The Electroencephalogram (EEG): a valuable investigation to aid in the diagnosis of Inborn Errors of Metabolism (IEM)

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Introduction

A number of IEM’s present with abnormal neurology or seizure activity during the acute illness with associated accumulation of neurotoxic metabolites. Examples include Molybdenum Co-factor deficiency (MoCD) and Maple Syrup Urine Disease (MSUD). Alongside biochemical investigations, EEGs are often performed, however there is only a limited description of diagnostic patterns seen in these conditions.

Methods

We carried out a retrospective search of the EEG database and Metabolic database from 2002 to 2020 at GOSH (UK) and Ferrara (IT). Patients with a confirmed diagnosis of MoCD and MSUD with at least 1 EEG were analysed alongside biochemical data.

Conclusion

The comb-like pattern seen in MSUD is distinct to the neonatal period, and may be the first diagnostic finding at initial presentation. In addition we can see a correlation with the presence of this pattern with higher leucine levels in the blood. There is a clear evolution of this pattern seen with gradual improvements in leucine levels, and subsequent resolution beyond the neonatal period.

Identification of the unique delta crown pattern and high seizure burden in MoCD patients separates these EEGs from previously non specific findings of burst suppression and multiple epileptiform charges.

Our findings indicate that the EEG is a valuable biomarker to aid in the diagnosis of MoCD and MSUD. The EEG may also be a valuable biomarker in the diagnosis of rare disorders, which may otherwise evade diagnosis, and thereby helping to improve the outcome of these diseases. We are expanding the search to include more IEM’s to determine the diagnostic role of the EEG.
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Maple Syrup Urine Disease (MSUD)

MSUD is an autosomal recessive inherited disorder of branched chain amino acid (BCAA) metabolism. It results from defective activity of the branched chain ketoacid dehydrogenase enzyme complex, causing elevated quantities of leucine, isoleucine and valine, and their corresponding ketoacids (Figure 1). The accumulation of the BCAA’s and their ketoacids results in a rapid progressive neurological deterioration within the first week of life. Typical symptoms include irritability, poor feeding and vomiting; stereotypical movements such as ‘fencing’ and ‘bicycling’, as well as seizures occur. These symptoms proceed to apnoea, coma and death by 2 weeks of life. Emergency treatment requires prompt reduction of leucine and other BCAA, followed by the introduction of BCAA restricted feeds.

Diagnosis is made through the measurement if BCAA on blood spot cards through tandem mass spectrometry, and since the introduction of day 5 new-born screening (NBS) for MSUD in the UK in 2008, earlier diagnosis is now possible. However, patients often present unwell before the availability of results from NBS. Therefore alternative diagnostic clues are helpful in guiding investigation, and earlier therapeutic intervention. A unique comb like pattern on the EEG has been identified in patients with MSUD (Neurodiagn J. 2021 Sep;61(3):123-131) however it remains poorly defined with regards to frequency, specificity, temporal evolution and relationship to biochemical markers.

Results

- EEG background activity was abnormal in all with a variable degree of dysmaturity. Electrographic seizures were recorded in only 2 patients, with an otherwise low seizure burden in our cohort.
- Comb-like pattern (figure 2) were found in 11 patients (76% EEGs in the neonatal period, 67% of all EEGs). A unique evolution was evident with initial confinement to the midline, followed by better definition and spread to the central regions. Subsequent resolution is noted with no comb like pattern seen outside the neonatal period. After their disappearance, transients and later a rhythmic delta-theta activity could be seen in the same regions.
- Neonates with a comb-like pattern on their EEG had significantly higher leucine levels than those who did not (p=0.002, figure 3)

Methods

We carried out a retrospective search of the EEG database and Metabolic database from 2002 to 2020 at GOSH (UK) and Ferrara (IT). Patients with a confirmed diagnosis of MSUD with at least 1 EEG were analysed alongside biochemical data. 24 EEGs were analysed from a cohort of 12 patients (5 females) aged 6-83 days of life.

Figure 1: Biochemical pathway in MSUD

Figure 2 – EEG demonstrating comb like pattern in MSUD patient on day 15 of life with leucine level of 350umol/L, clinically encephalopathic

Figure 3 – scatter plot demonstrating the presence and absence of comb like pattern in correlation with serum leucine levels. In general higher leucine levels corresponded with the presence of comb like pattern.
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Molybdenum Co-Factor Deficiency (MoCD)

Molybdenum Co-factor (MoCo) is essential for the functioning of 3 dependent enzymes; xanthine oxidase, sulfite oxidase and aldehyde oxidase. The biosynthesis of MoCo occurs in 4 genetically determined steps (Figure 1). Mutations anywhere in this pathway will lead to MoCD and therefore loss of activity of the 3 dependent enzymes. Of the three enzymes affected, loss of sulfite oxidase activity is particularly related to the underlying disease as it results in the accumulation of neurotoxic metabolites sulfite and s-sulfocysteine.

MoCD is characterised by neonatal onset encephalopathy and intractable seizures leading to early neonatal death. In some cases there is also evidence of antenatal disease onset. Despite novel anticonvulsants, the response to treatment and prognosis remain poor due to progressive neurodegeneration. At present there is a single effective treatment only for those with type A caused by the MOC51 mutation.

Key diagnostic markers include elevated urine sulfocysteine and urine (hypo)xanthine, and low serum urate. Neuroimaging findings can be similar to those seen in hypoxic ischaemic encephalopathy due to widespread cortical and subcortical atrophy. EEG background abnormalities in neonates with MoCD are typically characterized by burst-suppression pattern or encephalopathy with multifocal epileptiform discharges but to date no specific EEG findings have been described.

Methods

We carried out a retrospective search of the EEG database and Metabolic database from 2002 to 2020 at GOSH (UK) and Ferrara (IT). Patients with a confirmed diagnosis of MoCD with at least 1 EEG were analysed alongside biochemical data.

Eleven infants with MoCD (6 males) aged 1-120 days were included (7 within 28 days of life).

Results

In the neonatal period the background activity was abnormal in all with burst-suppression (n=4), excess discontinuity (n=3) and/or multifocal discharges over the parasagittal regions (n=6).

Seizures were recorded in all neonates (n=7) at 1-18 days which were electrographic-only in 6 and electro-clinical in 1. All had a high seizure burden and were resistant to treatment.

Ictal EEG pattern consisted predominantly of rhythmic delta frequencies with recruitment, arising independently from the central regions. Infants outside the neonatal period had lower seizure burden.

A unique Delta-crown pattern (high amplitude delta transients with ripples of superimposed fast activity) was observed in 7 (64%) patients between 3 and 74 days of life. Delta-crowns were seen over the central regions and frequency increased at times of seizures.

No biochemical correlations were identified.