Clinical Features, EEG Findings and Outcome in Patients with Bilateral Periventricular Nodular Heterotopia and Epilepsy

Aim: To review the clinical, electrophysiological and neuroimaging data of eight adult patients (4F/4M) with epilepsy and bilateral periventricular nodular heterotopia (PNH) after a long duration of follow-up.

Materials and Methods: The clinical charts were reviewed for demographic and clinical features, seizure types and frequency, treatment and prognosis of all eight patients who were under follow-up by one of the authors (SS). The recordings of video-EEG monitoring with scalp electrodes in five patients and routine EEGs in all patients were reviewed.

Results: The clinical semiology was in accord with seizures originating from temporal lobe region in four patients, while an extratemporal onset was assumed in the others (in one with additional temporal seizures). Interictal EEGs were normal in one patient, who was diagnosed as having psychogenic nonepileptic seizure. Abnormalities seen in interictal EEGs were bilateral independent temporal focus in three, unilateral epileptiform abnormalities in two, and generalized 3 cyc/sec discharges mimicking idiopathic generalized epilepsies in two patients. Only two patients’ MRI revealed bilaterally contiguous heterotopic nodules (symmetric and asymmetric type) and, interestingly, these two patients did not have intractable seizures while the other six patients with bilateral, asymmetric and noncontiguous heterotopic nodules suffered from intractable seizures.

Conclusions: Patients with bilateral PNH have different clinical features, EEG findings and extension of the heterotopic nodules. These patients may be misdiagnosed as having idiopathic generalized epilepsy, temporal lobe epilepsy or even psychogenic nonepileptic seizures without high quality MRI because of the misleading seizure semiology and interictal-ictal EEG findings. Seizures are usually drug-resistant but the patients who have diffuse symmetric or asymmetric contiguous heterotopic nodules may have good prognosis.

Key Words: Nodular heterotopia, periventricular heterotopia, subependymal heterotopia, epilepsy, EEG, MRI, prognosis

Bilateral Periventriküler Noduler Heterotopi ve Epilepsi - Klinik, Elektrografik Özellikler ve Prognoz

Amaç: Epilepsi tanısı alan ve bilateral periventrikal nodüler heterotopi (PNH) saptanan seks erişkin hastanın (4F/4M) klinik, elektrofizyoloji, görüntüleme ve prognoistik özelliklerini uzun süreli takip sonrasında değerlendiririz.

Yöntem ve Gereç: Olguların demografik ve klinik özellikleri, nöbet semiyolojileri, tedavi protokolleri ve klinik işlem özellikleri hastane takip dosyaları incelenerek elde edildi. Rutin EEG incelemeleri tüm olgularda yapılmış, ayrıca beg olgu video-EEG monitorizasyon incelemesi ile değerlendirilmiştir.

Bulgular: Klinik semiyolojisi dört hastada temporal lob, dört hastada ise ekstratemporal özellikli nöbetler (bir olguda eşlik eden temporal nöbetler de vardı) ile uyumlu bulundu. Interiktal EEG de üç hastada bilateral bağımsız temporal odak, iki olguda unilateral epileptiform bozukluk, ve iki olguda idyopatik jeneralize epilepsiyeye benzer jeneralize 3 Hz desarjları görüldü. Başvuru öncesinde psikojenik nonepileptik nöbet tanısı almış bir olguda normal olarak değerlendirildi. İki hastada MRG de bilateral devamlık gösteren heterotopik nodüler (simetrli ve asimetrli tipte) görüldü, bu olgularda nöbetler ilaca dirençti deildi. Diğer hastalarda bilateral asimetrlik ve devamlık göstermeyen nodüler görüldü, bu olgularda nöbetler ilaca dirençtiydi.


Anahtar Sözcükler: Nodüler heterotopi, periventrikal heterotopi, subependimal heterotopi, epilepsi, EEG, MRG, prognoz
**Introduction**

Heterotopias are malformations of cortical development characterized by the presence of apparently normal brain cells in abnormal position. Neurons that populate the adult cortex first occur in the germinal layer of the ventricular zone, and to get to their proper adult location, most cerebral cortical neurons migrate along tracks of radially oriented glial cells. In periventricular nodular heterotopia (PNH), there is a total failure of migration of some neurons. These neurons remain in the ventricular zone as clumps or nodules of differentiated neurons, while the remainder of the neurons migrate normally and completely to form the proper six-layered cortex (1-4).

An X-linked dominant inheritance has been established for familial bilateral PNH in females, a condition also characterized by a high incidence of spontaneous miscarriages particularly in male fetuses. Linkage analysis mapped this disorder to Xq28, and filamin 1 gene was identified as the related gene (5-7). Sporadic cases of bilateral PNH both in females and males have also been described (8,9). Nodular heterotopias are also observed in other conditions with multiple causative genes, and environmental etiologies are suggested (10).

Magnetic resonance imaging (MRI) is the best imaging modality to disclose PNH and describe the morphology, extension, and boundaries of the malformation, and it may display associated cortical dysplasias or other brain malformations. High resolution MRI has revolutionized the study of cortical dysplasia by showing how important these conditions are as a cause of epilepsy (11-14). MRI features of PNH are sufficient to identify it as a distinct neuronal migration disorder. However, while many recent papers have described the advances of neuroradiological aspects of cortical malformations, few studies have investigated the clinical, prognostic and long-term follow-up of patients with these malformations (10,14-16).

In this study, we investigated the clinical, neurophysiological, and neuroimaging features of eight epilepsy patients with bilateral PNH, focusing on the course and prognosis of epilepsy in this group of cortical malformations.

**Materials and Methods**

Six of the eight patients included in the study were referred to the epilepsy center of our hospital because of drug-resistant seizures. The presence of PNH was assessed by means of MRI in all cases (Figure 1). The patients were characterized by bilateral multiple nodules of heterotopic gray matter in the subependymal region of ventricles.

The clinical histories of the patients were analyzed with particular attention paid to a family history of epilepsy, spontaneous miscarriages, early infant or child deaths and other cardiac, renal or neurological diseases. The presence of risk factors for brain damage during prenatal or perinatal life; their motor, mental and speech development; their neurological status; and their mental level were all questioned in detail. The epileptic histories, the age and modality of seizure onset, and the semiology of the seizures were carefully reviewed. The electroclinical features and clinical course of the epilepsy as well as the response to different antiepileptic drug therapies were recorded.

The routine EEG was recorded after the 10-20 international systems of electrode positioning with 8-channel Grass EEG machine. Long-term video EEG monitoring, with 32 channels, and added T1-T2 and ECG electrodes, could be performed in five patients (Telefactor Beehive or Millennium). Videotapes and ictal-interictal EEGs were also reviewed in detail. The MRI scans were made at a field strength of 1.5 or 3.0 Tesla (including T1-weighted sagittal and transverse, T2-weighted and FLAIR transverse and coronal, 3B T1-weighted gradient echo coronal examinations) with 1.5mm slices.

**Results**

The studied group consisted of eight patients (4 males, 4 females; age range: 20 to 59 years). Consanguineous marriage was present in five patients. Miscarriage or early child death was reported in three families. Family history of epilepsy was not reported in any patient. Perinatal risk factors were reported in one patient with a threatened abortion at the third month of pregnancy, and she was delivered via caesarian section (Case 1). All patients except one (Case 5) had normal acquisition of early developmental milestones. Only Case 5 also had neurological deficit, dysmorphism and severe
mental retardation with chromosomal abnormality. Three patients had a junior high school diploma, three had a senior high school diploma and one had a university degree.

Median age at onset of recurrent seizures was 15 years (range: 6 months – 24 years). Complex partial seizures were reported by seven patients, but secondary generalized seizures in five patients. Falling attacks were also reported in four patients. The clinical semiology was in accord with seizures originating from temporal region in four, from extratemporal regions (frontal and parietal) in three, and extratemporal onset together with temporal onset was assumed in one patient (Table 1). The mean follow-up was 13.4 years, with a minimum of two and a maximum of 35 years from the onset of epilepsy. Although the frequency of seizures decreased with drugs, all patients except two continued to have disabling frequent seizures. Vagal nerve stimulation was used in one patient (Case 1). At least one drug was used in therapy. On the 35th year of follow-up, Case 4 still reported complex partial seizures with three antiepileptic drug combinations.

Routine interictal EEG recordings showed a normal background activity in five patients. Slow background activity was recorded in three patients. Focal abnormalities, nonspecific (theta activity) or epileptiform, were present in seven recordings. In one patient, all routine EEG examinations (6 recordings) were regarded as normal (Case 8). No patient showed photic driving or other EEG changes during photic stimulation. Isolated spike activity was recorded in two patients. 3-3.5cyc/sec generalized spike–wave activity mimicking primary generalized epilepsy was detected in two cases (Figure 2). Video-EEG monitorization with scalp electrodes was performed in five patients. Ictal rhythmic activity was recorded in four patients. Twenty-six seizures were recorded during 1-3 days (mean: 6.5 seizures per patient). Ictal EEGs of four patients showed rhythmic...
Table 1. Clinical, demographic, history, neuroimaging and follow-up results of the patients with bilateral PNH (BPNH).

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age/onset (months)</th>
<th>Parental consanguinity</th>
<th>Seizure in history</th>
<th>Nodule location</th>
<th>Antiepileptic</th>
<th>Drug response</th>
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<tbody>
<tr>
<td>1</td>
<td>22/F</td>
<td>15</td>
<td>First-degree</td>
<td>Unremarkable</td>
<td>BPNH</td>
<td>VNS</td>
<td>LTG 200 mg/d</td>
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<td>CBZ 800 mg</td>
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<td>LB 200 mg/d</td>
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<td>LTC 1000 mg/d</td>
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<td>PB 200 mg/d</td>
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<td>2</td>
<td>22/F</td>
<td>13</td>
<td>Second-degree</td>
<td>Unremarkable</td>
<td>BPNH</td>
<td>CLZ 400 mg/d</td>
<td>LTG 200 mg/d</td>
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<td>3</td>
<td>20/M</td>
<td>18</td>
<td>(-)</td>
<td>Mother had two miscarriages in the first trimester Has 2 healthy sisters</td>
<td>BPNH</td>
<td>OxCBZ 1500 mg/d</td>
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<td>4</td>
<td>59/M</td>
<td>24</td>
<td>Second-degree</td>
<td>A sister died in the first year; has a healthy son and a healthy daughter; His daughter has one miscarriage</td>
<td>BPNH</td>
<td>LTC 2000 mg/d</td>
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<tr>
<td>5</td>
<td>26/M</td>
<td>6 months</td>
<td>Second-degree</td>
<td>Mother reported 3 early infant deaths Maternal aunt experienced 3 early child deaths</td>
<td>BPNH</td>
<td>LTC 1000 mg/d</td>
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<td>6</td>
<td>20/M</td>
<td>14</td>
<td>First-degree</td>
<td>Unremarkable</td>
<td>BPNH</td>
<td>LTG 2000 mg/d</td>
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<td>7</td>
<td>27/F</td>
<td>15</td>
<td>(-)</td>
<td>Unremarkable</td>
<td>BPNH</td>
<td>CBZ 900 mg/d</td>
<td>LTG 200 mg/d</td>
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<td>(contiguous nodules)</td>
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<td>Seizure-free</td>
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<td>(Fig 3a)</td>
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<td>8</td>
<td>26/F</td>
<td>14</td>
<td>(-)</td>
<td>Unremarkable</td>
<td>BPNH</td>
<td>CBZ 200-600 mg/d</td>
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<td>(contiguous nodules, predominantly on the right side) (Fig 3b)</td>
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<td>SPS with autonomic symptoms: 1-2 t/w</td>
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</table>

<table>
<thead>
<tr>
<th>Case</th>
<th>Ictal EEG</th>
<th>Interictal EEG</th>
<th>Semiology of seizures</th>
<th>EEG focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left temporal 5-6 cyc/sec, rhythmic sharp waves, then generalized sharp and slow wave complexes (10-30 sec)</td>
<td>Background activity: 7-8 cyc/sec Isolated spike activity over left posterior temporal region and 3-3.5 cyc/sec generalized spike wave activity (Fig 2)</td>
<td>Loss of consciousness, blinking, with automatisms in hands and urinary incontinence (15-20 sec)</td>
<td>Bilateral temporal with left predominance</td>
</tr>
<tr>
<td>2</td>
<td>Seven seizures recorded; rhythmic sharp theta and alpha activity in the left temporal region in four and the same activity in the right temporal region in three of the seizures</td>
<td>Background activity: 9-10 cyc/sec Central, right centro-parietal and bilateral frontal spikes Paroxysmal activity of independent theta, delta slow and sharp waves over bilateral temporal regions</td>
<td>CPS without automatisms (20-30 sec)</td>
<td>Bilateral independent temporal</td>
</tr>
<tr>
<td>3</td>
<td>During 5 days monitorization no seizure was detected</td>
<td>Background activity: 9-10 cyc/sec</td>
<td>(Recorded during follow-up) Amnesia and confusion without automatisms (pure amnestic)</td>
<td>Left temporal region</td>
</tr>
<tr>
<td>4</td>
<td>Background activity: 9-10 cyc/sec parieto-occipital alpha and 5-7 cyc/sec central theta Bilateral fast activity for 5 sec, then 5-7 cyc/sec theta over right temporal region and bilateral delta and theta activity with voltage depression</td>
<td>Isolated sharp waves over right temporal region</td>
<td>Unforced deviation of head to right side, automatism in the right hand, dystonia in the left hand, unconsciousness (40-60 sec)</td>
<td>Right temporal region</td>
</tr>
<tr>
<td>5</td>
<td>Not performed</td>
<td>Background activity: 7-8 cyc/sec slow and sharp waves in left parieto-occipital region</td>
<td>(history) Clonic movements in the right arm spreading to right leg then secondary generalization.</td>
<td>L parieto-occipital region</td>
</tr>
<tr>
<td>6</td>
<td>3-4 cyc/sec high amplitude delta activity over right temporal region, spreading to ipsilateral hemisphere with amplitude asymmetry higher than 50%, then generalization</td>
<td>Background activity: 7-8 cyc/sec theta 1-2 cyc/sec slow-sharp wave delta activity over right temporal region</td>
<td>Vocalization, loss of consciousness, automatisms in both hands</td>
<td>Right temporal region</td>
</tr>
<tr>
<td>7</td>
<td>Not performed</td>
<td>Slow-sharp waves in bilateral temporal regions with left predominance</td>
<td>(history) Visual hallucinations, movements in her left arm and leg that would spread to involve the face and subsequently her entire body</td>
<td>Bilateral temporal regions with left predominance</td>
</tr>
<tr>
<td>8</td>
<td>Not performed</td>
<td>Normal, Background activity: 9-10 cyc/sec</td>
<td>(history) Left sided focal motor-sensory seizures w/wo secondary generalization Isolated seizures with autonomic symptoms (tachycardia, chest pain and sweating)</td>
<td>Could not be detected</td>
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</table>

CPS: Complex partial seizure. w/wo: With or without.
activities over the temporal lobes initially. Ictal and interictal EEG changes with seizure semiology are presented in Table 2.

Well-defined small nodules of heterotopic grey matter appeared isointense as normal grey matter on all imaging sequences. The nodules were localized along the walls of the ventricles bilaterally in all cases. Nodules were multiple, but not contiguous in six patients. Bilaterally located contiguous nodules were present in two patients; one symmetric and one asymmetric (Cases 7 and 8, Figure 3). None had nodules along the third or fourth ventricles. Nodules were located in occipital and temporal horns in four patients, and in occipital, temporal and frontal horns in two patients (Table 1). No patient was affected by PNH associated with other more pronounced brain malformations (i.e., schizencephaly and polymicrogyria) or structural abnormality, but in MRI of Case 8 hippocampal morphological asymmetry was seen.

**Discussion**

A wide variety and heterogeneity of clinical pictures have been reported in patients with PNH. Many reported series have included all kinds of heterotopias, or periventricular heterotopias with other cortical dysgenesis or structural brain abnormalities. Dubeau et al. (17) divided PNH patients according to the type of the heterotopic grey matter into two groups as simple PNH (patients with PNH without other cortical and/or cerebral malformations) and PNH-plus (PNH patients with other cortical and/or cerebral malformations). The nodules can also be anatomically subdivided into two types: unilateral or bilateral in disposition and focal or diffuse in localization (10,18,19). Therefore, it will be better to analyze PNH patients first in two groups as simple and plus, and then as bilateral symmetric, asymmetric, and unilateral. In this study, PNH demonstrated by high resolution MRI was found as an isolated anomaly (simple PNH), and all nodules were bilaterally located in the periventricular region. One was bilateral diffuse symmetric and the other seven were bilateral asymmetric.

Epilepsy has been reported in the second or third decade of life or earlier in PNH patients with no dysmorphic features (10,14). Seizure frequency ranges from rare to very frequent, and seizures are often resistant to polytherapy (5,14,18). Six of the eight patients in the presented study came to medical attention because of their intractable seizures. In two patients, with bilateral diffuse PNH, response to medical therapy was good (Cases 7 and 8). Resistant seizures and severe mental retardation with dysmorphic features were present in Case 5. He was followed-up for 25 years with the diagnosis of cerebral palsy and mental retardation. Case 6 and Case 4 were misdiagnosed and followed-up as temporal lobe epilepsy for years. Case 8 was diagnosed as anxiety and panic attack disorder and none of the routine
EEG examinations revealed any abnormality. Evaluation with detailed MRI was helpful in the proper diagnosis in all presented cases. Therefore, it is important firstly to know and call to mind PNH, and then to examine the periventricular walls, especially with high resolution MRI, in searching the cause of epilepsy.

Incidence of complex partial seizures with several clinical symptoms suggesting mesial or neocortical temporal and parieto-occipital onset was striking. Limbic and visual auras were recorded in two patients. Three patients presented with focal motor seizures suggesting central or frontal origin. Three patients tended to have bilateral independent temporal epileptic abnormalities. Isolated spike activity was recorded in two patients. 3-3.5cyc/sec generalized spike–wave activity mimicking primary generalized epilepsy was detected in two cases. Raymond et al. (18) first mentioned generalized discharges mimicking primary generalized epilepsy in 1994 in three of the 13 PNH patients in their series. In 1995, Dubeau et al. (17) mentioned the same activity in one patient. We evaluated the characteristics of these previously reported four cases; nodules were located bilaterally asymmetric in three of them, as in our cases, and unilateral in the remaining one. However, Battaglia et al. (10) in 1997 reported that EEG abnormalities were always focal in their cases, unlike previously described ones. In 14 cases of Battaglia’s series, PNH was associated with another structural abnormality of the brain. The remaining three cases were in simple PNH form, but the location and type of PNH was bilateral in only one of them. In five of the six patients with 3-3.5 Hz generalized spike-wave activity (including ours), nodules were located bilaterally and asymmetric.

Bilateral diffuse symmetrical form of PNH has been reported more than bilateral asymmetrical and unilateral forms in the literature. The patients with bilateral asymmetrical PNH were thought to share similar features with patients with bilateral symmetrical or unilateral PNH (16). Most of the reported patients with bilateral asymmetrical PNH in the literature have associated structural abnormalities of the posterior fossa, and a positive family history for epilepsy, as in the case of bilateral symmetrical PNH, but the localization of nodules are more pronounced in the paratrigonal regions, as in unilateral PNH. Although clear female predominance and frequent familial occurrence in bilateral, symmetrical, and diffuse cases have been reported, unilateral and bilateral asymmetric cases are not associated with sex prevalence. In accord with the previously reported bilateral asymmetric PNH cases, two of the six presented cases in this study were female.

Recent human and experimental studies have shown neuronal connections between heterotopic nodules and between nodules and cortex (6). These studies have suggested that intranodular neurons have altered excitatory or inhibitory transmission. Hannan et al. (20) showed, in surgical specimens obtained from epileptic children with nodular heterotopia, that the heterotopia, either subcortical or subependymal, had sparse connections with each other and with other parts of the hemisphere, including the cortex (21). Aghakhani et al. (22) analyzed the respective roles of heterotopia, temporal and extra-temporal neocortex and mesial temporal lobe structures in the generation of epileptic activity in a relatively large series of patients with PNH and focal epilepsy. They confirmed that nodules of heterotopic grey matter can generate both normal and abnormal electrical activity (23). Bilateral multiple or contiguous PNH were often associated with widespread epileptogenesis, where classical surgical approaches (temporal resection) are unlikely to be effective (24). Aghakhani et al. (22) used amygdalo-hippocampectomy in two patients (outcome: Engel class Ia and III), amygdalo-hippocampectomy plus removal of an adjacent heterotopia in two patients (class Ia), resection of two contiguous nodules plus a small rim of overlying occipital cortex in one patient (class Ia) and hippocampectomy plus removal of three adjacent heterotopia in one patient (class IV) as the surgical approaches. In unilateral nodules, they suggested that investigation by stereo-EEG may indicate a focal reseсtion, and a good outcome may be expected (Engel class I). In this study, there were two patients with bilateral noncontiguous asymmetric nodules and they were the most intractable ones of the operated cases (Engel class III and IV).

In 2003, d’Orsi et al. (14) compared clinical and electrophysiological findings of eight simple PNH patients with eight PNH-plus patients. PNH cases with unilateral or bilateral asymmetric localization were evaluated. They found that neurological deficits were more common and seizure frequency was higher in the PNH-plus group and drop attacks were experienced only in these patients. We recorded three patients with falling attacks similar to atonic seizures. Although the number of reported cases...
with falling attacks is so small, this finding suggests that
falling attacks is another seizure type that can be seen in
bilateral asymmetric PNH cases. It was exciting for us to
see that the clinical symptoms of one of the cases in
D’Orsi’s series were similar with those of Case 5: facial
dysmorphism, small penis and undescended testes,
hypoplastic distal and middle phalanges, obesity, mental
retardation and epilepsy.

Generalized tonic-clonic seizures occurred during
the early phases of epilepsy in five patients in our study,
and were completely controlled by treatment in all except
one. However, complex partial seizures were mainly
resistant to therapy. The oldest patient of published cases
is presented here, at 59 years of age; he is quite well
despite the intractable focal seizures. Surprisingly, two
patients became seizure-free.

In conclusion, patients with bilateral PNHs have
variable clinical features, EEG findings and extension of
the heterotopic nodules. These patients may be
misdiagnosed as having idiopathic generalized epilepsy,
temporal lobe epilepsy or even psychogenic nonepileptic
seizures without high quality MRI because of the
misleading seizure semiology and interictal-ictal EEG
findings. Seizures are usually drug-resistant but the
patients who have diffuse symmetric or asymmetric
contiguous heterotopic nodules may have good
prognosis. Studies taking into account the type,
multiplicity and localization of the nodules will be more
helpful in explaining the clinical characteristics and follow-
up strategies in patients with PNH.

References
1. Pearlman AL, Faust PL, Hatten ME, Brunstrom JE. New directions
   for neuronal migration. Curr Opin Neurobiol 1998; 8(1): 845-
2. Fox JW, Walsh CA. Periventricular heterotopia and the genetics of
   neuronal migration in the cerebral cortex. Am J Hum Genet
3. Pilz D, Stoodley N, Golden JA. Neuronal migration, cerebral
   cortical development, and cerebral cortical anomalies. J
4. Guerrini R. Genetic malformations of the cerebral cortex and
5. Huttenlocher PR, Taravath S, Mojtahedi S. Periventricular
6. Eksioglu YZ, Scheffer IE, Cardenas P, Knoll, J, DiMario F, Ramsby
   G et al. Periventricular heterotopia: an X linked dominant epilepsy
   locus causing aberrant cerebral cortical development. Neuron
7. Fink JM, Dobyns WB, Guerrini R, Hirsch BA. Identification of
   Xq28 associated with bilateral periventricular nodular
   Evidence for nodular epileptogenicity and gender differences in
   periventricular nodular heterotopia. Neurology 1999; 52: 336-
   341.
9. Sheen VL, Topcu M, Berkovic S, Yalinizoglu D, Blatt I, Bodell A et
   al. Autosomal recessive form of periventricular heterotopia.
   Neurology 2003; 60(7): 1108-1112.
10. Battaglia G, Granata T, Farina L, D’Incerti L, Franceschetti S,
    Avanzini G. Periventricular nodular heterotopia: epileptogenic
11. Barkovich AJ. Magnetic resonance imaging: role in the
    understanding of cerebral malformations. Brain Dev 2002; 24:
    2-12.
    Classification system for malformations of cortical development.
    characteristics and correlation with developmental and neurologic
   et al. Clinical features and long term outcome of epilepsy in
   periventricular nodular heterotopia. Simple compared with plus
    et al. Reading impairment in the neuronal migration disorder of
    periventricular nodular heterotopia. Neurology 2005; 64(5):
    799-803.
    S et al. Periventricular nodular heterotopia: classification, epileptic
    history, and genesis of epileptic discharges. Epilepsia 2006; 47(1):
    86-97.
17. Dubeau F, Tampieri D, Lee N, Andermann E, Carpenter S, Leblanc
    R et al. Periventricular and subcortical nodular heterotopia. A


