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Electro-clinical features and magnetic resonance imaging correlates in Menkes disease

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Abstract

Background: Epilepsy is an early and important feature in Menkes disease (MD), an X-linked recessive neurodegenerative disorder of childhood with defect in copper metabolism. There are only few reports on the electro-clinical and magnetic resonance imaging correlates in Menkes disease. The current study describes the electro-clinical features in MD in relation with the structural findings on MRI. *Patients and Methods:* Six patients from five families were evaluated between 2005 and 2011. Their diagnosis was based on the characteristic morphological features, microscopic evidence of pili torti and low copper and ceruloplasmin levels. All the patients underwent MRI and EEG as part of the evaluation. *Results:* All patients had classical form of MD with typical morphological features. All but one patient had refractory seizures. Seizure types included multifocal clonic seizures ($n = 3$), myoclonic jerks ($n = 4$) and tonic spasms ($n = 1$). EEG was markedly abnormal in all except in the patient without clinical seizures. While focal epileptiform discharges predominated before six months of age modified hypsarrhythmia was characteristically noted thereafter. MR Imaging revealed abnormalities in all patients, with cerebral atrophy and delayed myelination being the most common observations. Other features noted were subdural effusion ($n = 3$), leukoencephalopathy ($n = 3$) and basal ganglia signal changes ($n = 1$). Follow up imaging in three patients showed resolution of white matter signal intensity changes. *Conclusions:* Electro-clinical features in Menkes disease are age dependent and evolve sequentially. White matter changes coincided with acute exacerbation of seizures. There was fair correlation between the electro-clinical features and structural findings on MRI.

Keywords: Menkes disease; Epilepsy; Leukoencephalopathy; Copper transport deficiency; Myoclonic seizures; Hypsarrhythmia

1. Introduction

Menkes disease (OMIM #309400), first described in 1962 by Menkes et al., is an X-linked recessive disorder with primary defect in the copper metabolism, characterised by infantile neurodegeneration, seizures, failure to thrive and connective tissue abnormalities [1–3]. It is caused by loss of function mutations in the gene

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encoding ATP7a [4–6]. The copper-transporting ATPase, ATP7a has a role in neuronal activation, axonal targeting and synapse development and its functional deficiency contributes to the neuropathology of Menkes disease [7–9]. In addition, the impaired activity of the specific cuproenzymes namely tyrosinase, lysyl oxidase, dopamine beta hydroxylase, peptidyl glycine, alpha-amidating monooxygenase, cytochrome c oxidase and superoxide dismutase contribute to the pleiotropic clinical features seen in this disease [10].

Epilepsy is one of the well recognised features of Menkes disease and most patients develop therapy resistant seizures from about 2 to 3 months of age [3,11]. There are only few reports on the characteristics of epilepsy and electrophysiological features in Menkes disease [12–14]. Attempts have been made to correlate the presence of epilepsy with molecular diagnosis, prenatal diagnosis and copper histidine therapy [15]. There are a limited number of reports which correlate the electro-clinical and magnetic resonance imaging features in Menkes disease [16–18]. The current study reports the electro-clinical features in six patients with Menkes disease in relation with structural findings on magnetic resonance imaging.

2. Patients and methods

Six patients (age range: 5–17 months) all born of non consanguineous parentage, from five families were evaluated between May 2005 and May 2011. Their diagnosis was based on the typical morphological features, microscopic evidence of pili torti and low levels of serum copper and ceruloplasmin. Electroencephalographic and magnetic resonance imaging findings in one of the patient has already been reported [19].

Magnetic resonance imaging was done after obtaining informed consent on Achieva 3T MR imaging scanner (Philips medical systems, Netherlands) with an eight channel head coil (five patients) and on Siemens-Magnetom vision 1.5 Tesla MRI scanner (one patient), using standard protocols. MRI sequences included T1W (with and without contrast in axial and sagittal planes), T2W (axial and coronal planes), Fluid attenuated inversion recovery (FLAIR) sequences in axial plane in all, MR angiogram in five and DWI in one.

Scalp EEGs were recorded in all patients on 16 channel "Galileo NT(EB Neuro)" machine, employing international 10–20 system of electrode placement using standard parameters and procedures e.g. high filter – 70 Hz; low filter – 0.1 Hz; recording time: 30 min; sensitivity7 μV/mm; sweep speed: 10 s/page; sampling rate: 256 Hz. A total of ten EEGs were available for review.

All six patients underwent routine biochemical and haematological investigations and a metabolic panel consisting of urine screening for abnormal metabolites, tandem mass spectroscopy for acyl carnitine profile, serum ammonia and lactate and limited lysosomal enzyme profile (serum Aryl sulfatase A and B, Hexosamindase Total, A and B) which yielded normal or negative results. Mutational analysis was not done in any of the patients. The study was conducted as per the ethical committee guidelines of National Institute of Mental Health & Neurosciences, Bangalore, India.

3. Results

3.1. Phenotypic features

The phenotypic features of these patients are summarised in Table 1. In summary all patients had typical phenotypic features of Menkes disease viz. scarce hypo pigmented, stubby and friable hair with pudgy cheeks and occipital and frontal prominences and hypopigmented skin. (Fig. 1) Other features noted were skin rashes (5), seborrhoea of scalp (1), inguinal hernia (1) recurrent infections (5), and pectus excavatum (1). The most common neurological presentations were developmental delay (6), seizures (5) and neuro regression (2). Neurological examination showed generalised hypotonia with preserved stretch reflexes and extensor plantar in all.

Two of them were twins. In the same family there was history of early infantile death with the same phenotype. Referral diagnoses were strikingly other than Menkes syndrome in five patients; cerebral palsy, developmental delay with seizures, viral encephalitis and Tyrosinemia.

Seizure semiology and age of onset are summarised in Table 2. The type of seizures included multifocal clonic seizures ($n = 3$), Myoclonic seizures ($n = 4$), tonic seizures ($n = 1$). One patient did not have seizures. Multifocal clonic status was noted in patients who presented before six months (Patient 5 and 6). The seizures were resistant to treatment with multiple anticonvulsants in optimal dosages which included varying combinations of sodium valproate, clonazepam, levetiracetam and clobazam. None of the patients received lacosamide or rufinamide or ketogenetic diet.

3.2. EEG observations

The EEG findings are summarised in Table 2. EEGs were markedly abnormal in five patients. In the twins who presented with multifocal clonic status, focal spike and wave discharges predominantly from posterior leads evolving into continuous rhythmic discharges suggesting an ictal pattern was noted (Patient 5 and 6, Figs. 2E and 3C). Follow up EEGs at one year of age showed modified hypsarrhythmia pattern in one and focal spike wave discharges from occipital leads in the other (Figs. 2F and 3D). Modified hypsarrhythmia was present in the rest of the three patients. (Fig. 4C)