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Focal cortical dysplasia is more common in boys than girls

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Abstract

Genetics and environment likely contribute to the development of medically intractable epilepsy, however, in most patients the specific combination of etiologies remains unknown. Here we undertook a multicenter retrospective cohort study of sex distribution in pediatric patients undergoing epilepsy surgery, and carried out a secondary analysis of the same population subdivided by histopathologic diagnosis. In the multicenter cohort of intractable epilepsy patients undergoing surgery regardless of etiology (n=206), 63% were boys, which is significantly more boys than expected for the general population (Fisher exact two-tailed p=0.017). Subgroup analysis found that of the 90 patients with a histopathologic diagnosis of focal cortical dysplasia, 72% were boys, giving an odds ratio (OR) of 2.5 (95% CI, 1.34 to 4.62) for male sex. None of the other etiologies had a male sex predominance. Future studies could examine the biological relevance and potential genetic and pathophysiological mechanisms of this observation.

Keywords

focal cortical dysplasia; pediatric epilepsy; epilepsy surgery; gender; sex

Introduction

Epilepsy is a common disorder affecting >1% of the population (ILAE Commission Report, 1997). Up to 30% of patients are refractory to medications and some of these patients will benefit from a surgical resection. Epilepsy surgical case series have often but not always identified a male predominance. Chung and colleagues reported that 85 of 128 (66%) patients undergoing epilepsy surgery for focal cortical dysplasia (FCD) were male (1). A multicenter study including 49 children with mesial temporal sclerosis (MTS) undergoing

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temporal lobectomy reported that 57% were male (2). Another pediatric cohort from Utah (3) undergoing surgery for intractable epilepsy of mixed location and pathology reported 59% boys. In contrast, a report from pediatric patients in Toronto (4), where 126 patients underwent temporal lobectomy for intractable epilepsy due to multiple etiologies, had a more balanced distribution of 52% boys and 48% girls. If there is a male bias in pediatric epilepsy surgery cases, it may be indicative of a genetic predisposition in the underlying etiology of the epilepsy. Alternatively there might be a societal bias on the families' or doctors' part to preferentially pursue epilepsy surgery in males.

We sought to determine whether more boys than girls underwent epilepsy surgery at four pediatric epilepsy surgery centers in the United States. We next looked at whether the sex distribution varied by histological diagnosis. Finally, we surveyed MRI-based diagnosis of FCD to determine if there was a male predominance independent of surgical management.

Methods

Multicenter retrospective cohort study of pediatric epilepsy surgery patients

De-identified data from each center [Children's Hospital Boston (CHB), Children's Hospital of Philadelphia (CHOP), Doernbecher Children's Hospital at Oregon Health and Science University (OHSU), and University of California at San Francisco (UCSF)] were gathered including age, sex, and neuropathological diagnosis of children undergoing epilepsy surgery. Data were available for the following time periods: CHB 1993–2005, CHOP 2001–2009, UCSF 2007–2009, and OHSU 2001–2009. Data were pooled to analyze the sex distribution of patients according to underlying etiology. Sex distribution analysis was based on the "Age and Sex Composition 2010" report from the US Census bureau, which reported sex distribution in the general population under the age of 19 years as 51% male and 49% female (<http://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf>).

MRI Database Search

In order to examine if sex distribution in FCD was present in a non-surgical cohort, we performed a search of the CHOP radiology database. All brain MRI reports spanning from January 2000 to May 2011 were searched for the following key words: "dysplasia," "malformation of cortical development," "focal cortical dysplasia," "cortical dysgenesis," and "dysplastic." Over 70,000 brain MRI studies were performed at CHOP during this time period, corresponding to 41,780 patients. The duplicate patients and confounding diagnoses [e.g., neurofibromatosis type 1 (NF1) with dysplastic changes] that were felt not to be FCD based on the MRI report were eliminated. The study was conducted in accordance with regulations of the Institutional Review Board at CHOP.

Data Analysis

Statistical comparisons were carried out using InStat software (Graphpad Software, La Jolla CA).

Results

More boys undergo pediatric epilepsy surgery

There was a wide range of male predominance across centers, with the lowest percentage of boys being 52% boys at CHB and the highest 75% at UCSF (Table 1). Analysis of our pediatric multi-center cohort (n=206) found more males (130 or 63%) underwent epilepsy surgery than females as compared to the general population (Table 2, Fisher exact two-tailed $p=0.017$)

Focal Cortical Dysplasia is significantly more common in boys

Subgroup analysis to determine sex distribution based on etiology of the intractable epilepsy revealed that the FCD group (n=90, 44% of the cohort) was the only subgroup showing statistically significant difference in sex distribution over expected frequencies (with 65/90, Fisher exact two-tailed $p=0.006$). In comparison, all other etiologies were not found to be significantly different between boys and girls. This included tumors (15/23, $p=0.55$), tuberous sclerosis (14/31, $p=0.80$), or “other” (36/62, $p=0.59$) (Table 3). The “other” group included hypoxic-ischemic injury, infections, and vascular abnormalities. Therefore, FCD appears to be the primary cause for the preponderance of boys in our epilepsy surgery cohort.

The prevalence and sex distribution of FCD in a pediatric MRI based cohort

There were a total of 41,780 patients that underwent brain MRI imaging for any cause at CHOP over the time period January 2000 to May 2011. Searching the CHOP brain MRI PACS database for keywords “dysplasia,” “malformation of cortical development,” “focal cortical dysplasia,” “cortical dysgenesis,” and “dysplastic” resulted in 3093 studies identified, corresponding to 1724 patients. These reports were reviewed to eliminate false positives (NF1, tumors with dysplastic changes associated with lesion) and identify patients with possible FCD (n=444) per the impression of the neuroradiologist. The sex distribution within the radiologically diagnosed possible FCD category showed a statistically significant (Fisher exact two-tailed, $p=0.02$) male predominance with 59% boys (n=262) and 41% girls (n=182) relative to the distribution of the general population. However, the sex distribution of all patients undergoing brain MRI had a male predominance of 55% boys (22,784) and 45% girls (18,996). Because of this male predominance to MRIs performed, there was no statistical difference in the sex distribution of the radiologic possible FCD category compared to the population of patients undergoing brain MRI. Using this large radiology cohort of all patients undergoing brain MRI at our institution, we determined the prevalence of possible focal cortical dysplasia, amongst 41,780 patients undergoing MRI at CHOP over the 10 years, to be 1.1%.

Discussion

We have found a preponderance of males in the group of patients with FCD diagnosed both by histopathology and MRI as compared to the population of the United States, less than 19 years of age. In our multi-center cohort, FCD was more common in males (73%), as diagnosed by histopathology, following resective surgery for medically refractory epilepsy. The incidence of MRI diagnosis of FCD was 59% male in a single site pool of ~40,000 patients undergoing brain MRIs. FCD was the most common histopathologic diagnosis in our epilepsy surgery population and was mentioned as a possible diagnosis in 1.1% of children undergoing brain MRI studies for any cause.

In pediatric epilepsy incidence studies, sex distribution varies with etiology, generalized seizures had an equivalent sex distribution or female predominance, in contrast, focal seizures were more commonly diagnosed in males (5, 6). The studies did not parse the etiology of the focal epilepsy but it could be consistent with an increased incidence of FCD. In most patients, the specific molecular etiology of FCD is not identifiable, with only rare cases having a strong genetic basis (7). In a subset of patients with FCD there is a history and histological evidence of prenatal and perinatal brain injury (8–12). The connection might partially explain a male sex bias as boys are more likely to display cerebral palsy than girls, suggesting an increased susceptibility to brain injury in males and subsequent FCD (13, 14).

A variety of morphologic, molecular marker expression changes and electrophysiological abnormalities have been identified in FCD that suggest aberrant neuronal development (15–17). These include cells that co-express glial and neuronal phenotypic markers as well as immature neuronal markers. There also is a connection between over activation of the mTOR pathway and FCD, though none of the known genes associated with mTOR pathway disorders [e.g., tuberous sclerosis 1 (*TSC1*), tuberous sclerosis 2 (*TSC2*), phosphatase and tensin homolog (*PTEN*)] are X-linked (18, 19).

Even with our expanding knowledge about FCD, there remains a lack of fundamental understanding as to the etiology. Our finding that FCD appears to be more common in males suggests, but does not prove, that an X-linked risk factor is plausible in some patients. There are a few brain malformations known to be X-linked, such as periventricular heterotopias (filamin A, *FLNA*), lissencephaly (doublecortin, *DCX*), X-linked lissencephaly with abnormal genitalia (Aristaless-Related Homeobox, X-linked, *ARX*) and X-linked perisylvian polymicrogyria.(20). In addition, there is ample literature on the X-linked intellectual disabilities and the over 92 genes that have been associated with poor cognitive development in males (21, 22). Overall, our findings bring forth the question of whether X-linked or epigenetic factors preferentially affecting males play a role in the pathophysiology of focal cortical dysplasia.

FCD has historically been divided into two distinct types, type I or II based on the presence or absence of large dysmorphic neurons (23). Recently the pathology grading system was changed to include dual pathology of FCD and mesial temporal sclerosis or tumor classified as type III (24). While we had hoped to be able to further subdivide our histopathologic diagnosis of FCD, this was not possible based on pathology reports alone. Due to multiple reports suggesting suboptimal, poorly oriented tissue as well as preceding regular use of the FCD classification system, we grouped all our patients into FCD not otherwise specified. In the future studies to assess a distinct relationship between specific types of FCD I, II A or B, and sex would be warranted.

Similar to the male bias on histopathologic diagnosis of FCD, we also found a predominance of males with suspected FCD by MRI report. However, if we took into account that more males underwent brain MRIs in our cohort during the 10-year collection period, the male predominance was no longer significant. Retrospective analysis of clinical MRI reports is not optimal for identification of FCD and future studies with prospective review of MRIs for FCD would be warranted. A prior study of 109 children with malformations of cortical development (MCD) found on MRI had 58 males and 51 females (25), though these authors were not attempting to look at sex differences in their cohort. This cohort included all forms of MCD but similar to ours was not limited to patients with epilepsy. The combination of the increased number of males with a suspected diagnosis of FCD in the MRI database relative to the general population and the male predominance only in FCD within the epilepsy surgical patients suggests that there is not a strong societal or medical bias for males to undergo epilepsy surgery. Therefore, our findings support the hypothesis that X-linked or male-predominant epigenetic factors are involved in the ontogeny of focal cortical dysplasia.

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References

1. Chung CK, Lee SK, Kim KJ. Surgical outcome of epilepsy caused by cortical dysplasia. *Epilepsia*. 2005; 46 (Suppl 1):25–9. [Comparative Study]. [PubMed: 15816975]
2. Smyth MD, Limbrick DD Jr, Ojemann JG, Zempel J, Robinson S, O'Brien DF, et al. Outcome following surgery for temporal lobe epilepsy with hippocampal involvement in preadolescent children: emphasis on mesial temporal sclerosis. *J Neurosurg*. 2007 Mar; 106(3 Suppl):205–10. [Multicenter Study]. [PubMed: 17465386]
3. Kan P, Van Orman C, Kestle JR. Outcomes after surgery for focal epilepsy in children. *Childs Nerv Syst*. 2008 May; 24(5):587–91. [Clinical Trial]. [PubMed: 18058111]
4. Benifla M, Otsubo H, Ochi A, Weiss SK, Donner EJ, Shroff M, et al. Temporal lobe surgery for intractable epilepsy in children: an analysis of outcomes in 126 children. *Neurosurgery*. 2006 Dec; 59(6):1203–13. [Clinical Trial Research Support, Non-U.S. Gov't]. discussion 13–4. [PubMed: 17277683]
5. Wirrell EC, Grossardt BR, Wong-Kissel LC, Nickels KC. Incidence and classification of new-onset epilepsy and epilepsy syndromes in children in Olmsted County, Minnesota from 1980 to 2004: a population-based study. *Epilepsy Res*. 2011 Jun; 95(1–2):110–8. [PubMed: 21482075]
6. Camfield CS, Camfield PR, Gordon K, Wirrell E, Dooley JM. Incidence of epilepsy in childhood and adolescence: a population-based study in Nova Scotia from 1977 to 1985. *Epilepsia*. 1996 Jan; 37(1):19–23. [PubMed: 8603618]
7. Strauss KA, Puffenberger EG, Huentelman MJ, Gottlieb S, Dobrin SE, Parod JM, et al. Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. *N Engl J Med*. 2006 Mar 30; 354(13):1370–7. [PubMed: 16571880]
8. Marin-Padilla M. Developmental neuropathology and impact of perinatal brain damage. III: gray matter lesions of the neocortex. *J Neuropathol Exp Neurol*. 1999 May; 58(5):407–29. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. [PubMed: 10331430]
9. Marin-Padilla M. Developmental neuropathology and impact of perinatal brain damage. II: white matter lesions of the neocortex. *J Neuropathol Exp Neurol*. 1997 Mar; 56(3):219–35. [Research Support, U.S. Gov't, P.H.S.Review]. [PubMed: 9056536]
10. Marin-Padilla M. Developmental neuropathology and impact of perinatal brain damage. I: Hemorrhagic lesions of neocortex. *J Neuropathol Exp Neurol*. 1996 Jul; 55(7):758–73. [Research Support, U.S. Gov't, P.H.S.]. [PubMed: 8965092]
11. Marin-Padilla M. Perinatal brain damage, cortical reorganization (acquired cortical dysplasias), and epilepsy. *Adv Neurol*. 2000; 84:153–72. [Research Support, U.S. Gov't, P.H.S.]. [PubMed: 11091865]
12. Marin-Padilla M, Parisi JE, Armstrong DL, Sargent SK, Kaplan JA. Shaken infant syndrome: developmental neuropathology, progressive cortical dysplasia, and epilepsy. *Acta Neuropathol*. 2002 Apr; 103(4):321–32. [Case Reports Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. [PubMed: 11904751]
13. O'Callaghan ME, MacLennan AH, Gibson CS, McMichael GL, Haan EA, Broadbent JL, et al. Epidemiologic associations with cerebral palsy. *Obstet Gynecol*. 2011 Sep; 118(3):576–82. [Research Support, Non-U.S. Gov't]. [PubMed: 21860286]
14. Westbom L, Bergstrand L, Wagner P, Nordmark E. Survival at 19 years of age in a total population of children and young people with cerebral palsy. *Dev Med Child Neurol*. 2011 Sep; 53(9):808–14. [Research Support, Non-U.S. Gov't]. [PubMed: 21745199]
15. Calcagnotto ME, Paredes MF, Tihan T, Barbaro NM, Baraban SC. Dysfunction of synaptic inhibition in epilepsy associated with focal cortical dysplasia. *J Neurosci*. 2005 Oct 19; 25(42):9649–57. [Comparative Study Research Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S.]. [PubMed: 16237169]
16. Mischel PS, Nguyen LP, Vinters HV. Cerebral cortical dysplasia associated with pediatric epilepsy. Review of neuropathologic features and proposal for a grading system. *J Neuropathol Exp Neurol*. 1995 Mar; 54(2):137–53. [Research Support, U.S. Gov't, P.H.S. Review]. [PubMed: 7876884]

17. Lamparello P, Baybis M, Pollard J, Hol EM, Eisenstat DD, Aronica E, et al. Developmental lineage of cell types in cortical dysplasia with balloon cells. *Brain*. 2007 Sep; 130(Pt 9):2267–76. [Research Support, Non-U.S. Gov't]. [PubMed: 17711980]
18. Wong M. Mammalian target of rapamycin (mTOR) activation in focal cortical dysplasia and related focal cortical malformations. *Exp Neurol*. 2011 Oct 8.
19. Crino PB. Molecular pathogenesis of focal cortical dysplasia and hemimegalencephaly. *J Child Neurol*. 2005 Apr; 20(4):330–6. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. [PubMed: 15921235]
20. Leventer RJ, Mills PL, Dobyns WB. X-linked malformations of cortical development. *Am J Med Genet*. 2000 Fall;97(3):213–20. [Review]. [PubMed: 11449490]
21. Ropers HH. Genetics of early onset cognitive impairment. *Annu Rev Genomics Hum Genet*. 2010 Sep 22;11:161–87. [Research Support, Non-U.S. Gov't Review]. [PubMed: 20822471]
22. Stevenson RE, Schwartz CE. X-linked intellectual disability: unique vulnerability of the male genome. *Dev Disabil Res Rev*. 2009; 15(4):361–8. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. [PubMed: 20014364]
23. Palmini A, Najm I, Avanzini G, Babb T, Guerrini R, Foldvary-Schaefer N, et al. Terminology and classification of the cortical dysplasias. *Neurology*. 2004 Mar 23; 62(6 Suppl 3):S2–8. [Research Support, U.S. Gov't, P.H.S. Review]. [PubMed: 15037671]
24. Blumcke I, Thom M, Aronica E, Armstrong DD, Vinters HV, Palmini A, et al. The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. *Epilepsia*. 2011 Jan; 52(1):158–74. [Comparative Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. [PubMed: 21219302]
25. Leventer RJ, Phelan EM, Coleman LT, Kean MJ, Jackson GD, Harvey AS. Clinical and imaging features of cortical malformations in childhood. *Neurology*. 1999 Sep 11; 53(4):715–22. [Research Support, Non-U.S. Gov't]. [PubMed: 10489031]

Table 1

Sex distribution of pediatric epilepsy surgery patients per center

Center	Boys	Girls	% Boys
BCH	44	40	52%
CHOP	37	14	72%
OHSU	25	14	64%
UCSF	24	8	75%
TOTAL	130	76	63%

BCH: Boston Children's Hospital,

CHOP: Children's Hospital of Philadelphia

OHSU: Oregon Health and Science University

UCSF: University of California at San Francisco

Table 2

Sex distribution in multicenter pediatric epilepsy surgery cohort

	Observed	Expected
Boys	130 (63%) **	105 (51% *)
Girls	76 (37%)	101 (49% *)
Total	206	206

* 2010 census data for US, less than 19 years of age.

** Fisher exact test two-tailed p value= 0.017

Table 3

Sex distribution of pediatric epilepsy surgery patients by histopathological diagnosis

Center	Tuberous Sclerosis		Tumors		FCD		Others	
	BOYS	GIRLS	BOYS	GIRLS	BOYS	GIRLS	BOYS	GIRLS
CHB	12	15	5	1	23	12	4	12
CHOP	0	1	1	1	26	6	10	6
OHSU	0	1	3	4	9	4	13	5
UCSF	2	0	6	2	7	3	9	3
TOTALS	14	17	15	8	65	25	36	26
Fisher exact two-tailed p value	0.80		0.55		0.006		0.59	