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NEONATAL REFRACTORY SEIZURES – AN UNUSAL APPROACH TO MANAGEMENT

Jasmine Taylor (ST6, Paediatric Registrar), Deivasumathy Muthugovindan (Neurology Consultant)

Department of Paediatric Critical Care, Department of Paediatric Neurology, Royal Manchester Children's Hospital

BACKGROUND

We present a 5-month-old boy with refractory seizures secondary to alterations in the GRIN2D gene. This is the first case in the UK amongst a handful of cases worldwide. This gene mutation is linked to significant epilepsy and developmental delay. GRIN2D genetic variants are also linked to issues with feeding as seen in our case.

With no other licensed alternative to treatment, an interim solution of ketamine infusion was commenced whilst awaiting memantine approval.

Memantine was used as a trial novel agent to treat refractory seizures in genetic epilepsy. It is a glutamate receptor antagonist[1] commonly used for dementia and not licensed in neonatal seizures.

Other than occasional breakthrough seizures requiring acute treatment, memantine appears to have controlled this genetic form of epilepsy seen in our patient.

CONCLUSIONS

Since the commencement of memantine, the seizures have been well controlled however there has been some breakthrough seizures requiring rescue medications and some further hospital admissions.

Rapid exome sequencing is increasingly used in clinical practice to obtain a diagnosis[3]. A genetic diagnosis can inform prognosis and disease management and ultimately lead to an improvement of the individuals care and treatment.

Genetic counselling has been provided for the family and discussions around family planning has clarified that with a de novo mutation the chance of future children with the same genetic mutation is very small.

CASE SUMMARY

Baby boy conceived via IVF and delivered via emergency Caesarean section due to a pathological cardiotocography. No resuscitation was required at birth, however generalised hypertonia necessitated admission to the neonatal unit shortly after birth. Cord gases were normal and there were no concerns for hypoxic ischemic encephalopathy.

For the first 72 hours, clinical seizures associated with abnormal CFAM changes were treated with phenobarbital. The CFAM changes and generalised hypertonia persisted but the clinical seizures abated. He was ventilated for 4 days during his NICU admission. Microbiological samples were negative allowing cessation of anti-infective agents. Following clinical improvement, he was discharged home on day ten of life.

He re-presented with failure to thrive, severe reflux and irritability. Further seizures required anaesthesia and ventilation followed by two bradycardic arrests. MRI showed delay in myelination within the posterior limb of the internal capsule and possible white matter hyperintense signals. EEG remained abnormal. Rapid exome sequencing for R59[2] and a hyperekplexia panel revealed a de novo alteration in the GRIN2D gene.

During his first admission to PICU (19 days), he was having frequent seizures often requiring 4th line anti-epileptic drugs and was also commenced on a ketogenic diet. He had significant hypertonia whilst intubated and ventilated and required a midazolam infusion (360mcg/kg/hr) for dystonia with frequent rescue boluses. Subsequently, he spent a significant time on HDU before his second admission to PICU. During this admission (36 days), memantine for seizure control was considered as he was resistant to multiple anti-epileptic drugs (levetiracetam, lacosamide, gabapentin, clonazepam) and ketogenic diet.

Ketamine infusion was an interim measure until consensus between neurology, intensive care, pharmacy and the medical director was reached to commence memantine. Dosing started at 0.2mg/kg/day orally.

He is currently on 4.5mg/kg/day of memantine OD orally, gabapentin 30mg TDS, levetiracetam 130mg BD, clonazepam 500mcg BD and has been successfully discharged home. He is now 9 months old, self ventilating in air with a feeding gastrostomy and continues on a ketogenic diet.

REFERENCES

1. British National Formulary, 2022
2. https://bwc.nhs.uk/download.cfm?doc=docm93jijm4n4506.pdf&ver=6680
3. Genetic Alliance UK (https://geneticalliance.org.uk)