Clinical and genomic findings in brain heterotopia: Report of a pediatric patient cohort from Romania

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Abstract. Brain heterotopia is a group of rare malformations with a heterogeneous phenotype, ranging from asymptomatic to a severe clinical picture (drug-resistant epilepsy, severe developmental delay). The etiology is multifactorial, including both genetic and environmental factors. In the present study, a cohort of 15 pediatric patients with brain heterotopia were investigated by clinical examination, electroencephalographic studies, brain imaging, and genomic tests. Most of the patients had epileptic seizures, often difficult to control with one antiepileptic drug; another frequent characteristic in the cohort was developmental delay or intellectual disability, in some cases associated with behavioral problems. The genomic studies revealed an interstitial 22q11.2 microduplication, an anomaly not reported previously in heterotopia patients. Comparing the cohort of the present study with that of a previous series of heterotopia patients, both adult and pediatric, similar aspects, such as the high frequency of drug-resistant epilepsy were observed as well as some differences, such as no systemic malformations and no cases with fatal evolution. The current findings add new data to existing knowledge on a rare heterogeneous disorder. The detailed clinical description, including the epilepsy phenotypes, and genomic profiles bring new insights into a group of disorders, yet to be fully understood.

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Introduction

Brain heterotopias are a rare group of congenital disorders, with an extremely variable clinical picture, ranging from asymptomatic (incidental findings) to severe, including drug-resistant epilepsy, global developmental delay, and behavior problems. Grey matter heterotopia (GMH) are cortical malformations generated by abnormal neuronal migration (1). However, disruption of other developmental processes such as neuronal progenitor proliferation and differentiation, seems to play a role in the pathogenesis (2). These disorders are characterized by a high heterogeneity of genetic anomalies and brain anatomical defects. Heterotopia can be isolated or co-exist with other brain malformation, including lissencephaly, agyria, microgyria, pachygyria, polymicrogyria, agenesis of the corpus callosum, porencephaly, schizencephaly, and agenesis of the cranial nerves (3-5). The routine clinical use of magnetic resonance imaging (MRI) of the brain has significantly increased the sensitivity of detection and the accuracy of GMH morphological description (1,6). At the same time, recent technological advances in genetics and genomics have improved the capacity to unveil the complex genetic architecture of GMH and allowed identification of numerous pathogenic variants, mostly sequence changes, associated with a neuroanatomical or neurobehavioral phenotype. A wide range of genetic defects have been reported in GMH, from single nucleotide variants to copy number variations (CNVs) and chromosomal rearrangements (translocations, large deletions, and ring chromosomes) (2,7-11). However, the pathogenesis of GMH is multifactorial, the genetic factors interacting with environmental factors in different stages of neurodevelopment (3,5).

Several forms of heterotopia have been described: band heterotopia (or double cortex), subcortical heterotopia, and periventricular (subependymal) heterotopia (1,12).

Thus, subcortical band heterotopia (SBH) caused by the mutation of the doublecortin (*DCX*) gene on X chromosome, is present mostly in female patients and predominantly affects anterior brain regions. Females with this anomaly usually have developmental delay and epilepsy, but the severity of the symptoms can vary from mild to severe depending on the thickness of the heterotopia (13). Epileptic seizures can be generalized or focal or both, 65% of these patients having a drug-resistant form of epilepsy (14). The majority of male patients with *DCX* mutations present classical lissencephaly with more severe abnormalities of the anterior brain (15). By contrast, males with mosaic *DCX* mutations develop SBH. For a small number of cases autosomal-dominant mutations in the platelet activating factor acetylhydrolase 1b regulatory subunit 1 (*PAFAH1B1*) gene have been associated with SBH, the subcortical bands being localized predominantly in the parietal and occipital lobes (16). An autosomal recessive form of band heterotopia was described in patients with EMAP-like 1 (*EML1*) gene mutations (17). Patients with band heterotopia present, typically, with focal or generalized epileptic seizures, which evolve towards a severe, drug-resistant epilepsy, with different types of seizures (focal, generalized tonic clonic or tonic or atonic seizures) (18).

Periventricular nodular heterotopia (PVNH) is the most common type of heterotopia, with an X-linked or autosomal inheritance. The most common clinical feature is epilepsy (up to 80%) (13); epileptic seizures may be focal (aware or impaired awareness), generalized, or focal to bilateral tonic-clonic. Intellectual disability is a rare feature in unilateral localization (<20%) but is very common in bilateral heterotopia (up to 60%) (13). The X-linked PVNH is caused by mutations in Filamin A (*FLNA*), being reported in around 25% of sporadic cases and almost all familial forms (2,19,20). Males with *FLNA* mutations usually die pre- or perinatally; the few reported surviving males have mosaic mutations or mutations which are less detrimental for FLNA functions. Some authors reported a common association between PVNH and congenital heart malformations, such as bicuspid aortic valve and patent ductus arteriosus in cases with mutations of the *FLNA* gene (21). Chiari II malformations/myelomeningocele were also found in association with nodular heterotopia (21).

Autosomal recessive forms of PVNH have been associated with mutations in ADP-ribosylation factor guanine exchange factor 2 (*ARFGEF2)*, FAT atypical cadherin 4 (*FAT4*) and Dachsous cadherin-related 1 (*DCHS1*) (2,22). Heterozygous single nucleotide variants in ADP-ribosylation factor 1 (ARF1), ER membrane-associated RNA degradation (*ERMARD)*, NEDD4-like E3 ubiquitin protein ligase (*NEDD4L)* and microtubule-associated protein 1B (*MAP1B*) have been reported in autosomal-dominant PVNH (8,23,24).

Another genetic cause of grey matter heterotopia is represented by the genomic rearrangements, i.e., losses or gains of genetic material affecting genes involved in pathways regulating neuronal migration. CNVs disrupting the *FLNA* gene were reported in PVNH, the genomic rearrangements being mediated by FLNA locus architecture (20,25,26). Several well-characterized chromosomal syndromes associating heterotopia as part of the clinical picture were also reported: 5p deletion (Cri-du-chat) syndrome, 22q11.2 deletion syndrome, 1p36 deletion syndrome, 6q deletion syndrome or 7q11.23 deletion syndrome (26-28). Accurate genotype-phenotype correlations in these syndromes are difficult due to the large size of genomic imbalances and high gene content. Moreover, these genomic defects are not specifically and recurrently associated with neuronal migration disorders.

Genetic heterogeneity should be taken into consideration in the establishment of algorithm of genetic investigation; another essential element is represented by clinical description (including family history) corroborated with imagistic data and other paraclinical data.

The aim of the present study was clinical and genomic investigations in a rare disorder cohort of heterotopia pediatric patients from Romania.

Patients and methods

Patients. In total, 15 patients (6 females and 9 males, with age at last follow-up ranging from 2 months to 24 years) with GMH were included in this study. The patients were evaluated at a tertiary health care center, Department of Pediatric Neurology, 'Prof Dr. Alex. Obregia' Clinical Hospital of Psychiatry. The diagnosis of heterotopia was based on brain MRI imaging 1.5 T according to the standard protocol which included T1, T2, FLAIR, and diffusion sequences. In one case, with initial MRI interpretation of cortical dysplasia, heterotopia was confirmed after the pathology examination of the malformed tissue, removed during epilepsy surgery. Six patients were available to date for peripheral blood sampling.

Clinical methods. For all the patients, general clinical examination was performed, which included anthropometric data collection (weight, height, frontal occipital circumference), skin and/or connective tissue anomaly assessment, dysmorphological examination, neurological and psychiatric examination, psychological tests [for IQ scoring, Portage, Raven, and WISC scales; autistic feature detection, ADOS, and ADI-R; attention deficit and hyperactivity disorder (ADHD) and other behavior problems] as well as routine clinical evaluation of other organs and systems. The patients were followed up for various intervals, ranging between 1 and 23 years, except for a 2-month-old child recently admitted to The Department of Pediatric Neurology.

Genetic methods. Genomic DNA (gDNA) was isolated with PureLink™ Genomic DNA Mini kit (Thermo Fisher Scientific, Inc.) from the available peripheral blood samples according to the manufacturer's protocol. The quality of gDNA samples was assessed by spectrophotometry using Nanodrop 2000 (Thermo Fisher Scientific, Inc.). Array-based comparative genomic hybridization (array-CGH) was performed on gDNA using CytoSure Constitutional kit v3 4x180k (Oxford Gene Technology) and SurePrint G3 Human CGH Microarray kit, 4x180K (Agilent Technologies) according to the manufacturer's recommendations.

Table I. Demographic and clinical characteristics of the patients with heterotopia.

Patient	Sex	Age at first presentation	Age at last follow-up	DD/ID (degree of severity)	Behavioral problems	Epileptic seizures	Dysmorphic features	Type of heterotopia
1	Male	2 years	3 years	+ (Mild)	+ (Autism)	-	+	Left frontal nodular
	Male	5 years	6 years	-	-	+	-	Left nodular insular
3	Male	16 months	16 years	+ (Mild)	+ (ADHD)	+	-	Left occipital nodular
4	Female	6 months	2 years	-	-	+	-	Left frontal nodular
5	Male	4 years	16 years	+ (Mild)	+ (ADHD)	+	-	Right nodular periventricular
6	Female	1 months	4 years	-	-	+	-	Left nodular periventricular
7	Female	7 months	17 years	+ (Severe)	-	+	+	Left nodular periventricular
8	Female	4 months	24 years	+ (Severe)	+ (Autism)	+	-	Bilateral periventricular nodular
9	Male	16 months	3 years	+ (Mild)	-	-	+	Left nodular periventricular
10	Male	10 years	14 years	-	-	+	-	Left nodular and linear frontal
11	Male	11 years	11 years	-	-	+	-	Focal left nodular periventricular
12	Female	14 years	16 years	-	-	+	-	Bilateral periventricular nodular predominantly on the right
13	Female	2 months	5 months	+ (Mild)	-	+	+	Bilateral nodular periventricular
14	Male	15 years	17 years	-	+ (ADHD)	+	-	Right frontal nodular
15	Male	2 months	2 months	+ (Mild)	-	+	+	Band heterotopia; lissencephaly and corpus callosum agenesis

ADHD, attention deficit and hyperkinesia disorder; DD, developmental delay; ID, intellectual disability.

Detection of CNVs was performed with Cytosure Interpret Software and Agilent Cytogenomics v 5.0.2.5. CNVs were classified into five categories (benign, likely benign, variant of uncertain significance, likely pathogenic, and pathogenic) according to the American College of Medical Genetics Guidelines (29). Database interrogation was used for assessing the genomic context and gene content of CNVs (30), the frequency of CNVs in the general population (The Database of Genomic Variants, DGV, http://dgv.tcag.ca/dgv/app/home) and in various patients from the DECIPHER database (31) using UCSC Genome Browser (https://www.genome.ucsc.edu/).

Written informed consent for participation in the study and for data publication was obtained from all the patients. In addition, parents or legal guardians of the patients signed the written informed consent.

The project was approved by The Ethics Committee of our institutions (Prof. Dr. Alex. Obregia Clinical Hospital of Psychiatry, Bucharest and Victor Babes National Institute of Pathology, Bucharest).

Results

Patients and epilepsy. A total of 15 patients with heterotopia were included in the present study: 6 females and 9 males, with age at last follow-up ranging from 2 months to 24 years. The clinical characteristics of the patients are summarized in Tables I and II. Most patients (13 of 15) were referred for epileptic seizures, and only two children presented with developmental delay. Of note, 8 patients had intellectual disability or developmental delay, mild in 6 cases and severe in 2 cases. Speech was delayed in 4 patients, and 5 subjects presented behavioral problems, including autism (2 patients), and hyperkinesia with attention deficit (3 cases). Of the 15 patients, 5 patients had dysmorphic facial features, which included hypertelorism, synophrys, high forehead, malformed ears, short nasal philtrum, micrognathia, and thin lips. Association of heterotopia with other brain malformation was found in 2 of 15 patients.

Regarding the epileptic seizures, most patients had focal seizures with or without bilateral tonic-clonic seizures, with focal discharges on EEG. Most of these patients (9 patients)

Table II. Characteristics of the epileptic seizures.

Patient	Age of onset	Type of seizures	EEG	Antiepileptic drugs	Response to therapy
2	5 years	Bilateral tonic-clonic	Left temporal-occipital spike-waves discharges	Valproate, carbamazepine	+[a]
3	1.6 years	Focal impaired awareness	Left frontal-central spike-wave discharges	Valproate, lamotrigine, carbamazepine, clonazepam	-
4	6 months	Focal impaired awareness	Left frontal spike-wave discharges	Levetiracetam	+
5	4 years	Bilateral tonic-clonic; focal impaired awareness	Right frontal-central spikes-wave discharges	Valproate, topiramate, clonazepam	+
6	2 years	Bilateral tonic-clonic	Focal spikes-wave discharges	Levetiracetam	+
7	6 months	Focal impaired awareness	Left spike-wave discharges	Levetiracetam, lamotrigine, topiramate, valproate, clonazepam	-
8	4 months	Epileptic spasms, generalized tonic seizures and focal seizures	Continuous spike-wave discharges	Valproate, topiramate, clobazam	-
10	10 years	Focal to bilateral tonic-clonic	Focal left spikes	Levetiracetam	+
11	11 years	Focal seizures	Bilateral spike-wave and poly-spikes	Valproic acid, levetiracetam, clonazepam, carbamazepine	-
12	14 years	Focal seizures	Right temporal ictal activity	Oxcarbazepine, lamotrigine	-
13	2 months	Generalized and focal	No epileptiform abnormalities	Phenobarbital	+
14	15 years	Focal	Spikes and spike-wave in fronto-temporal right derivates	Carbamazepine, clobazam	+
14	First day of life	Tonic generalized and focal seizures	Hypsarrhythmia	Fenobarbital, levetiracetam	+[b]

[a]Seizure-free after epilepsy surgery; [b]The patient had a very short period of follow-up.

received more than one antiepileptic drug, in 7 cases with a good control of seizures; in 1 case the seizure control was obtained after surgical removal of the heterotopia.

None of our patients had a positive family history both for epilepsy and brain malformation.

Follow up. During the follow-up, the characteristic of seizures changed in 1 patient (patient 8, Table II) from epileptic spasms at onset (4 months of age) to tonic seizures and focal impaired awareness seizures (after the age of 2 years). A cognitive decline was noted in a patient with drug-resistant epilepsy (patient 3, Table II), with a decrease in IQ from 86 at the age of 9 years to 65 at 16 years. Patient 5 (Table I) had severe behavioral problems [attention deficit and hyperkinesia disorder (ADHD)], which preceded the first epileptic seizure; the severity of ADHD increased after epilepsy onset, even after seizure drug-control was achieved.

The screening for genomic imbalances by array-CGH was performed in 6 of 15 patients, as the first step in a multi-tiered genetic investigation algorithm. Five patients had only benign copy number variants (CNVs). An interstitial 22q11.2 microduplication was detected in one patient (patient 3, Table I). The genomic anomaly spans 2.61 Mb [arr[GRCh37]22q11.21 (18877583x2,18894835_21505417x3,21540288x2)] and includes 76 annotated genes out of which 42 are included in Online Mendelian Inheritance In Man (OMIM). The patient, a 16-year-old boy, presented drug-resistant epilepsy, mild intellectual disability, ADHD and left occipital heterotopia.

Discussion

The focus of the present study was on the clinical and genetic characteristics of a cohort of 15 pediatric patients with heterotopia, to the best of our knowledge, the first Romanian report on this condition. All 15 patients had nodular heterotopia with only one exception, an infant with a complex brain malformation, which included band heterotopia, lissencephaly and corpus callosum agenesis.

Few pediatric cohorts with heterotopia have been reported to date (21,32) with heterogeneous clinical and imagistic

presentations as well as genetic defects. As reported in previous patients, epilepsy and intellectual disability/developmental delay were the most common clinical findings in the group included in the present study. The epileptic seizures were the main clinical reason for presentation in our department. The number of antiepileptic drugs administered varied between 1 and 5 with a mean of 2 per patient. Of the 13 patients, 6 patients with epilepsy had drug-resistant seizures and 8 of the epilepsy patients were seizure-free at last follow-up; however, more than one antiepileptic drug was needed for seizure control in 3 patients and surgical intervention in 1 patient. Intellectual disability or developmental delay, which are common features reported in heterotopia (12,21,33), were present in 8 out of 15 patients, in most cases in a mild form. In addition, 5 patients presented behavioral problems, including autism and ADHD, similar with previous reports (34). Wegiel *et al* (33) found heterotopia in 4 of 13 children with autism, and Zając-Mnich *et al* (12) reported the presence of behavioral problems in 25-30% of patients with heterotopia.

Some clinical and evolution characteristics of the patients of the current study resembled more closely those of adult cohorts (19,33) and to a lesser degree the largest pediatric cohort reported by Srour *et al* (21). Thus, no systemic malformations besides those affecting the brain were detected in the present cohort and the rate of mortality was zero at last follow-up; similar data were reported for adult patients (19,35,36). In contrast, the cohort described by Srour *et al* (21) included 74% of cases with systemic malformations and a high rate of mortality in the neonatal period or childhood, mostly due to multiple congenital malformations. This may be explained by the small number of patients in the present cohort and by the differences in cohort set-up criteria (many newborns with a diagnosis of heterotopia established prenatally, in the published data).

One duplication of 22q11.2 region was detected by array-CGH in the present group, in a patient with left occipital nodular heterotopia. The 22q11.2 region is prone to genomic imbalances due to the presence of flanking blocks of low copy repeats, both deletions and duplications being reported. Deletion of 22q11.2, with a typical size of ~3 Mb or seldom of ~1.5 Mb, is responsible for the 22q11.2 deletion syndrome, formerly known as DiGeorge or velocardiofacial syndrome. The 22q11.2 deletion syndrome has a complex and variable phenotype with multiple organ and system anomalies (37), including GMH in rare patients (27,28,38). The same 22q11.2 region, when duplicated, can be responsible for 22q11.2 duplication syndrome (OMIM no. 608363). The duplication size is in most patients the typical ~3 Mb observed in the 22q11.2 deletion syndrome. However, atypical duplications, ranging from 1.5 to 6 Mb were reported. The patients with 22q11.2 duplication syndrome have a milder phenotype, compared to those with deletions of the same region, with high variability ranging from asymptomatic to severe forms. The most commonly reported features include delayed psychomotor development with learning and speech difficulties (39). However, at present, there are no published reports of patients with 22q11.2 duplication and GMH. Given the fact that the 22q11.2 imbalances (deletions only) are rarely associated with GMH, and that none of the genes in this region were specifically associated with heterotopia, the role of 22q11.2 rearrangements in heterotopia pathogenesis is difficult to assess.

The small size of the patient cohort is a limitation of the present study. However, as GMH is a rare disorder any new phenotypic and genomic data increase the knowledge regarding the clinical and biological characteristics of these diseases. With the exception of the cohort of Srour *et al* (21) with 31 patients, the remaining pediatric cohorts have less than 10 patients per study.

Future perspectives of the present study envisage increasing the patient group and expanding the genetic algorithm with mutational screening.

In conclusion, the results focused on clinical and genomic investigations on a small pediatric heterotopia cohort, consisting of 15 patients. New data on the clinical features and epilepsy phenotypes were identified. Moreover, the genomic investigation in the current patient group revealed a chromosomal anomaly not reported thus far in heterotopia patients.

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Availability of data and materials

The data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors made substantial contributions as follows: MB, SMP and AA substantially contributed to conception and design. AA, SMP, AE, MD, CI, DB, OTA, CM, AD, CS, CA, DC contributed to acquisition, analysis, and interpretation of data. MB, SMP and AA drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version for submission.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of 'Prof. Dr. Alex. Obregia' Clinical Hospital of Psychiatry, Bucharest (approval no. 32190/16.10.2019), and 'Victor Babes' National Institute of Pathology Bucharest, Romania (approval no. 68/14.09.2019). Written informed consent was obtained from all parents or legal guardians of patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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