A new form of alpha-dystroglycanopathy associated with severe drug-resistant epilepsy and unusual EEG features

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ABSTRACT – We describe two unrelated girls with congenital muscular dystrophy associated with alpha-dystroglycan deficit with no identified genetic defect, both presenting severe drug-resistant epilepsy with predominant myoclonic seizures and an unusual similar EEG pattern. Severe epilepsy has been unusually described in patients with congenital muscular dystrophies, mainly associated with Walker-Warburg, Fukuyama and muscle-eye-brain diseases. [Published with video sequences]

Key words: dystroglycanopathy, epilepsy, myoclonus

The dystroglycanopathies (DG) are a heterogeneous group of early-onset congenital muscular dystrophies (CMDs) characterised by severe hypotonia and frequent brain and eye involvement. Mutations in six known or putative glycosyltransferase genes have been associated with a wide spectrum of phenotypes ranging from the severe Walker-Warburg syndrome (WWS) to milder variants of limb-girdle muscle dystrophy (Brancaccio, 2005; Muntoni et al., 2007). Progressive neurocognitive impairment and drug-resistant epilepsy have been associated with some severe variants of CMDs, also predominantly with structural cortical malformations (Reed, 2009).

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Here, we describe two young patients affected by a new form of CMD with defective glycosylation of alpha-dystroglycan (α-DG) who presented with severe drug-resistant epilepsy with predominant myoclonic seizures and an unusual overlapping EEG pattern.

Case studies

Two unrelated girls from Southern Italy were investigated. Clinical data as well as brain scans were previously published (Messina et al., 2009). To summarize, both patients presented with weak cry, swallowing difficulties, severe hypotonia, and muscle weakness at birth. Patient 1 had microcephaly at birth (occipitofrontal circumference [OFC] 31.3 cm; <third percentile). Severe early-onset psychomotor delay and absent speech were present. Brain MRI showed more pronounced cerebellar hypoplasia in the vermis whilst there were no changes in the cortex or in the white matter. CK was sevenfold the normal value. Although immunohistochemical staining for α-DG was reduced or absent, mutations in known genes associated with hypoglycosylated α-DG were not found by direct sequencing. Patient 1 passed away at 13 years as a result of aspiration pneumonia. Patient 2 is now 10 years old, bedridden, with severe psychomotor impairment, absent speech and hypotonia. Both patients showed microcephaly at the last observation (OFC 50.1 cm in Patient 1 and 49 cm in Patient 2, both <third percentile).

Epilepsy and EEG features

At onset, Patient 1 had focal motor seizures at 10 months and Patient 2 presented recurrent episodes of unresponsiveness, fixed gaze and hypotonia at 22 months. At that time, seizures occurred on a monthly basis. The first EEG recordings showed slow background activity and multifocal, bilateral, asynchronous, paroxysmal discharges in both patients (figure 1A, B). Multiple daily myoclonic, focal motor, generalised tonic-clonic (GTCS) and atonic seizures occurred in both patients after two years of age. The most frequent seizure type, similar in the two girls, was video recorded for Patient 2 at two years. The girl presented right chin and eyelid myoclonic jerks, clonic jerks of the right arm and hand and subsequent diffusion to the right leg and foot (see video sequence). They were mainly clustered in series of five or six or more, in some cases configuring an epileptic status. The ictal recording was characterised by a rapid, medium-voltage, spiky, alpha-like activity with higher voltage in centro-temporal regions bilaterally (right-left). It then spread posteriorly, becoming

![Figure 1. Overlapping EEG patterns in Patients 1 and 2. At 1.5-2 years of age there was slow background activity and focal interictal discharges (A, B). At 2.5-3 years, both patients showed an ictal pattern of rapid, medium-voltage, spiky, alpha-like activity on bilateral central regions (right-left), followed by flattening (C, D). The last recording, respectively at 12 and 7 years, showed interictal bilateral periodic lateralised epileptiform discharges (BILPDEs) (E, F).](image-url)
diffuse, followed by diffuse slow waves or flattening (figure 1C, D; see video sequence). At two years, interictal EEG was mainly characterised by multifocal, bilateral, asynchronous, paroxysmal discharges. Erratic myoclonic jerks were unrelated to EEG paroxysmal activity. The final recording was obtained at 12 years in Patient 1 and at 10 years in Patient 2. They both showed bilateral periodic lateralized epileptiform discharges (BIPLEDs), mostly asynchronous, with interposed ictal activity characterised by a rapid, spiky, alpha-like pattern (figure 1E, F). In summary, the two girls presented early-onset, severe, drug-resistant epilepsy before two years of age with predominant myoclonic seizures. The EEG showed progressive disorganisation of background activity and ictal alpha-like pattern, similar in both patients.

**Discussion**

We describe a very rare epileptic clinical and EEG phenotype in two children with a new form of CMD associated with an α-DG defect. Electroclinical features and outcome were very similar according to age between the two patients, and to date have so far not been reported. Patients with partial or generalised seizures have been reported for several types of muscular dystrophies including CMDs (Tsao and Mendell, 2006; Hehr et al., 2007; Yoshioka et al., 2008). The most severe epileptic phenotypes have been described for Walker-Warburg. Fukuyama and muscle-eye-brain diseases in which severe drug-resistant epilepsy was associated with brain migration defects and lissencephaly type II (Reed, 2009; Pini et al., 1996). Patients without cortical malformations usually have epileptic seizures that are well controlled by antiepileptic treatment (Pini et al., 2006). Our patients did not present clinical or molecular features suggesting these disorders. Moreover, serial MRI scans performed at different ages ruled out cortical malformations or white matter abnormalities and showed unchanged features suggesting a non-progressive brain involvement. The role of cerebellar hypoplasia in epileptogenesis could not be excluded in our patients. Although recent reports showed abnormal neurodevelopmental changes involving cerebellum in children affected with epilepsy, its specific role in epileptogenesis remains unclear (Tosun et al., 2011). In particular, the role of cerebellar hypoplasia itself in refractory epilepsy was not supported by antecedent cases of CMD. Similar speculations can be made about the genesis of myoclonus in our cases. Although myoclonus associated with cerebellar pathology may be due to abnormal output from the cerebellar nuclei, the role of cerebellum as myoclonus generator is still controversial (Mink et al., 2003). Therefore, a clear explanation for the severe electroclinical picture was difficult to determine and a correlation between epilepsy and neurocognitive worsening with MRI features was not plausible in our patients. In fact, although cognitive skills markedly worsened after the onset of seizures and a role of drug-resistant epilepsy itself on neurocognitive skills may be hypothesized, the very early onset of psychomotor delay made it difficult to understand to what extent epilepsy influenced neurodevelopmental outcome in our two patients. In conclusion, this, rare, new form of CMD with α-DG defect was associated with severe drug-resistant epilepsy in our two patients. The patients showed overlapping seizure features and an unusual EEG pattern. Additional reports with a similar electroclinical outcome as well extensive genetic investigations may help to delineate this novel form of CMD. □

**Disclosure.**

None of the authors has any conflict of interest or financial support to disclose.

**Legend for video sequence**

Ictal video EEG (with low volume). Seizures were characterised by right chin and eyelid myoclonic jerks, clonic jerks of the right arm and hand and subsequent diffusion to the right leg and foot. The EEG preceding the seizures showed slow background activity with subcontinuous spike-wave complexes on bilateral central regions (right>left). At the onset of the seizures, a rapid, medium-voltage, spiky, alpha-like activity with higher voltage on bilateral centro-temporal regions (right>light), spreading posteriorly to become diffuse and followed by diffuse slow-waves or flattening, was evident. The interictal activity resumed as the seizure ended.

**Key words for video research**

on www.epilepticdisorders.com

Etiology: congenital muscular dystrophy

Phenomenology: myoclonic seizure, focal seizure not otherwise specified, tonic-clonic seizure

Localization: —

Syndrome: epileptic encephalopathy not otherwise classified

**References**

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