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Epilepsy in Menkes disease: An electroclinical long-term study of 28 patients

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KEYWORDS
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Summary
Background: Epilepsy is a frequent and severe feature of Menkes disease (MD) but only few studies described the long-term evolution of these children. We report a series of 28 epileptic MD

Abbreviations: MD, Menkes disease; MRI, magnetic resonance images; angio-RM, angio-magnetic resonance; TC, computed tomography; FS, focal seizure; IS, infantile spasms; AEDs, antiepileptic drugs; SE, status epilepticus; GTC, generalized tonic clonic seizures; MS, myoclonic jerks.

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Status epilepticus;
EEG

patients, with clinical characteristics, EEG abnormalities, brain malformations and long-term outcome.
Methods: EEG, clinical characteristics and neuroimaging features in 28 MD patients were analyzed at the onset of epilepsy and after long-term follow-up (at least 4 years). We subdivided the patients into two groups: Group 1, 16 patients who received a subcutaneous copper—histidine treatment, and Group 2 including 12 patients who did not get any therapies.
Results: The large majority of our patients presented at the onset of epilepsy focal seizures (FS) and infantile spasms (IS). Five patients had recurrent status epilepticus (SE). During the follow-up, patients showed multiple seizure types: 6 patients had generalized tonic clonic seizures (GCT), 6 patients presented IS, 10 children had FS, 11 had myoclonic jerks and 3 had SE. Therapy with various antiepileptic drugs had poor efficacy, except in three patients who showed seizure disappearance with consequent discontinuation of antiepileptic therapy. There was no difference of neurological outcome among the two groups analyzed.
Conclusions: Epilepsy in MD is a difficult to treat problem. At the onset, the most frequent type of seizures are FC and IS; in the next months, other kinds of seizures can appear. Many children are drug resistant. Institution of replacement therapy with copper—histidine seems to be not beneficial for epilepsy.

Introduction

Menkes disease (MD), first described in 1962 by Menkes et al., is an X-linked recessive neurodegenerative disorder of copper metabolism (Desai et al., 2011; Menkes et al., 1962; Horn and Morton, 1986; Sirleto et al., 2009; Tümer and Møller, 2010), caused by mutations in a copper-transporting P-type adenosine triphosphatase (ATPase), type A (ATP7A) which plays a critical role in the development of the central nervous system. Absence or severe reduction in ATP7A activity compromises the intestinal uptake of copper and its consecutive transport into the developing brain (Kaler, 2013; Schlief et al., 2006; Schlief and Gitlin, 2006), and results in a significant reduction of normal copper levels in the blood, liver, and brain (Danks et al., 1973).

Patients with classic MD (90—95% of patients) usually exhibit a severe neurodegenerative course, with death before the third year of life. From about 2—3 months of age, most patients develop seizures (Horn et al., 1992; Tümer and Møller, 2010). Epilepsy is a frequent feature with different clinical presentations: myoclonic jerks (MS), generalized (tonic—clonic) seizures (GTC) and infantile spasms (IS) have been reported, but the natural history of epilepsy and its EEG abnormalities have not been clearly defined. Some patients, in fact, showed IS or multifocal clonic seizures without any previous history of clonic focal seizures (FS) (Bindu et al., 2007; Sfaello et al., 2000), while other children can present status epilepticus (SE) as first manifestation (Bahi-Buisson et al., 2006). Although few authors (Fister et al., 2006; Gemme et al., 1993; Ozawa et al., 2001) underline that the course of disease is marked by uncontrolled seizures, the evolution of epileptic manifestations and their EEG abnormalities and an eventual improvement of replacement copper—hystidine therapy remain unclear.

Our objectives were to analyze epileptic features, EEG patterns, response to antiepileptic therapy and long-term evaluation in patients with MD.

Methods and subjects

This multicenter study was carried out at 10 Pediatric Neurologic Departments in Italy. We included children affected by MD diagnosed in these departments over a 21-year period (1988—2009) and with a follow-up of at least 4 years. The initial diagnosis of MD was suggested by clinical features and was supported by laboratory tests which demonstrated reduced levels of serum copper and ceruloplasmin, and an increase of ratio DOPA/dihydroxyphenylglycol indicative of dopamine b-hydroxylase deficiency (Kaler et al., 2008). Light microscopy of hair showed individual hairs that were twisted about their own axes (pili torti), fragmented at regular intervals (trichorrhexis nodosa) with varying shaft diameters (monilethrix). A definitive biochemical test for MD was based on intracellular accumulation of copper due to impaired efflux which could be evaluated in cultured fibroblasts. In addition, as previously suggested (Tümer and Møller, 2010), the demonstration of the molecular defect in ATP7A has been carried out in 16 patients: in particular, five children had large deletions, three children had small deletions, three children had missense mutations and two nonsense mutations and three splice-site mutations. A total of 30 patients, all males, were identified based on above criteria; two of them were excluded from the study, the first because did not show seizures, the second one because was lost at follow-up. The following data were recorded: age, gender, family history of epilepsy, epileptic manifestations, age at onset of epilepsy, EEG abnormalities, angio-RM and brain magnetic resonance images (RMI), computed tomography (TC) and response to replacement therapy with copper—histidine. Description of clinical characteristics and seizures was based on the neuropediatric evaluations. The classification of seizures was based on the clinical and EEG findings according to the criteria of the International League Against Epilepsy (Blume et al., 2001). EEG was performed in accordance with the International 10—20 system and all recordings were visually interpreted by a blind EEG-certified neurologist. We analyzed EEG