Short Communication

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Neuronal Migration Disorders in Children; A Case Series highlighting importance of Neuroimaging in diagnosing Epilepsy

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Abstract

Introduction: Neuronal migration disorders comprise a heterogeneous group of neurological conditions caused by abnormal neuronal positioning during brain development. We aimed to study the clinical profile, neuroimaging features, genetics, and treatment of neuronal migration disorders.

Materials & Methods: This was a retrospective case series of 15 pediatric patients diagnosed with neuronal migration disorders at a tertiary care hospital over a 5 year period. Detailed clinical evaluation, neuroimaging, EEG, and genetic analysis were performed.

Results: Global developmental delay and epilepsy were the most common presenting features. Neuroimaging revealed spectrum of cortical dysgenesis including pachygyria, polymicrogyria, lissencephaly, heterotopia, and schizencephaly, predominantly involving fronto-parietal regions. MRI coupled with clinical findings enabled definitive diagnosis. Genetic analysis identified mutations in PAFAH1B1, ADGRG1, DHDDS, TMTC3, and other genes.

Anti-seizure medications like valproate, levetiracetam, and clobazam were the mainstay of therapy. Non-pharmacological interventions including physiotherapy, occupational therapy, and speech therapy were employed.

Conclusion: This study demonstrates the diverse clinical, genetic, and radiological spectrum of neuronal migration disorders. Comprehensive evaluation along with neuroimaging and genetic analysis enables accurate diagnosis and guides management. A multimodal approach is required focusing on seizures, neurodevelopmental disabilities, and improving quality of life.

Key words: Epilepsy, Lissencephaly, Neurodevelopmental Disabilities, Neuroimaging, Neuronal Migration Disorders, Polymicrogyria

Introduction

Neuronal migration disorders comprise a heterogeneous group of neurological conditions caused by abnormal positioning of neurons during brain development. These disorders are characterized by disturbances in the migration of neuronal cells to their proper locations during corticogenesis. This results in abnormalities of cortical gyration and layering, often detectable through neuroimaging[1,2]. The most common neuronal migration disorders seen in children include lissencephaly, pachygyria, polymicrogyria, and heterotopias[3,4] .

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Children with neuronal migration disorders present with a variety of symptoms including developmental delay, intellectual disability, seizures, motor abnormalities, and structural brain anomalies1. Careful clinical evaluation coupled with neuroimaging studies such as MRI allows definitive diagnosis[2]. Understanding the genotype-phenotype correlation in these disorders has shed light on the underlying pathogenesis[5]. Advances in genetic testing have enabled identification of causative mutations in many patients[3].

Treatment is aimed at symptomatic management of developmental delay, cognitive impairment, epilepsy, and movement disorders[1]. A multidisciplinary approach with physical, occupational and speech therapy is beneficia[l6]. Novel therapies targeting associated abnormalities in neurotransmitters and neuronal signaling pathways are emerging7.

Methods & Materials

In Our tertiary centre Neurology OPD all the pediatric patients having proven Neuronal Migration Disorders were included with recording of clinical details, treatment modalities , Neuroimaging studies and Genetics wherever tested.

Below is the comprehensive data of all patients presented in tabulated form.

Table1: Demography, Clinical Features, Neuroimaging Findings, Treatment details and Genotype of Pediatric patients with Neuronal Migration Disorders

Sr. No.		Age/Sex	Complaints	Investigations	Treatment
1.	SP	2 years/ Female	Global developmental delay Spasticity of all four limbs	CT Brain: Cortical thickening in the bilateral fronto-parietal and occipito-temporal lobes with blunting of the sulci suggestive of polymicrogyria. EEG: Multifocal epileptiform discharges	Levetiracetam, Valproate, Clobazam, Lamotrigine
2.	RS	2 months/ Male	Flexor spasms and abnormal oculogyric eye movements	MRI Brain: Right hemispheric hemihyperplasia EEG: Right hemispheric bursts of epileptiform discharges and background suppression	Steroids, Topiramate Valproic acid
3.	JK	2 years/ Male	Global Refractory status epilepticus	MRI Brain: Right sided open lip schizencephaly and polymicrogyria involving Right parietal lobe EEG: Right sided epileptiform discharges with background changes.	Phenytoin, Valproate Clobazam
4.	SP	8 months/ Male	developmental delay, seizures	MRI Brain: Periventricular Nodular Heterotopia EEG: Multifocal epileptiform discharges.	Valproate Phenytoin , Topiramate, Clobazam
5.	KL	15 months/ Male	Spasms and encephalopathy	MRI Brain: Focal Cortical Dysplasia involving Left Frontal LobeEEG: Hypsarrhythmia	Steroids, Valproic acid, Clobazam
6.	HD	3 months/ Female	Hypertonia of limbs and tonic posturing	MRI Brain: The supratentorial brain shows grossly abnormal cortical formation characterised by smooth brain with absent/ hypoplastic sulci and shallow sylvian fissures. Diffuse symmetric subcortical band heterotopia seen. Features suggestive of lissencephaly type 1 subcortical band heterotopia spectrum. Genetics: Heterozygous mutation in intron 7 on PAFAH1B1 gene on chromosome [17].	Levetiracetam, Phenobarbitone, Phenytoin, Topiramate Levetiracetam, Phenobarbitone, Phenytoin, Topiramate Risperidone
7.	HP	13 daysMale	Neonatal Seizures		
8.	MS	9 years/ Female	Seizures developmental delay hypertonia and spasticity in all limbs	MRI Brain: Agyria-pachygyria complex Affecting bilateral perisylvian areas	Valproate
9.	HG	1 year 6 months/ Male	Left sided congenital hemiparesis with evolving left parietal epilepsy left sided dystonia and spasticity	MRI Brain: Right parietal lobe polymicrogyria EEG : Central theta activity with occasional right hemispheric epileptiform activity	Valproate Clobazam
10.	AS	6 years/ Male	Intractable seizures	MRI brain: Bilateral fronto-pareital abnormal sylvian sulcation with cortical gyral thickening with associated dysplastic subcortical & periventricular confluent white matter hyperintensities suggestive of partial pachygyria- agyria complex. EEG: suggestive generalised epileptiform discharges with normal background activity Genetics: ADGRG 1 gene mutation	Levetiracetam, Valproate, Clobazam, Topiramate
11.	PS	1 year/ Male	Seizures	MRI brain : Bilateral temporal polygyria with left temporal polymicrogyria	Valproate, Clobazam, Lamotrigine, Vigabatrin
12	AL	15 months/ Male	Tonic seizures global developmental delay	MRI Brain Lag in myelination affecting internal capsule, corpus callosum and dorsal pons EEG: Left fronto-central epileptiform discharges Genetics: Homozygous mutation in exon 7 at TMTC3 gene on chromosome [12].	
13	SG	4 years/ Male	Epilepsy Global developmental delay	MRI Brain:Polymicrogyria diffusely involving bilateral frontal, parietal and temporal lobes with thickened and dysorganised gyri in these areas	Valproate, Clobazam

14	KV	1 year 6 months/ Female	Neonatal seizures Global developmental delay	MRI Brain: Pachygyria-polymicrogyria involving bilateral cerebral hemispheres with relative sparing of bilateral occipito-parietal lobes. Periventricular abnormal signalling with periventricular cysts and multiple periventricular calcifications. Mild ventriculomegaly involving bilateral lateral hemispheres.	Levetiracetam
15.	AS	1 year 6 months/ Female	Global developmental delay, seizures, myoclonic jerks, hypotonia, feeding difficulties, poor eye contact, drooling.	MRI Brain: Thick cerebral cortex is noted bilaterally with reduced cortical sulci noted at these regions and diminished white matter. Multiple hyperintense signal areas are seen on the T2W and FLAIR images in the periventricular, subcortical bilateral fronto-parietal white matter. Features are suggestive of pachygyria-lissencephaly spectrum. Genetics: Homozygous mutation in the exon 7 on ADGRG1 gene on chromosome 16	AEDs: Clobazam, Valproate, Topiramate
16.	DM	3 years/ Male	Delayed walking	MRI Brain: Cortical thickening with abnormal sulcation in the left temporo-parietal parenchyma suggestive of pachygyria complex	
17	ST	7 years/ Male	Left focal seizures	Periventricular Nodular Heterotopia in right parieto-occipital area adjacent to occipital horn of lateral ventricle	Levetiracetum Valproate

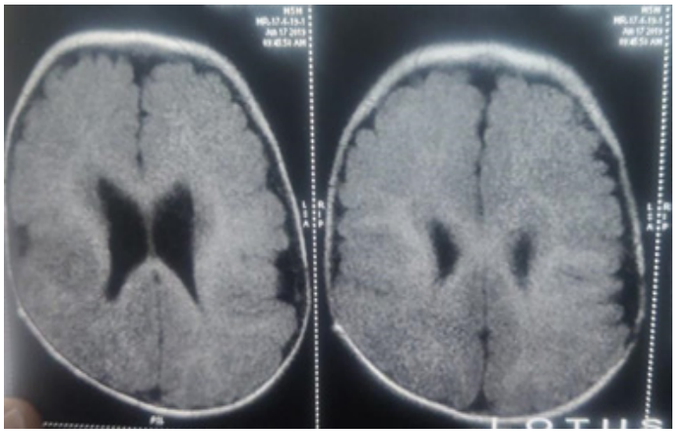

Figure 1: patient 1 CT findings suggestive of Cortical thickening in the bilateral fronto-parietal and occipito-temporal lobes with blunting of the sulci suggestive of polymicrogyria.

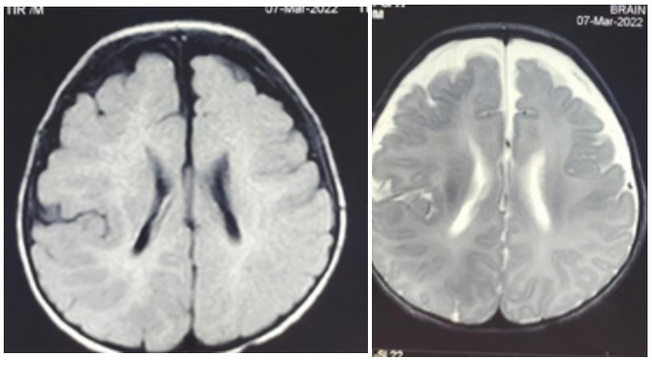

Figure 2: patient 2 MRI Brain suggestive ofEnlargement of right hemisphere with herniation towards left
Enlarged right lateral ventricle with predominant involvement and dysmorphism of occipital horn,Abnormal gyration pattern with deeper central sulcus as compared to left
S/O Hemimegalencephaly of Right side

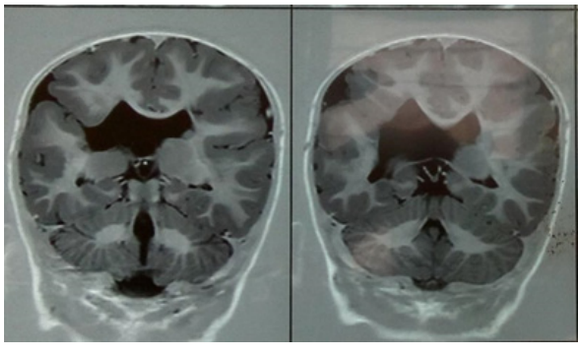

Figure3: Patient 3 MRI suggestive of Right sided open lip schizencephaly and polymicrogyria involving Right parietal lobe

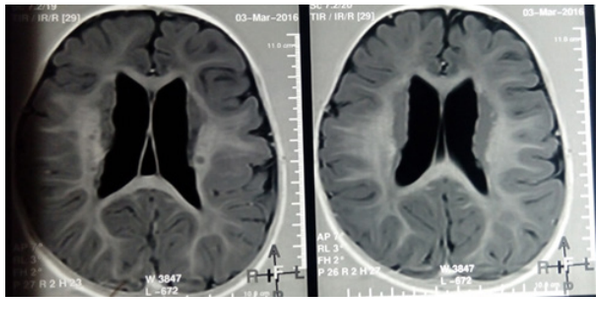

Figure 4: Patient 4 MRI suggestive of Periventricular nodular heterotopias

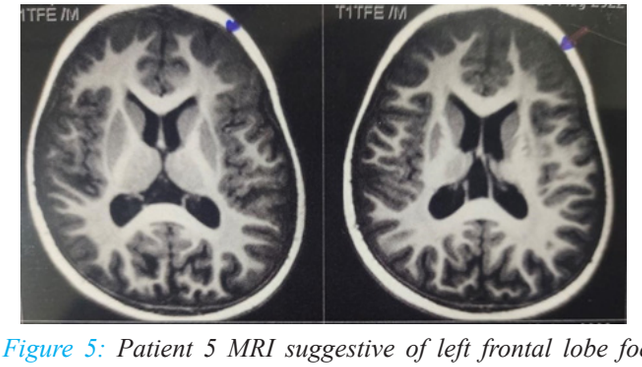

Figure 5: Patient 5 MRI suggestive of left frontal lobe focal cortical dysplasia with abnormal gyration and sulcation

Discussion

This case series illustrates the diverse clinical and radiological features seen in children with neuronal migration disorders[1,8]. The most common presenting symptoms were global developmental delay and seizures, experienced by nearly all patients3. Other frequent symptoms included limb spasticity, dystonia, and poor eye contact[9].

Neuroimaging showed a range of cortical malformations indicating abnormal neuronal migration, including pachygyria, polymicrogyria, lissencephaly, heterotopia, and schizencephaly[2,10]. Both generalized and focal patterns were observed, most often affecting the fronto-parietal lobes10. Associated findings such as ventriculomegaly, white matter abnormalities, and calcifications were also noted[8].

Genetic analysis enabled etiological diagnosis in several instances. Mutations were found in genes such as PAFAH1B1, ADGRG1, DHDDS, and TMTC3, known to be associated with neuronal migration disorders[5,11]. Identifying causative mutations facilitates prognosis and genetic counseling for families[12].

Anti-seizure medications including valproate, levetiracetam, and clobazam were primarily used for treatment[13]. Most patients needed polytherapy to adequately control seizures[14]. Other pharmacological options utilized were lamotrigine, vigabatrin, topiramate, and phenobarbitone[3]. Non-pharmacological therapies like physiotherapy, occupational therapy, and speech therapy are key for neurodevelopmental rehabilitation[6].

In summary, this case series demonstrates the clinical heterogeneity of neuronal migration disorders stemming from diverse genetic underpinnings[5]. Comprehensive assessment along with neuroimaging and genetic testing allows accurate diagnosis and directs management[2,15]. A multimodal approach combining medications and rehabilitative therapies aims to enhance neurodevelopmental outcomes and quality of life.

Conclusion

This retrospective case series of 17 pediatric patients highlights the diverse clinical and radiological spectrum of neuronal migration disorders. Global developmental delay and seizures were the most common presenting features. Neuroimaging revealed a range of cortical malformations including pachygyria, polymicrogyria, lissencephaly, heterotopia, and schizencephaly, predominantly involving the fronto-parietal regions. Genetic analysis identified mutations in several genes known to cause neuronal migration defects.

Anti-seizure medications like valproate, levetiracetam, and clobazam were the mainstay of pharmacological management. Non-pharmacological interventions including physiotherapy, occupational therapy, and speech therapy were also employed for neurodevelopmental rehabilitation.

This study adds that comprehensive assessment aids in determining prognosis and directing genetic counselling. Further research on elucidating genotype-phenotype correlations and novel therapeutic targets may advance clinical care and outcomes in these disorders.

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