females, therefore a mechanism of "cellular interference" has been hypothesized (Depienne and LeGuern, 2012). Genotype-phenotype correlation is not jet clearly defined. Currently, clinical phenotype ranges from well-controlled epilepsy with normal cognitive development to drug-resistant epilepsy with severe cognitive delay (Depienne et al., 2009, 2011; Dibbens et al., 2008; Higurashi et al., 2012; Marini et al., 2010, 2012; Specchio et al., 2011a,b).

PCDH19 gene mutations were firstly associated with epilepsy in 2008, when seven Australian families with *Female-restricted Epilepsy and Mental Retardation* (EFMR) were reported (Dibbens et al., 2008). Afterword, first sporadic cases were identified within a cohort of patients with Dravet Syndrome (DS) that had been resulted negative for *SCN1A* gene mutation (Depienne et al., 2009). Also DS is a genetic epileptic syndrome, with onset mainly in the first year of life and characterized by the occurrence of mostly fever-

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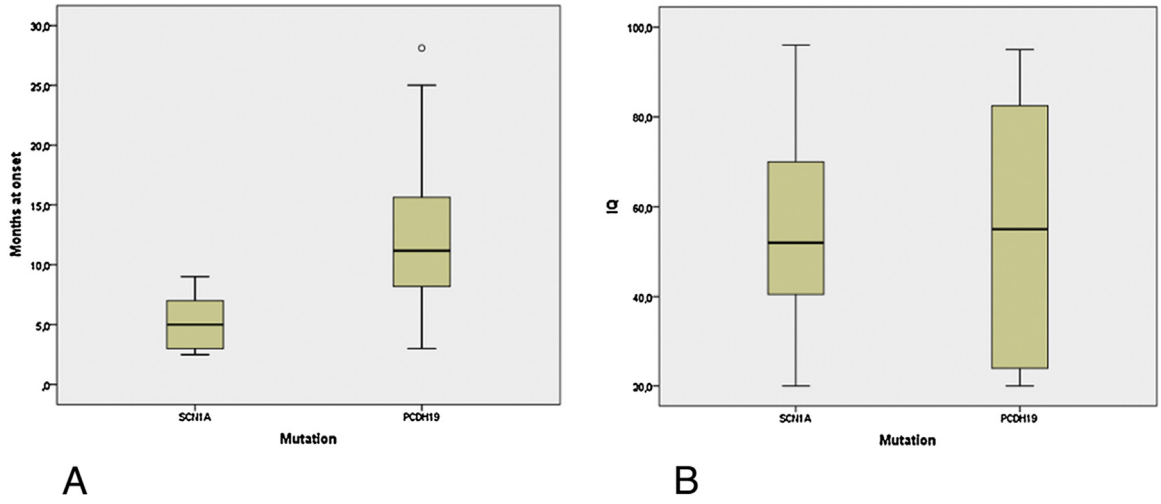

Fig. 1. A. Age at onset by mutation. B. Intelligence Quotient (IQ) by mutation.

induced seizures. *SCN1A* is the major gene for DS, however in about 30% a causative gene has not yet been found (Depienne et al., 2009).

Since 2008, the number of patient with PCDH19-realted epilepsy has progressively grown-up and a more detailed phenotype came out (Depienne et al., 2009, 2011; Dibbens et al., 2008; Higurashi et al., 2012; Jamal et al., 2010; Marini et al., 2010, 2012; Specchio et al., 2011a,b). Nevertheless, PCDH19-related epilepsy has been consistently linked with DS, both because first sporadic cases were identified among patients with a Dravet-like phenotype, and because of the occurrence of fever-induced seizures. Moreover, in some papers *PCDH19* gene has been considered as the second gene of DS (Akiyamaet al., 2012; Gaily et al., 2013; Kwong et al., 2012; Marini et al., 2010).

Aim of this study is to compare PCDH19-related epilepsy and DS in order to find out differences between these two epileptic syndromes that can address the diagnosis toward one or the other at disease presentation. Nevertheless, a clear-cut distinction between PCDH19-related epilepsy and DS, could be relevant also for classification purposes.

2. Material and methods

We retrospectively reviewed the medical records of all consecutive patients with a diagnosis of PCDH19-related Epilepsy or *SCN1A*-positive DS, who have been treated from 1 January 2012 to 30 June 2015 at the Neurology Unit of Bambino Gesù Children's Hospital in Rome, Italy. We identified 15 patients with PCDH19-related epilepsy and 19 patients with *SCN1A*-positive DS. We excluded patients with *SCN1A* gene mutation without a clinical diagnosis of DS (*i.e.* GEFS+ and others) and *SCN1A*-negative DS patients. For both groups of patients, genetic tests ascertaining the *PCDH19* or *SCN1A* gene mutation should have been available.

Informed consent for this study was obtained from patients' parents. We analysed familiar and personal medical antecedents, age at epilepsy onset, fever sensitivity, seizure semiology and frequency, EEG, treatment and neuropsychological outcome. Overall we collected 125 seizures in 30 out of 34 cases. All available ictal EEG have been analysed. Data on cognitive outcome have been collected retrospectively on cognitive assessment routinely performed during period of observation. Epileptic seizures were classified according the ILAE classification and terminology (Berg et al., 2010; Blume et al., 2001). We considered both classifications because they were complementary. Seizure cluster was defined as the incidence of seizures within a given period (usually one or a few days) that exceeds the average incidence over a longer period for the patient (Blume et al., 2001). Prolonged seizures were defined as seizure lasting more than 5 minutes (Shinnar et al., 2001). Status Epilepticus (SE) was defined as a seizure lasting more than 30 minutes (Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus, 1993; Commission on Epidemiology and Prognosis, International League Against Epilepsy, 1993).

2.1. Statistical analysis

Comparisons were performed with Fisher's exact test or Student's *t*-test, as required. The software SPSS was used to store and analyzed the data. A p value < 0.05 was considered statistically significant.

3. Results

Table 1 shows demographic, clinical and electrophysiological features for the two groups of patients, affected by DS or PCDH19-related epilepsy. Age at follow-up was similar in both groups. PCDH19-related epilepsy patients were all female. Epilepsy onset was earlier in patients with DS (5.0 ± 2.1 *vs* 11.2 ± 7.0 months; $p = 0.001$) (Fig. 1A). The first seizure/cluster was fever-induced in both groups with almost the same rate (66.6% in PCDH19-related epilepsy *vs* 78.9% in DS; $p = 0.68$). Differently, the second seizure/cluster occurred after a longer latency in PCDH19-related epilepsy rather than in DS (10.1 ± 13.6 *vs* 2.2 ± 2.1 months; $p = 0.04$). No differences in terms of quantity of fever have been found. Clustered seizures were much more frequent in PCDH19-related epilepsy than in DS ($p < 0.001$) (Fig. 2). Myoclonic and clonic seizures occurred only in patients with DS. Generalized tonic-clonic seizures (GTCS) and atypical absences were more frequent in DS ($p < 0.05$), while focal motor and hypomotor seizures and seizures with affective symptoms mostly occurred in patients with PCDH19-related epilepsy ($p < 0.05$). Patients with DS manifested more frequently prolonged seizures ($p = 0.001$) (Fig. 2), while Status Epilepticus (SE) occurred in both groups with almost the same rate (36.8% *vs* 40.0%; $p = 1.0$). Photosensitivity was detected only in DS ($p = 0.005$). Patients with PCDH19-related epilepsy had a smaller number of AEDs at last follow-up visit (1.9 ± 0.8 *vs* 2.9 ± 0.6; $p < 0.001$). No differences were found about the presence of ID and behavioural disturbances at the last follow-up (Fig. 1B).