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FOUR CASE STUDIES OF NEURONAL MIGRATION DISORDERS: A CASE REPORT

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ABSTRACT Neuronal migration disorders (NMDs) are developmental abnormalities of cerebral hemispheres that cause malpositioning and improper differentiation of cortical grey matter. NMDs are frequently associated with microcephaly and refractory epilepsy. Here we are presenting a series of four cases of NMDs, discussing the history, clinical presentation, imaging and electroencephalogram (EEG) findings.

KEYWORDS : neuronal migration disorders, microcephaly, epilepsy, elecetroencephalogram

INTRODUCTION

Neuronal migration is a process required for the development of the mammalian nervous system. In humans establishing the various laminae of the cortex requires a highly coordinated and regulated set of neuronal migratory events. When these pathways are disrupted, malformations of cortical development (MCDs) or NMDs can occur, resulting in a variety of physiological and functional effects. NMDs are a documented cause of developmental delay, intellectual disability, and refractory epilepsy, as well as related with dysmorphic characteristics[1,2,3].

NMDs were classified according on the stage or process of cortical development that was disrupted[4,5].

The most common NMDs are lissencephaly, heterotopia, polymicrogyria and schizencephaly. Here we are discussing four cases of NMDs.

CASE STUDY

Case 1: Schizencephaly with global developmental delay (GDD)

A 14-month-old male child from a non-consanguineous marriage, fourth in birth order, presented with complaints of not achieving milestones since 6 months of age. Initially normal until the age of six months, followed by three occurrences of atypical febrile seizures at six, eight, and thirteen months of age. Generalized tonic-clonic seizures, with 2-3 episodes each day, each lasting 3-5 minutes and followed by postictal drowsiness. Birth history is uneventful. Developmental age: 6 months (overall developmental quotient: DQ 40%). The mother developed malaria fever in the sixth month of her pregnancy. The oldest sibling, who was three years old, had a history of febrile seizures, and his paternal grandfather suffered from epilepsy. On examination, the vital signs were 98.6 degrees Fahrenheit, 101 beats per minute, 27 breaths per minute, and 99% saturation in room air. The The child's weight was 10kg (50th centile), length was 73 cm (3rd to 50th centile), and head circumference (HC) was 43 cm (<3rd centile). There are no facial dysmorphisms or neurocutaneous markers. There are no localized neurological impairments, deep tendon reflexes were intact, and both plantars have an extensor response. Other systemic examinations were normal. The MRI brain revealed closed lip schizencephaly with grey matter-lined CSF clefts in both parietal lobes and corpus callosum thinning. EEG- abnormal, background activity consisting of posterior dominating alpha activity with a frequency of 8-9 HZ, which was accompanied by symmetrical and asynchronous bitemporal spike and wave discharges.

Case 2: Lissencephaly with microcephaly with GDD with refractory epilepsy

A 22-month-old male infant born from a third-degree consanguineous marriage, first in birth order, with refractory seizures and global developmental delay, who had a history of increased seizure frequency for 5 days. Multiple instances of eye blinking, mouth twitching, and limb stiffness lasted 30 seconds each, 20 such occurrences every day. Anomaly scan revealed microcephaly. The baby was delivered via emergency cesarean section and did not cry immediately after birth. On the third day of life, the child experienced his first seizure and was prescribed antiepileptic medications. Even with medication, the baby continued to experience seizures 1-2 times a week; the first EEG suggested epileptic encephalopathy. History of febrile seizures in the first cousin present.DQ was 6%. Vital signs: 98.4 degrees Celsius, 110 beats per minute, 26 breaths per minute, and 98% saturation. The child weighs 10kgs (third to 50th centile), measures 84.5cms in length (3rd to 50th centile), and has a HC of 38cms (less than the first centile: microcephaly). On inspection, the boy had small head, a receding forehead with a triangular shaped skull, nystagmus, micrognathia, a high arched palate, and scissoring of the lower limb. On motor system assessment, power in four limbs was 2/5, with hypertonia and exagarated deep tendon reflexes(DTRs), accompanied with clonus. Both plantars exhibit extensor reaction.Other system examinations were normal. The MRI brain revealed lissencephaly, colpocephaly, partial corpus callosum agenesis, and tiny CSF signal intensity regions in bilateral deep periventricular white matter.

Case 3: Lissencephaly with band heterotopia with normal development

2 year 1 month old female child, a product of a non-consanguineous marriage, second in birth order, with a history of seizures for the past three months. Seizures were described as blinking of eyes and bending of head lasting <1 minute, with 4-5 events each day. There were no family h/o seizures. The birth history was uneventful. Milestones appropriate for the age. On examination, the infant is alert; there are no visible signs of dysmorphism; vitals: temperature 98.3 degrees, pulse rate 99/min, respiration rate 24/min. The child's weight was 12.5 kg (50th-97th centile), height was 86cm (50th centile), and HC was 44cm (<3rd centile). The central nervous system and systems examination entirely normal. The MRI brain revealed Lissencephaly type 1 with a pachygyria complex and band heterotopia in both cerebral hemispheres.

Case 4:Probabale MPPH (Megalencephaly- Polymicrogyria-Polydactyly-Hydrocephalus) syndrome.

A 14-month-old male child born from a non-consanguineous marriage with symptoms of increased head size and difficulty upholding the neck, which the mother noted at 5 months of age. Birth details were uneventful. No h/o seizures. DQ was 30%. Upon examination, there was macrocephaly (HC was

51cms, > 97th centile) with a widely open anterior fontanelle polydactyly and bilateral undescended testis. On pull to sit, there was head lag, vertical suspension-scissoring, axial hypotonia, and appendicular spasticity. Deep tendon reflexes were exaggerated, and both plantars were extensors. The MRI scan revealed a thickened cortex with a smooth grey matter interface, multiple and shallow sulcal spaces, and white matter thinning mostly in the b/l frontal, perisyvian, and temporal lobes, indicating cortical dysplasia with polymicrogyria complex. Ventriculomegaly was also observed.

DISCUSSION

The majority of NMDs are caused by underlying genetic abnormalities that disrupt the encoded proteins and associated molecular processes involved in early and/or late cerebral cortex development[4]. Various genes involved are *LIS1* (lissencephaly 1)[6], *DCX (doublecortin)*[7], *TUBA1A (tubulin alpha 1a)*[8], *and a few others*. Environmental insults such as infection or ischemia in utero at various phases of brain development, as well as during the perinatal or postnatal period, may contribute to NMDs[9,10]. The timing of the damage during corticogenesis appears to influence the severity of cortical malformation[11].Over the last decade, researchers have found many molecules involved in controlling neuronal migration and directing neurons to their particular destination.

Molecules can be classified into four categories: cytoskeleton, signaling, glycosylation, neurotransmitters, trophic factors, peroxisomal metabolism, and environmental factors (e.g. ethanol, cocaine)[12]. They frequently present with eating problems, global developmental delay, seizures, unusually small or large heads, and other congenital defects[1]. In this case series, out of 4 children, two had lissencephaly, one had schizencephaly, and another child had polymicrogyria with ventriculomegaly. Two children were presented with GDD, refractory epilepsy, and lower head centiles/microcephaly. One child with lissencephaly with band heterotopia had refractory seizures but was developmentally normal. One child with polymicrogyria had GDD with macrocephaly.

CONCLUSIONS

Children less than 2 years of age presenting with refractory epilepsy associated with developmental delay, lower head centiles, and no significant history of perinatal asphyxia suspect NMDs. Evaluation with MRI brain and genetic testing is important.

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