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Non-syndromic Patients with Infantile Spasms and Malformations of Cortical Development: Absence of Seizures in Siblings

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ABSTRACT

Background: Parents of children with infantile spasms undergoing epilepsy surgery typically inquire about the risk of other children for a similar affliction. Here, we determined whether non-syndromic patients with infantile spasms and malformation of cortical development (MCD) have a family history of seizures, particularly in siblings.

Patients and methods: We selected 29 children with intractable infantile/epileptic spasms who underwent surgery (mean age at surgery: 4.4±3.8 years; 12 males, 17 females; age range 0.8-14.9 years). A pathological diagnosis of MCD was confirmed in all the patients. Family (including parents and siblings) history of seizures was acquired in all patients through neurology chart review/telephonic interview.

Results: Pathological diagnosis of migration disorder (n=16) and cortical dysplasia (n=9) was made in these patients. Diagnosis of hemimegalencephaly, dysembryoplastic neuroepithelial tumor (DNET), lissencephaly type1, and porencephaly was also confirmed in 4 different patients. None of the siblings in any family (total number of siblings in the group = 30) was affected by infantile spasms or other types of seizures. The maternal aunt of one patient and mother of another patient had a history of childhood seizures for short durations.

Conclusions: Our retrospective study showed that the siblings of patients with infantile spasms with MCD who underwent resective surgery have low risk for seizures. Our study suggests that de novo mutations and non-genetic or epigenetic factors are major causes of infantile spasms due to MCD.

Keywords: Infantile spasms; malformations of cortical development; family history; epilepsy surgery

BACKGROUND

Infantile spasms is a form of epilepsy characterized by clusters of brief jerks involving the neck, trunk, or extremities resulting in flexion, extension, or a combination of the two. These seizures typically arise in the first 2 years of life and are often associated with a 'hypsarrhythmic' pattern on the electroencephalogram (EEG) [1].

Both genetic and environmental causes have been implicated in infantile spasms [2]. In a study of familial epilepsy in Sweden, infantile spasms had the highest sibling standardized incidence ratio (observed vs. expected) of 10.45, suggesting a significant role of genetic mechanisms [3]. Recently, we have also reported association of various pathogenic and de novo copy number variations in patients with infantile spasms [4].

Even when the magnetic resonance imaging (MRI) scan is normal, positron emission tomography (PET) scanning of glucose metabolism provides important clues and insights into the etiology of infantile spasms. The focal and multifocal patterns indicate underlying cortical dysplasias that may or may not be apparent on MRI [5]. Malformation of cortical development (MCD), including cortical dysplasia, is a known cause of severe intractable epilepsy (including infantile spasms) and has been associated with mutations in various genes such as L1S1, DCX, ARX, RELN, and TUBA1A [7].

In our experience, many patients with infantile spasms and suspected MCD have benefitted immensely from surgical resection of the cortical focus, often achieving total seizure freedom. A common question raised by the parents of these children is whether they could potentially have another child with the same disorder. Since published studies on the familial recurrence of infantile spasms comprise a heterogeneous population (e.g., [3]), we sought to answer this question of sibling recurrence in the specific group of children with infantile spasms who had undergone cortical resection and had neuropathologically proven MCD.

METHODS

Subjects

The study group consisted of 29 children with a diagnosis of intractable infantile/epileptic spasms who underwent epilepsy surgery between 2001 and 2011 at the Children's Hospital of Michigan/Wayne State University in Detroit (mean age at surgery: 4.4±3.8 years; 12 males, 17 females; age range

0.8-14.9 years). All patients had undergone preoperative evaluation with interictal and ictal EEG recordings, MRI, and 18-fluorodeoxyglucose (FDG)-PET scanning. Subsequently, they underwent cortical resection after extensive subdural electrode placement for recording seizures, defining epileptogenic cortex, as well as mapping motor and language cortex when applicable. For the purposes of this study, we selected only those patients who showed clear evidence of MCD in histopathological examination of the resected tissues.

A pediatric neuropathologist (WK) established the diagnosis of MCD. All resected specimens were subjected to detailed histopathological evaluation following a protocol established by one of the authors (WK) as described previously [9]. Since this is a retrospective analysis, the resected brain specimens were re-reviewed by the same neuropathologist, blinded to all clinical information. MCD were classified into cortical migration disorders (band heterotopias, polymicrogyria, microdysgenesis, and increased number of white matter neurons), cortical dysplasia, dysembryoplastic neuroepithelial tumor (DNET), hemimegalencephaly, lissencephaly, and porencephaly [10, 11]. Cortical dysplasia (CD), where present, was classified according to Palmini et al., (2004). CD was classified as: i) mild malformation of cortical development (mMCD) if cortex was essentially normal with excess ectopic neurons in the molecular layer (layer I) or subcortical white matter; ii) type I if cortical disorganization and dyslamination was present without abnormal dysmorphic–cytomegalic neurons or balloon cells (type IA if only cortical disorganization without any other abnormalities or type IB if cortical disorganization was present along with immature or hypertrophic but not dysmorphic neurons); or iii) type II if there was cortical disorganization and dyslamination along with abnormal dysmorphic–cytomegalic neurons and balloon cells (type IIA if only dysmorphic–cytomegalic neurons were present without balloon cells, or type IIB if balloon cells were also present).

Family history of seizures was obtained in all patients through neurology chart review/telephonic interview. The Human Investigations Committee at Wayne State University granted permission for the retrieval and analysis of data that had been obtained clinically for these children.

RESULTS

Histopathologic Findings

All patients had a pathologic diagnosis of MCD as evaluated by the neuropathologist after surgical resection and on review of the histopathology (Table 1). Sixteen patients had the diagnosis of migratory disorder polymicrogyria=6; band heterotopias =4; heterotopias + polymicrogyria =3; increased white matter neurons=2; microdysgenesis=1). Cortical dysplasia was confirmed in 9 patients (type 1b=3; type IIa=1; type IIb=5). Diagnosis of hemimegalencephaly (n=1), DNET (n=1), lissencephaly type1 (n=1), and porencephaly (n=1) was also confirmed in 4 different patients.

Family History of Seizures

None of the siblings in any family was affected by infantile spasms (Table 1). There were a total of 30 siblings in this cohort of patients. One of these patients had a maternal aunt who'd had some seizures at a young age, which were described as blackout episodes for short periods. Onset of infantile spasms in this child was 7 months and he had a neuropathological diagnosis of cortical dysplasia type IIb (Table 1; patient #2).

The mother of another patient had a history of complex partial seizures for a short duration; these seizures were controlled by medications that were subsequently weaned off. Onset of infantile spasms in this child was 3 months and a neuropathological diagnosis of cortical migration disorder (focal band heterotopia) was made in this patient (Table 1; patient #7).

DISCUSSION

The role of genetic factors in patients with 'cryptogenic' infantile spasms is increasingly being recognized [4, 13]. Similarly, MCD themselves may have underlying genetic bases since all 3 fundamental stages of cortical development, including proliferation-apoptosis, migration, and post-migratory cortical organization, involve action of many genes (Barkovich et al., 1996). In fact, abnormal cell migration resulting in cortical dysplasia is the most common histopathological diagnosis found in patients with infantile spasms who undergo epilepsy surgery because of intractability of the seizures [14].

In the present, albeit relatively small, series of patients, there was not a single subject who had a sibling with infantile spasms (Table 1). This finding suggests a very low recurrence risk in a sibling of a child with infantile spasms and non-syndromic MCD. There are several possible explanations for this finding. Since we could not find any significant prenatal or postnatal environmental causative factors in any of these children, sporadic de novo mutations could be one of the possible reasons for a negative sibling history of seizures in these patients. It is also important to note that in one of the previous studies [3], although the standardized risk ratio (SIR= observed vs expected) was 10.45, out of 304 hospitalized infantile spasms cases, only 15 siblings had infantile spasms (1:20 ratio or 4.9 %). Assuming the same frequency in this smaller dataset (29), one would expect only 1 sibling to be affected by infantile spasms. Thus, absence of any sibling affected by infantile spasms in our study is not totally unexpected and again points towards the role of de novo mutation. It is also important to note that since infantile spasms represents an early onset reproductive lethal condition, de novo mutation seems to be the most logical explanation behind our observed findings. However, a recessive inheritance could still have been missed in these cases since our series is relatively small. A negative family history in these patients may also point towards other environmental influences or epigenetic factors that could affect the early developmental process of the brain [15].

Family history is most useful for common, highly heritable conditions with complex inheritance, but for diseases of moderate or low frequency (such as infantile spasms), family history accounts for a very tiny fraction of disease heritability [16]. Therefore, another possible explanation for lack of family history could be oligogenic inheritance. In fact, in our recent microarray study, we found some copy number variants (2q32.3, 16p11.2 and Xp22.13) that were present both in infantile spasms children and unaffected parents [4] suggesting that infantile spasms may have an oligogenic inheritance pattern.

Although in the present study family history for seizures was positive only in 2 infantile spasms patients (maternal aunt of one patient and mother of another patient), a pre-

Table 1: Demographic Profile and Histopathological Findings

Pt.	Gender	Age at surgery(y)	Histopathological finding	No. of siblings	History of seizures in siblings
1	M	4.8	Microdysgenesis	1	Negative
2	M	5.7	CD type IIb	2	Negative
3	M	0.9	CD type IIa	1	Negative
4	M	4	Polymicrogyria	2	Negative
5	F	0.9	CD type IIb	1	Negative
6	M	2.5	Increased white matter neurons	2	Negative
7	M	1.4	Focal band heterotopia	0	Negative
8	M	7.4	CD type IIb	1	Negative
9	F	1	Type 1 lissencephaly	1	Negative
10	F	11.7	Focal band heterotopia	2	Negative
11	M	14.9	CD type IIb	0	Negative
12	F	5.7	Polymicrogyria	0	Negative
13	F	2.3	CD type Ib	0	Negative
14	M	5.7	CD type Ib	1	Negative
15	M	1.3	Increased white matter neurons	1	Negative
16	F	2.3	Hemimegalencephaly	0	Negative
17	F	8.5	CD type Ib	1	Negative
18	F	3.8	Focal band heterotopia	1	Negative
19	F	1.8	Heterotopias+focal polymicrogyria	1	Negative
20	F	0.8	Heterotopias+focal polymicrogyria	1	Negative
21	F	4.6	Polymicrogyria	2	Negative
22	F	1.3	Polymicrogyria	3	Negative
23	M	7	CD type IIb	1	Negative
24	F	4.8	Heterotopias+focal polymicrogyria	0	Negative
25	F	11.2	Polymicrogyria	0	Negative
26	F	10.2	Focal band heterotopias	2	Negative
27	M	0.9	Polymicrogyria	1	Negative
28	F	1.8	Porencephalic defect	1	Negative
29	F	1.3	DNT	1	Negative

Pt.=Patient; CD = Cortical Dysplasia (cortical dysplasia was classified according to Palmini's classification); DNET= dysembryoplastic neuroepithelial tumor; No. of siblings: excludes the infantile spasms subject.

vious study from Brazil reported positive family history in at least 50% of cases (9 out of 19) [8]. While we included several types of cortical migration disorders in our study, the previous study was comprised of 19 patients (including adult patients) with pure focal cortical dysplasia defined by MRI findings. Difference in the patient population and a founder effect may account for the difference in familial risk between the previous report and our study. However, it is to be noted that out of the 19 patients in the previous report, only one patient had a first-degree relative with history of seizures. The authors did not report whether the first-degree relative was a sibling. In another eight cases, only second or third degree relatives were affected. Thus, similar to our study, this previous report also suggests a very low recurrence risk of seizure in a sibling.

Limitations of this Study

This is a retrospective analysis of patients studied over 10 years; therefore, a proper, structured, questionnaire-based telephonic interview could not be performed for all the patients.

CONCLUSIONS

Our retrospective study showed that patients with infantile spasms and non-syndromic MCD who underwent resective surgery have negative sibling history for seizures. This small study will provide some reassurance to the families of children with refractory infantile spasms and non-syndromic MCD, but, clearly, larger studies are warranted.

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None

Competing interests

The authors declare that they have no competing interests.

Author contributions

VNT participated in the formulation of the hypothesis and data analysis and wrote the first draft of the manuscript. HC participated in the design of the study, formulated the hypothesis, and substantially revised the manuscript. WK participated in the design of the study, data collection, and substantially revised the manuscript. AHMH participated in the design of the study, formulated the hypothesis, supervised the follow-up data collection, and substantially revised the manuscript.

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