Journal of Pediatric Sciences

Familiar periventricular nodular heterotopia in a 1year old female child

Anastasia Gkampeta, Dimitrios Cassimos, Paraskevi Argiropoulou, Efterpi Pavlidou, Evangelos Pavlou

Journal of Pediatric Sciences 2013;5:e177

How to cite this article:

Gkampeta A, Cassimos D, Argiropoulou P, Pavlidou E, Pavlou E. Familiar periventricular nodular heterotopia in a 1year old female child. Journal of Pediatric Sciences. 2013;5:e177

CASE REPORT

Familiar periventricular nodular heterotopia in a 1year old female child

Anastasia Gkampeta[1], Dimitrios Cassimos[2], Paraskevi Argiropoulou[3], Efterpi Pavlidou[1], Evangelos Pavlou[1].

[1]Second Department of Pediatrics, Aristotle University of Thessaloniki, 'AHEPA' General Hospital, [2]Department of Paediatrics, [3]Department of Radiology, Univesity General Hospital of Alexandroupolis, Democritus University of Thrace, Greece

Abstract:
Heterotopia is defined as a cluster of normal neurons in abnormal locations in the cerebral hemispheres. This neuronal migration disorder occurs during the gestation. Patients with periventricular nodular heterotopias typically demonstrate the clinical triad of localization-related epilepsy, normal intelligence and an isolated form of dyslexia affecting reading fluency. The majority of patients are female. We describe the case of a 1year old female child, with normal psychomotor development with no clinical findings and a family history of Tuberous Sclerosis Complex (TSC). The investigations for TSC was negative, while the Magnetic Resonance Imaging revealed multiple irregular periventricular nodules suggestive for bilateral periventricular nodular heterotopia. The aim of this case presentation is to describe this rare neuronal migration disorder which in some cases mimics TSC.

Keywords: *Children, MRI, Periventricular, Nodules*
Corresponding author: *Gkampeta Anastasia, St. Kyriakidi 1, Thessaloniki, 54636, Greece*
Telephone :00302310994815
Fax: 00302310993514
e-mail: anastagab@yahoo.gr

Introduction

The cerebral cortex develops from migration of primitive neuroblasts outwards from the germinal matrix starting from the 8th week of embryonic life. Disorders of neuronal migration are heterogeneous disorders of nervous system development, which can be classified according to their appearance on neuroimaging and include lissencephaly, polymicrogyria, schizencephaly, focal cortical dysgenesis and heterotopias [1]. They commonly lead to cognitive impairment, motor disability and epilepsy [2]. They arise from disruptions in the normal process of migration of neuroblasts from progenitor zones towards the developing cortical plate, during fetal brain development [1].

Many migrational disorders are associated with the presence of gray matter heterotopia, located somewhere between the periventricular region and the overlying cerebral cortex. Heterotopia is defined as a cluster of normal neurons in abnormal locations, and divided into three main groups: periventricular nodular heterotopia, subcortical heterotopia and marginal glioneural heterotopia.

We describe the case of a 1 year old female child with normal psychomotor development, with no clinical findings and investigations negative for

Tuberous Sclerosis Complex (TSC), but with a family history of TSC and periventricular nodules at the Magnetic Resonance Imaging (MRI).

Case report

A 1year old female child was hospitalized to the pediatric neurology department for further evaluation. Her mother, 28 years old, was diagnosed recently as suffering from TSC, after an episode of generalized tonic-clonic seizure, of 2-3 minutes duration, few weeks ago. The diagnostic evaluation of the mother included a brain MRI that revealed extensive periventricular nodules, suggestive of TSC (fig.1a,b). In view of the possibility that the child has inherited TSC, she was referred to our department.

The child was born at 38 weeks of gestation, after an uneventful pregnancy and a normal delivery. Her growth and development were normal. The child did not experience any seizures. We proceeded to further investigations including echocardiography (ECG), electro-encephalography (EEG) and renal ultrasound that all were normal. Despite the fact that there were no clinical signs, clinical examination and investigations were unremarkable, a brain MRI was performed. MRI revealed multiple, irregular periventricular nodules (fig.2a,b).

Considering that these multiple periventricular nodules were the only findings in a otherwise normal child and in view of how important is for a developing child to have an accurate diagnosis, we proceeded to the following actions: firstly we reviewed the literature for other causes of periventricular nodules and secondly we brought our query to the adult neurologists regarding the diagnosis of the mother. So, we proceeded with further investigation of the mother.

The mother's EEG was reported normal and MRI was characterized by visible extensive periventricular nodules, which are common in examination including intellect was normal. Examination under Wood's light was patients unremarkable and there were no stigmata of TSC with TSC. Her detailed neurological

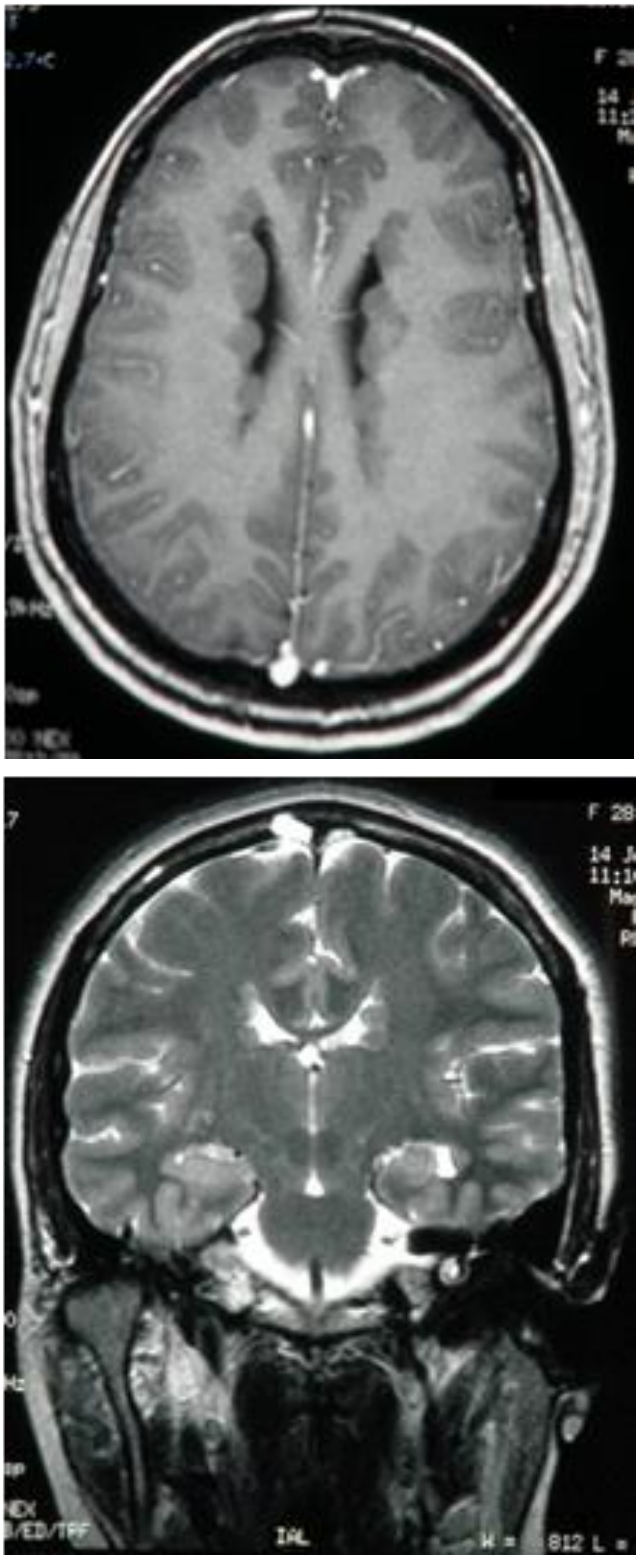
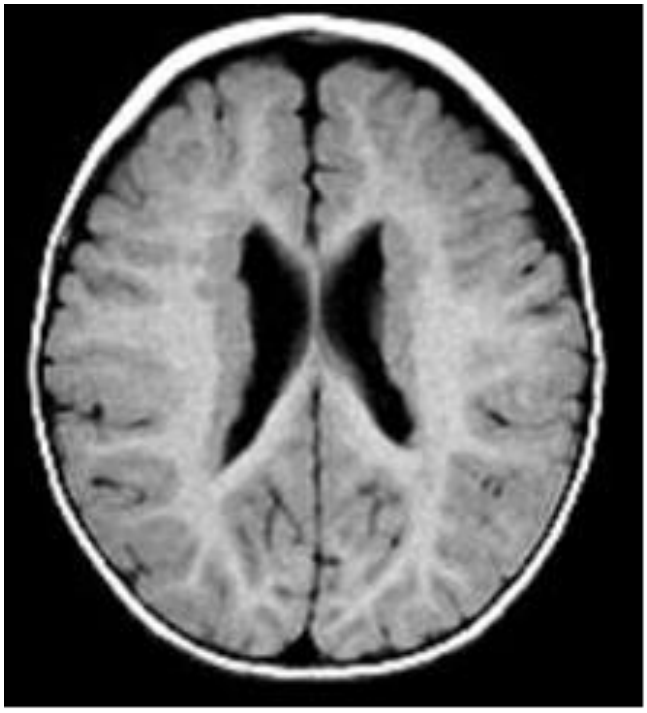


Figure 1a,b: T1 and T2 MRI images of the 28 year old mother showing periventricular nodules isointense to cortical gray matter on MRI, that did not enhance with gadolinium



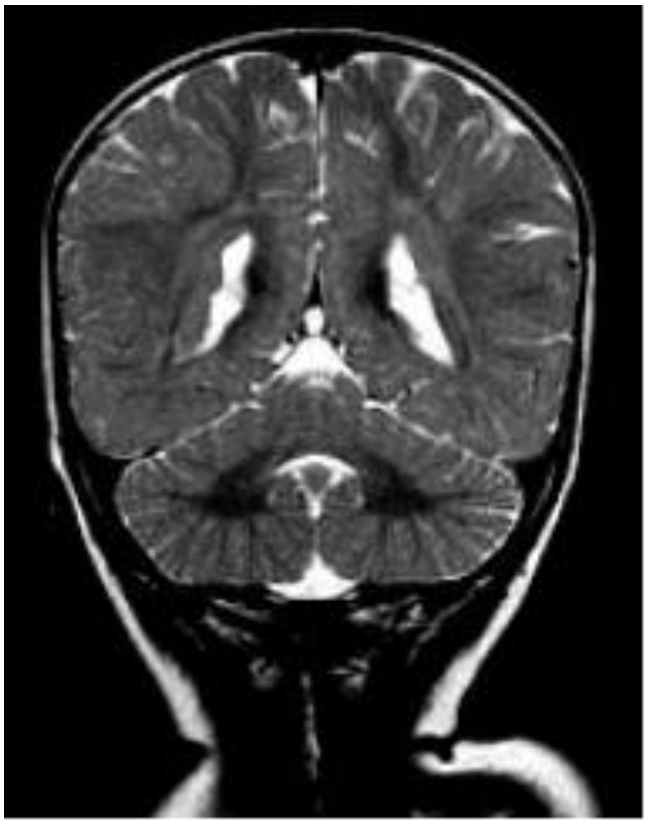


Figure 2a,b: T1 and T2 MRI images of the 1 year old child demonstrating multiple uncalcified nodules on the lateral ventricular walls (the intensity of the nodules was the same as that of the cerebral gray matter).

in her nails, teeth or optic fundi. Also, renal ultrasound, heart echocardiography and heart electrocardiography gave normal results. Taking the above under consideration, the possibility of an initial misdiagnosis regarding the mother emerged.

Discussion

Heterotopia is defined as a cluster of normal neurons in abnormal locations, and divided into three main groups: periventricular nodular heterotopia, subcortical heterotopia and marginal glioneural heterotopia. Genetically, heterotopia is related to Filamin A (FLNA) or ADP-ribosylation factor guanine exchange factor 2 (ARFGEF2) genes mutations. Familiar periventricular nodular heterotopia (FNH) is characterized by irregular nodules in the periventricular white matter, mild mental retardation and seizures. The location of the heterotopia is often bilateral and placed along lateral ventricles. The spectrum of clinical presentation is wide. Epilepsy is the main aspect. In fact approximately 90% of patients have epilepsy, which can begin at any time. Patients mainly have partial attacks with temporoparieto-occipital auras [3]. The majority of individuals with bilateral periventricular nodular heterotopia are female (X linked dominant type of inheritance) and may present with, in addition to epilepsy, mental retardation and multiple anomalies including short-gut syndrome, congenital nephrosis and frontonasal dysplasia [4,5,6]. Patients with bilateral periventricular nodular heterotopias (PNH), in which the ventricles are lined throughout with nodules of misplaced gray matter, typically demonstrate the clinical triad of localization-related epilepsy, normal intelligence and an isolated form of dyslexia affecting reading fluency [7].

In all patients the PNH are isodense and isointense to cortical gray matter on Computed Tomography (CT) and MRI, respectively, and do not enhance with gadolinium. These indent the lateral ventricles and are often continuous, involving the frontal horns, trigones, bodies and occipital horns of the lateral ventricles [8].

The diagnosis of PNH is best made with MRI and must be distinguished from the periventricular nodules in tuberous sclerosis. In tuberous sclerosis there are subependymal and cortical tubers, white matter lesions and subependymal giant cell astrocytoma. Both conditions, tuberous sclerosis and FNH, characterized by periventricular nodules on computed tomography (CT) or MRI, but are also distinguishable on clinical, radiological and genetic criteria. In PNH the subependymal lesions have the same appearance as the cortical layer, whereas subependymal nodules in TCS show variable appearance in T2 as well as T1 weighted images. The latter one may also calcify, thus giving more distinguished patterns in MRI.

TSC is an autosomal dominant, multisystem disorder characterized by the formation of hamartomas in multiple organ systems, most commonly the brain, skin, kidney, and eye. The clinical presentations of TSC result from mutations in either of two tumor suppressor genes: TSC1 (located on 9q34) or TSC2 (located on 16p13). One third of patients have TSC history in their families, whereas two thirds of all cases are caused by a "de novo" mutation or are the effect of the parental gonadal mosaicism [9].

Diagnosis of TSC may be difficult because no single symptom is present in all patients, and also the symptoms are not pathognomonic. Currently, clinical criteria defined by the Tuberous Sclerosis Consensus Conference in 1998 are used to diagnose TSC. Definite TSC is diagnosed when either 2 major features or 1 major and 2 minor features are present [10].

Brain lesions in TSC include cortical tubers, subependymal nodules, radial hypomyelinated tracts extending from subependymal area to the cortex, and subependymal giant cell astrocytomas (SEGAs). The MRI pattern of these lesions changes with the age of patients. Subependymal nodules are present in about 80% of TSC patients and they are located around the wall of the lateral and third ventricle. These lesions develop in fetal life and often degenerate or calcify during later life. Macroscopically, SENs are nodular lesions, less than 1 cm in size. They occur singly or in rows (candle guttering) and sometimes they are completely calcified [11].

In our case we described a mother and her daughter whose abnormalities on neuroimaging were originally interpreted as evidence of tuberous sclerosis. After detailed examinations of multiple organs function (heart, kidneys), wood's light examination, which were all normal, and because of the lack of clinical symptoms and the normal intelligence, we excluded the possibility of tuberous sclerosis. Both mother's and daughter's MRI showed multiple uncalcified nodules on the lateral ventricular walls. On brain MRI the intensity of the nodules was the same as that of the cerebral gray matter, suggesting heterotopia, and no other cerebral abnormalities were observed. The MRI findings of both mother and daughter were more compatible with FNH. Considering that the maternal grandmother was not affected and the mother had no affected sisters, we did not perform genetic investigations of the family in order to look for mutations of the Filamin A or the ARFGEF2 gene. Moreover, we did not perform karyotyping because the clinical features of both mother and child were not compatible with those of patients with chromosomal abnormalities (such as monosomy1p36.3, trisomy 19p13.3 and 5q14.3-q15 deletion) that have been associated with periventricular heterotopia [12,13].

Conclusively, periventricular nodules are not always TSC. In pediatric practice it is fundamental to consider family history however this can be misleading as in our case. Therefore, it is also crucial to base the diagnosis to properly and thoroughly evaluated clinical findings. The identification of familiar neuronal migration disorders is important not only for accurate genetic counseling but also for the management of neurologic complications such as seizures.

References

1. Kanatani S, Tabata H, Nakajima K. Neuronal migration in cortical development. J Child Neurol. 2005;20: 274–279.
2. Sisodiya SM. Malformations of cortical development: burdens and insights from important causes of human epilepsy. Lancet Neurol. 2004;3: 29-38.
3. Leventer RJ, Guerrini R, Dobyns WB. Malformations of cortical development and epilepsy. Dialogues Clin Neurosci. 2008;10: 47–62.
4. Dobyns WB, Andermann E, Andermann F, Czapansky-Beilman D, Dubeau F, Dulac O, et al. X-linked malformations of neuronal migration. Neurology. 1996;47: 331-339.
5. Fox JW, Lamperti ED, Ekşioğlu YZ, Hong SE, Feng Y, Graham DA, et al. Mutations in filamin 1 prevent migration of cerebral cortical neurons in human periventricular heterotopia. Neuron. 1998;21:1315-1325.
6. Huttenlocher PR, Taravath S, Mojtahedi S. Periventricular heterotopia and epilepsy. Neurology. 1994;44:51-55.
7. Chang BS, Ly J, Appignani B, Bodell A, Apse KA, Ravenscroft RS, et al. Reading impairment in the neuronal migration disorder of periventricular nodular heterotopia. Neurology. 2005;64:799–803.
8. Hayden SA, Davis KA, Stears JC, Cole M. MR imaging of heterotopic gray matter. J Comput Assist Tomogr. 1987;11:878-879.
9. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet. 2008;32:657-668.
10. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol. 1998;13:624-628.
11. Baskin HJ Jr. The pathogenesis and imaging of the tuberous sclerosis complex. Pediatr Radiol. 2008;38:936-952.
12. Cardoso C, Boys A, Parrini E, Mignon-Ravix C, McMahon JM, Khantane S, et al. Periventricular heterotopia, mental retardation, and epilepsy associated with 5q14.3-q15 deletion. Neurology. 2009;72:784-792.
13. Descartes M, Mikhail FM, Franklin JC, McGrath TM, Bebin M. Monosomy1p36.3 and trisomy 19p13.3 in a child with periventricular nodular heterotopia. Pediatr Neurol. 2011;45:274-278.