Pattern of childhood neuronal migrational disorders in Oman

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ABSTRACT

الأهداف: النظر في نمط مختلف من أمراض هجرة الأعصاب الطفولية NMD والتعرف على الأمراض العصبية المصاحبة لها.

الطريقة: تم جمع المعلومات من خلال وحدة أعصاب الأطفال في مستشفى جامعة السلطان قابوس – عُمان، خلال الفترة مابين يناير 1993م وحتى سبتمبر2006م، من الأطفال الذين لديهم تأخر في النمو العقلي ومصابين بالصرع واللذين اجري لهم فحص لمرض هجرة العصب الطفولية NMD عن طريق الأشعة المغناطيسية (MRI).

النتائج: كان هناك 86 حالة من أمراض هجرة الأعصاب NMD. شكلت حالات عدم تكون الجسم الثفني، وانعدام التلافيف / ثخن التلافيف الغالبية العظمى. كان هناك 48 حالة من عدم تكون الجسم الثفني و16 حالة من انعدام التلافيف / ثخن التلافيف. الحالات الأخرى شملت 10 حالات من التوضع المغاير، 5 حالات من انشقاق الدماغ وحالة واحدة من الأتي: كثرة التلافيف، اِنْدمَاجُ مُقَدَّم الدِّماغ، استسقاء الدماغ وتضخم الدماغ النصفي. كَان تأخر تطَور النمو أكثر الحالات المصاحبة في 80 حالة (93%)، 67 حالة (77.9%) كان لديها عوق حركي. أربعون حالة من أصل 86 (46.5%) هي حالات الصرع. الصرع الجزئي والجزئي المعقد هو الأكثر شيوعاً، 13 حالة من اصل 40 (32.5%). ظهرت المتلازمات الصرعية في 11 حالة من أصل 40 (27.5%). تمت السيطرة على 3 حالات من اصل 40 (7.5%) من حالات الصرع فقط.

خاتمة: تشكل مختلف أمراض هجرة الأعصاب الطفولية NMD عدداً كبيراً من الأطفال المرضى الذين يعانون من الأمراض العصبية، الحركية، النفسية المستعصية ومن حالات الصرع. هذه الإضطرابات متصلة بعوامل خارجية ووراثية من الأسبوع السادس وحتى الأسبوع السادس والعشرين من الحمل. البحوث الجينية الجزيئية هي التي تحدد آلية هذه الإضطرابات، هذا ويمكن أن تساعد في التشخيص المبكر والوقاية من هذه الأمراض.

Objectives: To record the pattern of different neuronal migrational disorders (NMD) and their associated neurological conditions.

Methods: The data were collected at the Child Neurology Services of Sultan Qaboos University Hospital, Oman, from January 1993 to September 2006 from all children with psychomotor delay and epilepsy, who underwent brain imaging (mostly MRI). The MR imaging was used for the diagnosis of a neuronal migration anomaly.

Results: There were 86 cases of NMD. Corpus callosum agenesis and lissencephaly/pachygyria formed the major group. There were 48 cases of corpus callosum agenesis, and 16 cases of lissencephaly/pachygyria. Other disorders were 10 cases of heterotopias, 5 schizencephaly, 3 holoprosencephaly, 2 polymicrogyria, and one each of hemimegalencephaly, and hydranencephaly. Developmental delay was the most common associated finding noted in 80 (93%) cases. Sixty-seven (77.9%) cases had motor deficit. Forty out of 86 (46.5%) cases had epilepsy. Partial/partial complex seizures were the most common at 13 out of 40 (32.5%). Syndromic seizures were seen in 11 out of 40 (27.5%) cases. The seizures were controlled in only 3/40 (7.5%) cases.

Conclusions: The NMD constitute a significant number of child neurology patients with psychomotor delay and intractable epilepsy. Exogenic and genetic factors affecting the early embryonic and fetal development from sixth to twenty-sixth weeks of gestation result in NMD. Recent genetic studies are defining the underlying mechanism and these studies will help in early diagnosis and possible prevention of NMD.

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Neuronal migration disorders (NMD) are not uncommon in childhood. These children present with developmental delay, epilepsy, mental retardation, or cerebral palsy. On examination, there are no obvious clinical features indicating an underlying brain migration disorder. However, NMD can be suspected in association with certain syndromes. Minor forms of NMD may not present with neurologic features and go unnoticed unless imaging is performed for other reasons. The brain in humans is highly organized in its cytoarchitecture. Three major phases are involved in normal adult brain morphogenesis. These are cell production, cell migration, and cortical differentiation and growth. Neuron production and migration proceed simultaneously from the sixth to twenty-sixth weeks of gestation. Complex chemical guides and signals control this stage.[1] Any exogenous or genetic interference during this stage of development will result in NMD. Cortical growth, differentiation, and maturation begin simultaneously and differentiation continues until the age of 15 years postnatal.[1] Psychomotor delay, epilepsy and the mental retardation are the main features of presentation of NMD, epilepsy being the significant associated morbidity in more than 50%. Only a few reports are available on NMD from this region,[2,3] and so, the objective of our study was to record the pattern of different NMD and their associated neurological conditions in Oman.

Methods. This study was conducted at Sultan Qaboos University Hospital, Oman. The data were collected from January 1993 to September 2006 from all children with psychomotor delay and epilepsy, who underwent brain imaging (mostly MRI). The MR imaging was used for the diagnosis of a neuronal migration anomaly as MR is an excellent tool for diagnosing the migrational anomalies of the brain.[4] Any child with dysmorphism and NMD on MR was also included in the study. The work up in all children included complete blood count, liver function test, urea and electrolytes, bone profile, serum lactate, tandem mass spectrometry, TORCH profile, and chromosomal analysis. The NMD children with epilepsy also had an EEG. The diagnosis of NMD was based on the established criteria.[5-9] Tuberous sclerosis children were not included in the study of NMD. There are increased chances of NMD in association with tuberous sclerosis. Children with psychomotor delay, mental retardation, epilepsy, but normal imaging studies were also excluded from the study. Institutional ethical committee approval was obtained for the study.

Results. There were 86 children with different NMD seen (**Table 1**); 45 males (52.3%), and 41 females (46.7%). Age range was 2 days to 15 years with a mean of 4 years, 4 months and 12 days. Many cases with NMD had more than one anomaly. Corpus callosum agenesis (CCA) was the most common NMD, followed by lissencephaly, and heterotopias. The CCA (**Figure 1**) was complete in 25, partial in 17, and hypoplastic in 6. The age ranged from 2 days to 15 years with a mean age of 3 years and 10 months. Twenty-five cases were males and 23 females. Most cases of CCA were nonsyndromic, 45 of 48 (93.75%), epilepsy was noted in 37.5% of CCA cases, and the most common seizures were infantile spasms. Details of seizures are given in **Table 2**. Associated anomalies in CCA were seen in 9 cases (schizencephaly in 2, colpocephaly in 2, heterotopias in 2, holoprosencephaly in one, lissencephaly in one, and hydrocephalus in one). There were 16 cases (10 male and 6 female) of lissencephaly (**Figure 2**). The age ranged between 15 days to 6 years with a mean of 2 years and 2 months. Fifty percent had epilepsy. The clinicoradiological features suggested Walker-Warburg features in 2 and Miller Dicker in 3. The type of epilepsy found in the cases is shown in **Table 2**. The family history of developmental delay, similar to the index case, was present in 2 children with lissencephaly. However, the brain imaging did not reveal the abnormality. Lissencephaly cases had associated anomalies in 9 (polymicrogyria in 2, calcifications in 2, megalencephaly in one, porencephaly in one, band heterotopias in one, hydrocephalus in one, and CCA in one). Heterotopias were seen in 10 cases (5 male

Table 1 - The percentage of different neuronal migrational disorders and associated other features (N=86).

Neuronal migration anomaly (no. of cases, %)	Associated features, n (%)				
	Developmental delay	Motor deficit	Epilepsy	Associated anomalies	Others
CCA (48, 55.8%)	45 (93.7)	35 (72.9)	18 (37.5)	9 (18.7)	Microcephaly in 23 (47.9)
Lissencephaly (16, 18.6%)	16 (100)	16 (100)	8 (50)	9 (56.2)	
Heterotopias* (10, 11.6%)	9 (90)	6 (60)	8 (80)	5 (50)	
Schizencephaly (5, 5.8%)	5 (100)	5 (100)	4 (80)	4 (80)	
Polymicrogyria (2, 2.3%)	1 (50)	2 (100)	1 (50)	1 (50)	
Holoprosencephaly (3, 3.5%)	3 (100)	3 (100)	0	3 (30)	
Hemimegalencephaly* (1, 1.1%)	0	0	1		Klippel-Trenaunay-Weber syndrome
Hydranencephaly (1, 1.1%)	1 (100)	0	0		
Total (86)	**80 (93)**	**67 (77.9)**	**40 (46.5)**		

*one case included in both, CCA - corpus callosum agenesis

Figure 1 - Axial CT scan showing corpus callosum agenesis (arrows).

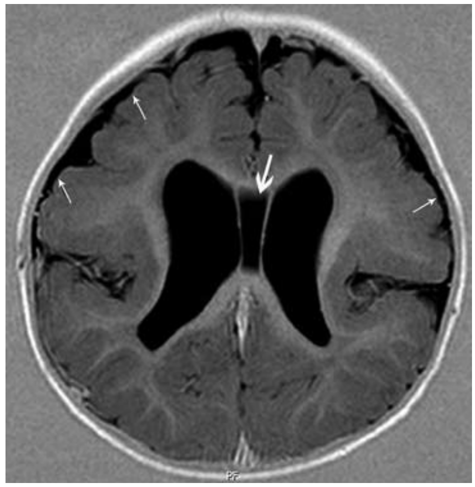

Figure 2 - An MRI T1 weighted (inversion recovery) image of the patient shows thick gyri, smooth brain (arrows on sides) and cavum septum pellucidum (thick arrow in center).

Table 2 - Type of epilepsy in neuronal migrational disorders (N=40).

Neuronal migration anomaly	Type of epilepsy				
	Partial/ partial complex	Generalized tonic clonic	Myoclonic	Infantile spasms	Lennox-Gastaut syndrome
CCA	4	4	2	6	2
Lissencephaly		6	2	1	
Heterotopias	6*		1	1	
Schizencephaly	1		2	1	
Polymicrogyria	1				
Hemimegalencephaly	1*				
Total, n (%)	**13 (32.5)**	**10 (25)**	**7 (17.5)**	**9 (22.5)**	**2 (2.3)**

*one case included in both, CCA - corpus callosum agenesis

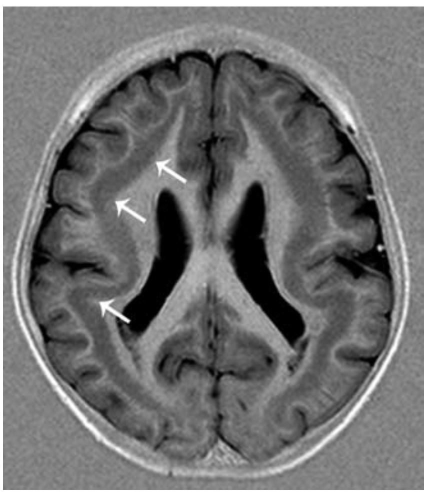

Figure 3 - An MRI T1 weighted (inversion recovery) image shows bilateral band heterotopia, double cortex (arrows).

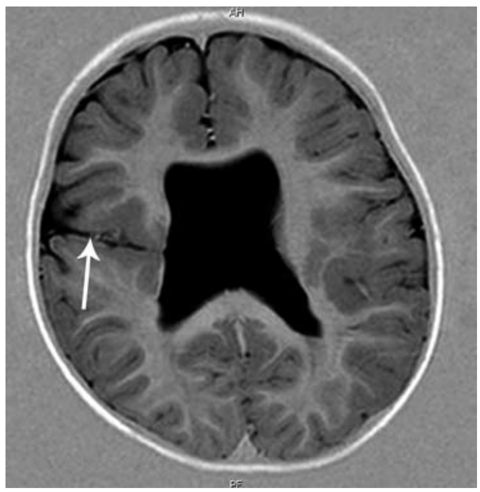

Figure 4 - An MRI T1 weighted (inversion recovery) shows right-sided open lip schizencephaly (arrow).

and 5 female). The age ranged between 2 years and 8 months to 15 years, with a mean of 9 years and 9 months. One 10-year-old girl with mental retardation and seizures had complete bilateral band heterotopia giving an appearance of double cortex (**Figure 3**). Her intelligence quotient was 51. Seizures were present in 7 out of 10 (70%) heterotopias cases (**Table 2**). Associated anomalies were noted in 5 (schizencephaly in one, lissencephaly in 2, and CCA in 2). One girl with heterotopias had hemimegalencephaly and features of Klippel-Trenaunay-Weber syndrome. Schizencephaly was seen in 5 cases (2 male and 3 female) with an age range from 2 years and 8 months to 14 years (**Figure 4**). Their mean age was 6 years and 4 months. The type of schizencephaly was closed lip in 3, open lip in one and bilateral in 2. Seizures were found in 4 (**Table 2**). Associated anomalies were found in 4 (CCA in 2, and heterotopias in 2). Holoprosencephaly was found in 3 cases, 2 males, and one female, with ages of 3 months, 11 years, and 15 years. All 3 had associated anomalies and none had seizures. Polymicrogyria was found in 2 female children aged 2 years and 3 months and 6 years. Only one had seizures. Associated lissencephaly was noted in one. There was one case of hemimegalencephaly with partial motor seizures. This was a 15-year-old girl diagnosed at 8 years of age with partial motor seizures. She had all the features of Klippel-Trenaunay-Weber syndrome. There was one case with hydranencephaly. Forty out of 86 (46.5%) cases had epilepsy (**Table 2**).

Discussion. The corpus callosum is the main connection between 2 cerebral hemispheres. It may be totally absent (agenesis), partially absent or hypoplasic. Agenesis of the corpus callosum in isolation is usually asymptomatic.[10] The neurological signs are due to the other associated brain abnormalities. Corpus callosum agenesis was detected in 1% of all CT scans of children less than 12 years age at our hospital.[11] In a previously reported study,[12] CCA was found in 14% of CNS malformations. Corpus callosum agenesis is a common component in some malformative syndromes, chromosomal aberrations, neurocutaneous diseases, and less frequently in inborn errors of metabolism.[12] Any type of epilepsy at any age is seen in cases with CCA. In the present series, 18 out of 48 (37.5%) cases, had epilepsy. Microcephaly was noted in 23 (47.9%) cases. Epileptic seizures were reported in 23-39% of the CCA cases in the literature.[3,13] All the types of seizures, with neonatal onset, infantile spasms, partial and generalized seizures are seen in CCA. In 70% of our cases, the onset of seizures was during the first year. This is similar to the other reported figures.[13] Infantile spasms were the most common type of seizures. Generalized tonic and clonic seizures and Lennox-Gastaut syndrome formed the other group. The outcome of patients with seizures is poor on drug therapy alone, and surgical intervention in selected cases may be useful. More often, the associated anomalies of the brain dictate the outcome in these cases. It is common to see more than one anomaly in the brain in a case of NMD. This was noted in 48% of cases, in a report on NMD from Jordan.[2]

Absent or decreased convolutions are the features of lissencephaly. Lissencephaly means a smooth brain. Epilepsy, developmental delay, and motor weakness are the features of classic lissencephaly.[6] The degree of pachygria correlates with phenotypic severity. On the basis of the severity of gyral malformation and site of brain involvement, a grading system of 1-6 has been developed.[6,14] Five different gene mutations are known in lissencephaly.[15] There are many nonneurologic features, and even dysmorphism may be seen in association with lissencephaly. An association with abnormal genitalia and refractory epilepsy was recently reported.[16] No association with abnormal genitalia was seen in our cases. Seizures constitute a major handicap in this disorder. Fifty percent of children in this study had epilepsy. Generalized tonic clonic seizures were the most common. In a previously published study of 21 patients with lissencephaly, 75% of the patients had epileptic seizures resistant to conventional treatment.[17,18] Lissencephaly was the second most common NMD found in our patients (18.6% of cases). It was the single most common abnormality in 58.6% of cases of NMD from Jordan.[2] This high number in their series could be due to non-inclusion of CCA cases.

Heterotopias are groups of ectopic gray matter cells in inappropriate locations in the brain. This group of cells may be present between the periventricular region to the leptomeninges. Leptomeningeal heterotopias, also called marginal neuroglial heterotopias, are due to loss of movement restraint, due to loss of the glia limitans. The cluster of non-migrated gray matter localized to the subependymal region is called subependymal nodular heterotopia. Subcortical band heterotopias may be small isolated areas of clusters of gray matter or may be circumferential beneath the cortex and separate from it by a thin band of white matter (double cortex) as found in one of our children (**Figure 3**). Heterotopias may be isolated or in association with other malformations of the brain. Several syndromes have been associated with heterotopias. Heterotopias constituted 11.6% of cases in our study, almost similar to 13.8% reported previously.[2]

Schizencephaly is one of the severe forms of NMD. Seizures were present in 4 out of 5 children with schizencephaly. Twenty-eight out of 51 (55%) children with unilateral closed lip schizencephaly had partial motor seizures.[19] Atypical absences, atonic seizures, and epileptic negative myoclonus were also seen. The EEGs had spike-wave activity or bilateral high frequency spike discharges during sleep. In our 5 cases of schizencephaly, 3 (60%) had unilateral lesions, and 2 had bilateral. In a previous study of 9 patients, 6 (66%) had unilateral lesions and 3 bilateral, similar to our study. Somehow children with unilateral schizencephaly have mild neurologic handicaps but more seizures as compared to the cases with bilateral lesions having more neurologic handicaps and less seizures.[7,19] Genetic factors may play a key role in the pathogenesis of schizencephaly. This was reported as a mutation in homeobox gene EMX2 recently.[7,20]

Generalized tonic clonic seizures were seen in one case of polymicrogyria and hydranencephaly. One girl with Klippel-Trenaunay-Weber syndrome had partial motor seizures.[21]

In conclusion, epilepsy is a major handicap in children with NMD.[3,18,22] In children with developmental delay and dysmorphism with refractory seizures one should consider underlying NMD. Forty out of 86 (46.5%) cases had epilepsy. Partial/partial complex seizures were the most common type seen in 32.5% cases, syndromic in 27.5%, generalized tonic clonic in 25%, and myoclonic in 17.5%. The EEG abnormalities in children with epilepsy and underlying NMD is related to age of onset and type of seizures.[20] Hypsarrhythmia, burst suppression, generalized spikes, multifocal spike discharges, and focal seizure discharges have been reported. The seizures in children with NMD are refractory to medical treatment. Only 3 children achieved seizure control. Early surgical intervention in selected cases would help in these cases. The NMD are related to exogenous and genetic factors in the sixth to twenty-sixth weeks of gestation.[1] Molecular and genetic research is defining the mechanism of these disorders, which could help in early diagnosis and prevention. Limitations of the study were genetic work up not carried out in any case, and none of the children underwent neurosurgery. In the future, plans will be to work up the cases for genetic studies, with local or international collaboration. This will help in antenatal diagnosis and possible medical termination of pregnancies.

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