# DRUG RESISTANT EPILEPSY DUE TO BILATERAL PERIVENTRICULAR NODULAR HETEROTOPIA. CASE REPORT

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DRUG RESISTANT EPILEPSY DUE TO BILATERAL PERIVENTRICULAR NODULAR HETEROTOPIA. CASE REPORT (Abstract): Periventricular nodular heterotopia (PNH) is among the most frequent malformations of cortical development due to disturbance in neuronal migration and is associated with intractable epilepsy. Neuronal migration disorders cause severe syndromes, including refractory epilepsy and major psychomotor development disorders. It has been demonstrating that approximately 80% of familial cases of PNH are related to FLNA mutation, gene located on the long arm of the X-chromosome inherited in a dominant fashion. A constellation of syndromes, including heterotopic nodules with intractable epilepsy, microcephaly, and severe develop-mental delay is seen in ARFGEF2 mutations, a gene located in chromosome 20 with an autosomal recessive inheritance pattern. We present a case of 18-years old patient, right-handed, without remarkable findings in personal history of childhood, with normal social and psychiatric development. At the age of 15 she was admitted in the department of Psychiatry for depression and behavioral disorder (irritability and aggressive behavior) and she was treated with selective serotonin reuptake inhibitors (this happens frequently showed a small study which revealed that EEG can be abnormal in patients with neurotic disorders. **Keywords:** PERIVENTRICULAR NODULAR HETEROTOPIA, EPILEPSY, DRUG.

Periventricular nodular heterotopia (PNH) is among the most frequent malformation of cortical development, due to disturbance in neuronal migration and is associated with intractable epilepsy.

Neuronal migration disorders cause severe syndromes, including refractory epilepsy and major psychomotor development disorders. Several of these disorders are caused by mutations in genes encoding cytoskeleton proteins.

PNH correspond to a groups of neuronal cells that didn't migrate, remaining in the subependymal region (periventricular heterotopia) or have stopped from migration, in their way towards the cortex surface (subcortical heterotopia). During first trimester of gestation, post mitotic neurons migrate along the scaffold of radial glia, to form the multi-layered cortex (1).

The prevalence of PNH in the general population is unknown, although some reports suggest that it represents 15-20% of the various forms of cortical malformations. It has been demonstrating that approximately 80% of familial cases of PNH are related to FLNA mutation, gene located on the long arm of the X-chromosome, inherited in a

dominant fashion. Heterozygous mutation in females with bilateral and symmetrical PNH is usually associated with normal intellect, with or without epilepsy. Mutations in males are thought to be lethal, usually with intrauterine death (2).

FLNA is a cytoskeleton molecule, that plays an important role in the initiation and progression of neuronal movement, in the process of migration, possibly by maintaining these cells attached to supporting cells, until they receive the signal for locomotion (2).

A constellation of syndromes, including heterotopic nodules with intractable epilepsy, microcephaly and severe developmental delay, is found in ARFGEF2 mutations, a gene located on chromosome 20, with an autosomal recessive inheritance pattern, that encodes a protein BIG2, localized along the Golgi system and recycling endosomes (3).

Other genes implicated in this disease are C6orf70 (6q27), that encodes ER-MARD protein and is responsible for bilateral PNH, FAT4 (4q28.1), which codes FAT atypical cadherin 4 and DCHS1 (11p15.4) with Dachsous cadherin-related 1 protein, responsible for posterior PNH (3).

PNH has also been associated with duplication 5p15, deletion 6q26-q27 or 7q11.33, fragile X syndrome, Williams syndrome, 22q11 microdeletion syndrome and 6q terminal deletion syndrome, demonstrating that PNH is a genetically heterogeneous disorder (2).

There are complex interactions between PNH and allo- or neocortex , which shows that PNH is part of a network, implicated in epileptogenesis and higher cortical functions. Interictal spiking activity was found in ectopic grey matter, in the cortex overlying the nodules and in the mesial temporal structures (4, 5, 6).

Tractography and functional MRI (fMRI) studies have suggested anatomic and functional connections between heterotopic nodules and overlying cortex, as well as connections between nodules and regions of contralateral cortex, other heterotopic nodules and ipsilateral cortex (3).

## CASE REPORT

We present a case of 18-years old patient, right-handed, without remarkable findings in personal history of childhood, with normal social and psychiatric development. At the age of 15, she was admitted in the department of Psychiatry for depression and behavioral disorder (irritability and aggressive behavior) and she was treated with selective serotonin reuptake inhibitors. A year later, she was admitted in the department of Neurology for recurrent seizures, manifested with rising epigastric sensation, visual hallucinations, associated with cognitive seizures such as déjà vu and oral automatisms. Despite the association of two antiepileptic drugs (Levetiracetam 2,000 mg/day and Carbamazepine 800 mg/day), the frequency of seizures remained high (1-2 seizures/ week).

The MRI with high resolution revealed hyperintense T2 and hypointense T1 bilateral bands located adjacent to the temporo-occipital horn of the lateral ventricle, with the same signal as the cortex. PET-CT scan showed left mesial temporal lobe hypometabolism (fig. 1, 2).

The patient underwent prolonged video-EEG monitoring, that detected interictal epileptiform discharges, such as sharp waves, spike-wave complexes and polispike-waves in left posterior temporal and basal-temporal region, with phase reversing over T6. There have also been recorded multiple seizures, manifested clinically with epigastric aura, speech arrest, oral automatisms, hyper motor behavior, with a duration of approximately three minutes. During the seizure, she was unresponsive, unable to carry out simple com-

mands and she had no recollection of the seizure. EEG showed a teta rhythm of 5 Hz, with low amplitude, started initially in FB1, then in T3 and T5, followed by ictal rhythm observed in FB1 and T3, with rapidly bilateral propagation (fig. 3).

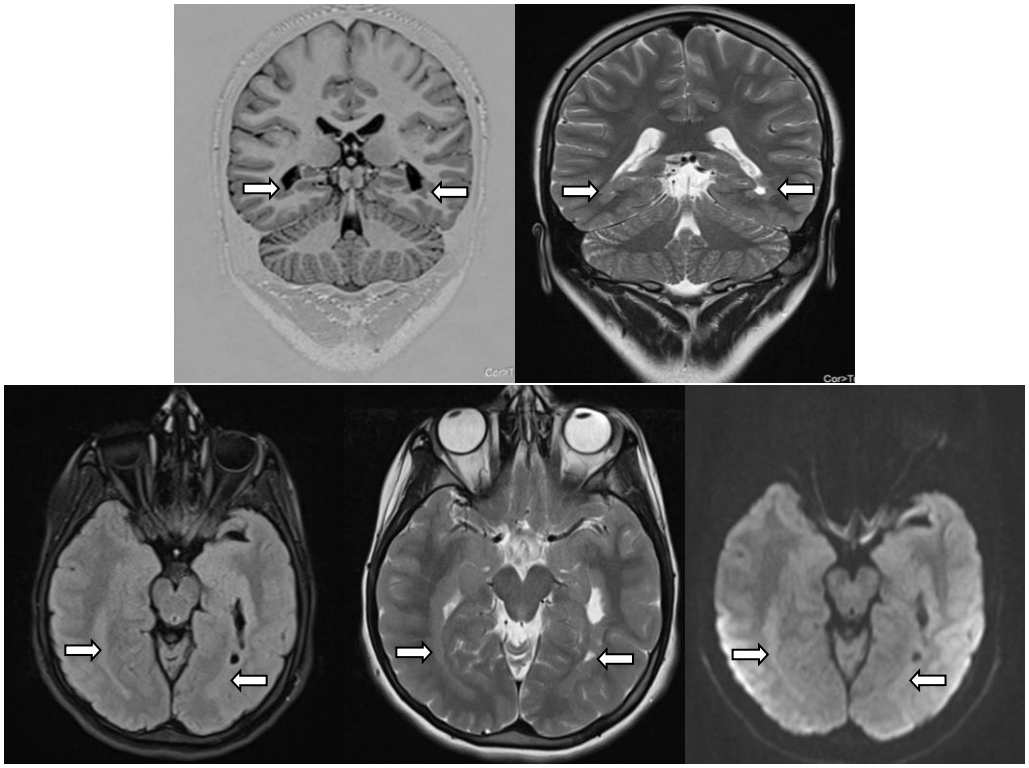

**Fig. 1.** MRI scan shows bilateral symmetrical bands of ectopic cortex adjacent the temporal-occipital horn of lateral ventricle

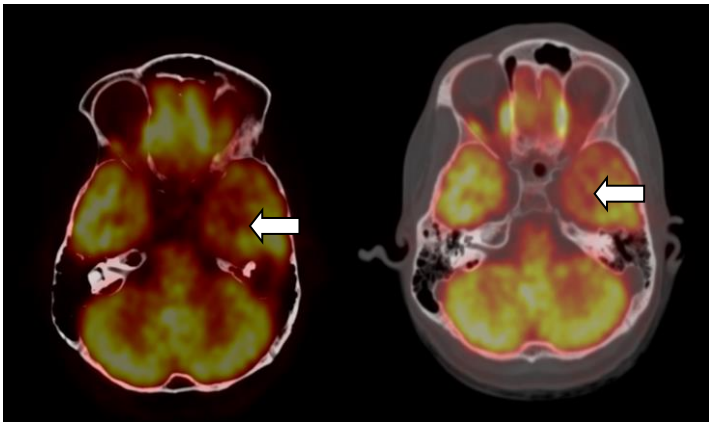

**Fig. 2.** PET-CT scan shows mesial temporal lobe hypometabolism;

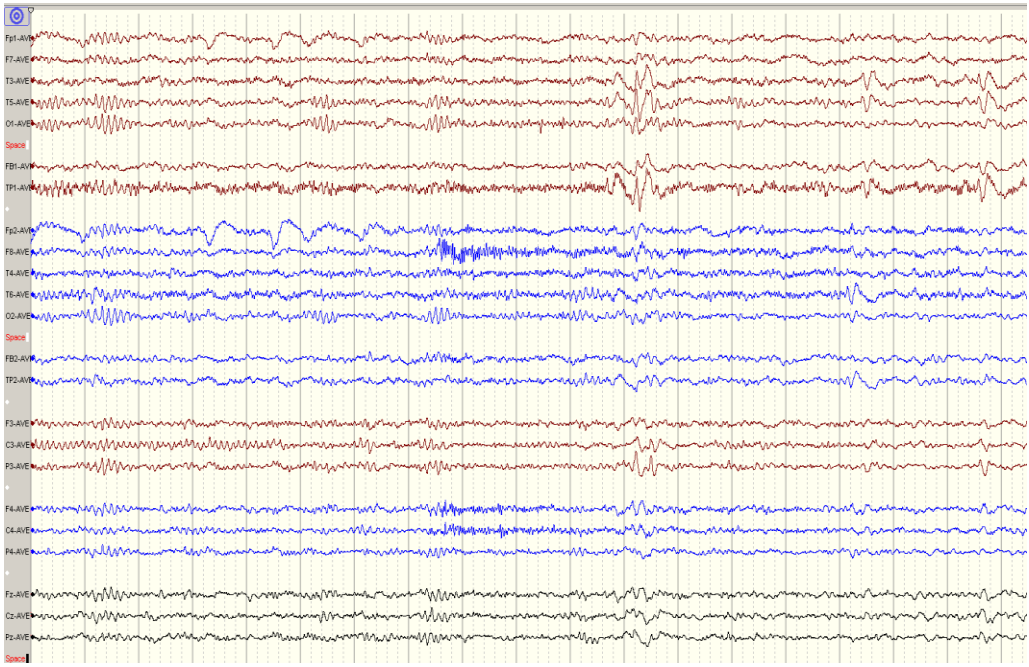


**Fig. 3.** Interictal EEG: sharp-waves with maximum electronegativity in T3, T5, FB1 and TP1

The patient was referred to an epilepsy center, in order to establish the opportunity for epilepsy surgery. Because of the large and bilateral lesions and the hypometabolism in the left mesial temporal lobe, a conservatory treatment was chosen.

The diagnosis in this case was especially imagistic by highlighting the presence of bilateral band of heterotopia adjacent to the temporo-occipital horn of the lateral ventricle as a marker of neuronal migration disorders.

## DISCUSSION

Periventricular nodular heterotopia is a malformation of cortical development, associated with intractable epilepsy. Pharmacoresistant focal epilepsies due to periventricular nodular heterotopia pose a diagnostic and therapeutic challenge, because of the need of invasive presurgical exploration of the brain and the selection of an optimal surgical approach. Invasive electrophysiological exploration in the recent studies, showed that focal epileptic activity can be correlated predominantly, either with one of the nodular heterotopia or with neocortical epileptogenic areas, distant to the periventricular nodules. Thus, using stereo – electro – encephalography (SEEG) methods, it has been showed that both heterotopic and underlying cortex are responsible for ictal onset and interictal discharges (8, 9, 11). The connectivity between the nodular heterotopia and underlying cortex was observed in almost all patients included in studies, using functional imaging studies (PET-CT scans) and diffusion tensor tractography (7).

F-fluorodeoxyglucose (FDG) positron emission tomography (PET) / computed tomography (CT) has been suggested in

patients with PNHs-related epilepsy, to assess the functional activity of ectopic neurons and to identify the epileptogenic foci. Hypometabolic regions in the brain correspond with foci of altered glucose metabolism, due to excessive neuronal and synaptic activity (10).

In our patient, PET-CT scan showed left temporal hypometabolism, demonstrating the connectivity with left heterotopia. The explanation why the activation of cortex was unilateral remains unresolved in our case, due to the lack of neuronal connectivity studies.

From the epilepsy onset, the seizures have not responded to treatment, the frequency being 1-2 per week under treatment with Carbamazepine 800 mg/day and Levetiracetam 2000 mg/day, demonstrating pharmacoresistance. Subsequently, seizures became daily (1-2 seizures/day), which is why the patient was directed to an epilepsy surgery center to determine the opportunity for surgery.

Due to the polymorphism of epileptic seizures, it was concluded that the neural network involved in the initiation and propagation of the epileptic seizures is complex, involving probably both the ectopic cortex and the cortex adjacent to heterotopia, bilaterally. Interesting is the fact that although brain injuries are large and bilateral, the EEG showed preponderant unilateral left interictal and ictal discharge, corresponding with semiological aspects, suggested left temporal lobe epilepsy.

Temporal resections in patients with periventricular nodular heterotopia and intractable focal seizures often yield poor results. In order to define the role of the heterotopic grey matter tissue in epileptogenesis for selective surgery, invasive recordings were necessary up to now. In our case, those investigations were not being performed.

Because of the presence of bilateral and large lesion size, increased operator risk and high rate of recurrence of seizures after surgery, conservative treatment was chosen. The patient is currently undergoing treatment with Levetiracetam 2,000 mg/day, Carbamazepine 1,200 mg/day and Topiramate 200 mg/day (13, 14). It would be of great interest for the patient to benefit from vagus nerve stimulation, but she refused this intervention (12).

Throughout this period, the patient managed to have good school performance, to integrate into society and to have a normal life, but in the last year she accused a decrease in concentration and memory capacity.

## CONCLUSIONS

We have presented a rare case of bilateral heterotopia, with pharmacoresistant epilepsy and psychiatric manifestation, in a young girl with normal intellect, with left temporal lobe seizures.

In those cases, the necessity of intracerebral recording and functional imaging is mandatory, to evaluate the connectivity between the heterotopia and adjacent cortex and to predict the benefit of surgery.

Because PNH is bilateral, symmetrical, in a female patient intellectually normal, the genetic test would be of great interest, suggesting the implication of FLNA mutation on X chromosome, but this test was not performed for financial reasons.

The peculiarity of this case is the onset of disease, with psychiatric manifestations and the tendency of recruitment of the left temporal cortex, despite the bilateral heterotopia.

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**NEWS**

### COULD BEHAVIOUR CHANGE AND WEIGHT LOSS BE RESTRICTED ?

It is known that Biochemical remission of type 2 diabetes in the absence of pharmacological or surgical intervention has been shown to be achievable. According to new studies, weight loss of ≥10% in the first few years after diagnosis was strongly associated with remission of Type 2 diabetes at 5 years. The most interesting is that this was achieved without intensive lifestyle interventions or extreme calorie restrictions. These results were obtained from a prospective cohort study on 867 people with newly diagnosed diabetes aged 40–69 years, which had a 5-year follow-up. These findings should inform discussions with people who have newly diagnosed type 2 diabetes as motivation towards remission of the disease without restrictive and sometimes unachievable calorie restrictions (Papakitsou I, Vougiouklakis G, Elisaf MS, Filippatos TD. Differential pharmacology and clinical utility of dapagliflozin in type 2 diabetes. *Clin Pharmacol* 2019; 11: 133-143).