ORIGINAL ARTICLE

Childhood Absence Epilepsy Requiring More than One Medication for Seizure Control

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ABSTRACT: ***Introduction:*** Absence epilepsy is the most common primary generalized epilepsy syndrome encountered in pediatric practice. Treatment is pharmacologically specific and usually successful with a single medication. The objective of this study was to identify any clinical or electroencephalographic features at initial presentation in a consecutive cohort of children with absence epilepsy that may be associated with the need for a second medication. ***Methods:*** A computerized pediatric neurology database (1991-2007 inclusive) was retrospectively searched for all patients with typical absence seizures, 3 Hz spike and wave on EEG and no apparent symptomatic etiology who were over the age of two years at seizure onset with at least one year of follow-up. All such children were then divided into two groups; a) those requiring a single medication for seizure control (Group 1), and b) those requiring two medications for seizure control despite optimal management with the initial medication as determined by serum drug monitoring (Group 2). Clinical and electrographic features evident at diagnosis were then contrasted between Group 1 and 2. ***Results:*** Seventy-five children with absence seizures were initially identified with 52 meeting the study's inclusion and none of the exclusion criteria. Of these 52 children, 43 required a single medication for seizure control (Group 1), while 9 required two or more medications for seizure control (Group 2). A significant difference ($p<0.05$) was apparent between Group 1 and 2 with respect to gender (16/43 males vs 8/9 males) and mean age of diagnosis (8.19 years +/- 3.00 vs 6.06 years +/- 2.22). Age of onset of seizures, interval duration of seizures prior to treatment initiation, duration of seizures, presence of automatisms, family history, presence of co-morbid conditions and EEG findings were not found to be significantly different between the two Groups. ***Conclusions:*** Male gender and an earlier age of diagnosis is associated with the need for two medications for seizure control in children with absence epilepsy. This observation may suggest the need for more intensive early programmatic follow-up for young male children with newly diagnosed absence epilepsy to effect more rapid attainment of seizure control.

RÉSUMÉ: L'absence épileptique de l'enfance dont le contrôle nécessite plus d'un médicament. ***Introduction :*** L'absence épileptique est le syndrome épileptique généralisé primaire le plus fréquent dans la clientèle pédiatrique. Son traitement est spécifique au point de vue pharmacologique et ne requiert habituellement qu'un seul médicament. L'objectif de cette étude était d'identifier des caractéristiques cliniques ou électroencéphalographiques au moment de la consultation initiale qui sont associées à la nécessité de prescrire une bithérapie chez une cohorte d'enfants présentant un syndrome d'absence épileptique. ***Méthodes :*** Nous avons procédé à une étude rétrospective de tous les cas consécutifs de patients présentant des crises d'absence typiques, une fréquence du complexe pointe-onde à 3Hz à l'ÉEG et sans étiologie symptomatique apparente, dans une base de données informatisées de patients ayant consulté en neurologie pédiatrique entre 1991 et 2007 inclusivement. Les enfants devaient avoir plus de deux ans au moment du début des crises et avoir été suivis pendant au moins un an. Ils ont été répartis en deux groupes : a) ceux dont les crises étaient contrôlées par la prise d'un seul médicament (groupe 1); b) ceux à qui on a dû prescrire une bithérapie pour contrôler les crises, malgré un traitement optimal par le premier médicament avec taux sériques à l'appui (groupe 2). Nous avons ensuite comparé les caractéristiques cliniques et électroencéphalographiques des deux groupes au moment du diagnostic. ***Résultats :*** Soixante-quinze enfants présentant des crises d'absence ont été identifiés initialement, dont 52 satisfaisaient aux critères d'inclusion, sans critères d'exclusion. Parmi ces 52 enfants, les crises ont été contrôlées par un seul médicament chez 43 enfants (groupe 1) et 9 ont eu besoin de deux médicaments ou plus (groupe 2). La différence quant au sexe était significative ($p < 0,05$) entre les groupes 1 et 2 (16/43 garçons vs 8/9 garçons) de même que l'âge moyen au moment du diagnostic (8,19 ans ±3,00 vs 6,06 ans ± 2,22). L'âge au début des crises, le temps écoulé entre le début des crises et le début du traitement, la durée des crises, la présence d'automatismes, l'histoire familiale, la présence de comorbidités et les caractéristiques ÉEG n'étaient pas significativement différentes entre les deux groupes. ***Conclusions :*** Le sexe masculin et le jeune âge au moment du diagnostic sont associés à la nécessité de recourir à deux médicaments pour contrôler les crises chez les enfants atteints du syndrome d'absence épileptique. Selon cette observation, les jeunes garçons pourraient avoir besoin d'un suivi plus serré après le diagnostic initial afin d'obtenir plus rapidement le contrôle des crises.

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Absence seizures are characterized by an abrupt cessation of activity, change in facial expression, impairment of consciousness, eye fluttering and sometimes associated automatisms.[1] As defined by the International League Against Epilepsy (ILAE) criteria, childhood absence epilepsy is defined as typical absence seizures beginning under the age of ten, with an EEG discharge of symmetrical, synchronous spike-wave complexes, recurring regularly at a rhythm of about 3 Hz.[2] Typical absence seizures, may occur many times a day usually not surpassing 30 seconds in duration.[3] The end of the attack is as sudden as its onset, often with the child unaware of the seizure.[3] The prevalence of typical absence seizures is highest during the first decade of life and then drops dramatically.[4]

Although absence seizures are not common, accounting for less than ten percent of all seizure types, it may be the most common seizure type to go undetected.[4] Absence seizures are often overlooked, as they may be mistaken for a child's inability to remain attentive or may be confused with daydreaming.[5] Frequent seizures may result in learning difficulties that can affect academic progress. Some comorbid conditions (eg, learning disabilities, tics, ADD/ADHD) have been documented to occur with an increased frequency in children with absence epilepsy.[6]

Therapy for typical absence seizures is pharmacologically specific. Valproic Acid (Depakene®/Depakote®/Epival®) is often regarded as the drug of first choice because it permits complete control in 80% of children with typical absence seizures, and it is also effective in controlling generalized tonic-clonic seizures that can occur concurrently in 40% to 60% of children who have absence epilepsy.[5] The other drug option is Ethosuximide (Zarontin). Ethosuximide is equally effective against absence seizures but does not appear to have an appreciable effect against generalized tonic clonic seizures.[7] More recently lamotrigene has emerged as an effective treatment option.[8] If seizure control is not attained with these drugs, their combination may be more efficacious.[3] Unfortunately, there is presently insufficient data to suggest which patients may require the combination of both valproic acid and ethosuximide for seizure control.

The objective of this study was to identify children with absence epilepsy at initial assessment who may have an increased risk for sub-optimal seizure control with one medication and thus require a second medication for effective seizure control. It was hypothesized that a subset of children with typical childhood absence epilepsy requiring two medications for seizure control would correlate with certain clinical and electrographic features that can differentiate those patients who will require two medications from those only requiring one medication at the initiation of therapy.

Methods

Study Population

A comprehensive computerized database containing all patients seen in the context of a single academic pediatric neurology practice was systematically scanned for patients with childhood absence epilepsy seen during a 16 year inclusive interval (July 1991-August 2007). The local standard of practice is for all children with epilepsy to be followed by a university-hospital based child neurologist. This single practice source ensures consistency of diagnosis, evaluation, management, follow-up and data entry. Information in this database is entered at initial neurological assessment and is updated at each follow-up appointment or as results of investigations become available. Patients contained in this database have been seen in four different locales: university hospital-based outpatient clinic (together with resident house-staff), university hospital-based private office (1991-1996 only), university hospital-based neonatal neurology clinic, and suburban private consultation practice.[9]

Data Abstraction

Medical charts were then systematically retrospectively reviewed. Medical and EEG records were then examined to verify the diagnosis of childhood absence epilepsy. The diagnosis was made according to the ILAE classification scheme for epilepsy syndromes.[2] Additional features forming the study's inclusion criteria consisted of patients being two years of age or older at diagnosis and EEG findings featuring spontaneous or provoked 3 Hz spike-wave. Exclusion criteria consisted of patients without a follow-up duration of at least one year as well as those patients with suspected non-idiopathic epilepsy. Children so identified with absence epilepsy were then divided into two groups: those in whom seizure control was attained with the use of a single medication (Group 1), and those in whom two medications were ultimately required for either seizure control or partial control (Group 2). A second medication was added only if seizures persisted despite compliance with adequate amounts of the initial medication selected, with both medications continued for ongoing seizure control. Compliance was ascertained by routine serum drug-level monitoring with established therapeutic ranges utilized to individualize drug dosing.

An assortment of information was extracted and contrasted between the two groups including gender, family history, age of onset, age of diagnosis, interval duration of seizures prior to treatment initiation, type of seizures experienced (staring, automatisms, generalized tonic-clinic seizures, myoclonic seizures), EEG findings (eg, spontaneous, photic or hyper-ventilation induced 3 Hz spike/wave, presence of electrographic and clinical seizures during recording, background disturbances, focal abnormalities, polyspikes), comorbid conditions (ADD, tics, learning difficulties, migraines, behavior problems), type of school attended, anticonvulsant medication utilized, duration of treatment, and status at the patient's last follow-up.

Statistical Analysis

Student's t-tests were used to compare group means for age of onset, age of diagnosis, interval duration of seizures prior to treatment initiation, and duration of treatment. Chi-square and Fisher's Exact Test was used to search for bivariate association among gender, type of initial seizure, duration of seizures, EEG findings, and comorbid conditions with membership in either Group 1 or Group 2. A p value of .05 or less was used for statistical significance.

Results

A total of 75 individual patient cases with childhood onset absence seizures were initially identified from scanning of the

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computerized database and 52 individuals met the study's inclusion and exclusion criteria. Excluded from subsequent analysis (n = 23) were children with an age of onset under two-years-old (n = 4) and follow-up duration of under one year (n = 10). In addition, other subject exclusions included children with suspected non-idiopathic epilepsy (n = 4) and those who did not strictly fit the ILAE criteria for childhood absence epilepsy in that absences were atypical in character (n = 5).

Of the 52 patients included in the study, 43 (82.7%) required a single medication (Group 1) and nine (17.3%) required two medications (Group 2).

As shown in the Figure, the majority of patients showed 3 Hz spike-wave spontaneously or hyperventilation-induced or both. The Table shows much of the relevant data collected from the patients' electroencephalograms, family history, type of seizures experienced, typical duration of seizures, gender and status at last follow-up. All had been started on either valproic acid (n=48) or ethosuximide (n=4).

There was a high predominance of males in Group 2 (8/9; 88.9%) compared to Group 1 (16/47;37.2%) and this difference was significant with the Chi-Square analysis revealing a p value of 0.005 ($x^2 = 7.998$) and on Fisher's Exact Test a p value of .008 (2-sided). The mean age of diagnosis of absence epilepsy was also significantly different using the student *t*-test, with a mean age of 8.19 years +/- 3.00 in Group 1 and 6.06 years +/- 2.22 in Group 2, with a p value of 0.05 (t = -2.005) with equal variance assumed. The differences between the two Groups observed regarding age of onset of seizures, interval duration of seizures prior to treatment initiation, duration of actual seizures, presence of automatisms, family history, presence of co-morbid conditions, EEG findings and initial drug selected (either valproic acid or ethosuximide) were not found to be statistically significantly different. The variables of gender and age at diagnosis each remained statistically significant ($p<0.01$) subsequent to multivariate analysis.

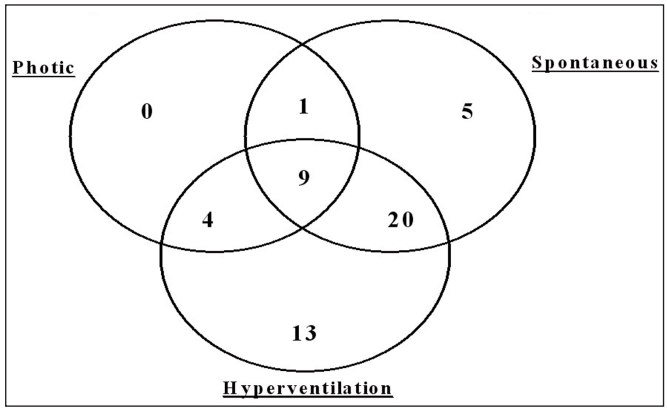

Figure: *EEG report of the 52 patients (Group 1 & 2) showing a generalized spike/wave discharge at three cycles per second spontaneously, through photic stimulation and hyperventilation.*

Table: Frequencies of all 52 patients

		Frequency
Family history of epilepsy present	Yes	28 (53.8%)
	No	24 (46.2%)
Presence of febrile seizures (Both atypical and typical)	Yes	6 (11.5%)
	No	46 (88.5%)
Seizures present as staring with automatisms (not including eye movements)	Yes	25 (48.1%)
	No	27 (51.9%)
Successful control of seizures using monotherapy	Yes	43 (82.7%)
	No	9 (17.3%)
Typical duration of seizures	Under 15 seconds	40 (76.9%)
	Over 15 seconds	12 (23.1%)
EEG background disturbance	Normal	45 (86.5%)
	Focal & general	7 (13.5%)
Gender	Males	24 (46.2%)
	Females	28 (53.8%)
Status at last follow-up	Off medication	35 (67.3%)
	Single medication controlled	12 (23.1%)
	Two medications controlled	5 (9.6%)

Discussion

Epidemiologically, typical childhood absence epilepsy affects girls more commonly than it affects boys in a 60-to-40% ratio.[3,5] This is consistent with the gender distribution observed in Group 1 (62.8% females). However, this trend does not remain true when referring to children who require two medications to control their absence attacks (Group 2). It has been shown in this report that there is a higher risk in males for sub-optimal seizure control with one medication and they will more often require a second medication for seizure control. As well, children diagnosed with absence epilepsy at a younger age (a mean difference of over two years in this study) showed an increased risk for sub-optimal seizure control with one medication

The pathogenesis of absence epilepsy is still not fully identified. What is known about absence epilepsy pathogenesis is that there are intrinsic properties of the thalamic neurons that give them the ability to release or preserve oscillatory, low-frequency neuronal discharges, in the thalamo-cortical feedback circuit. The pathogenesis involves GABA receptors in the regulation of membrane calcium channels, as well as genetically-induced changes.[10] There is no research to date explaining why gender or age may play a role in the relative effectiveness of the

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antiepileptic drugs as noted in our study. Furthermore, one study suggests that there are no differences in the binding characteristics of valproic acid to serum proteins between males and females or younger and older patients.[11]

A study by Wirrell and colleagues concluded that there was no correlation between success of initial antiepileptic therapy and gender, age at seizure onset or treatment onset, pubertal status at seizure onset, absence status, perinatal complications, cognitive difficulties, family history of seizures in first-degree relatives, neurological examination findings, or EEG findings.[12] Contrarily, in this study, a correlation was found between success of initial antiepileptic therapy, gender and age of diagnosis. Many more patients in the Wirrell study were unsuccessful in controlling their absence seizures with monotherapy (40%), perhaps due to their inclusion of far more absence epilepsy patients who experienced generalized clonic-tonic seizures (40%) and the diverse medications selected for therapy intervention used by the physicians in that particular study reflecting a diversity of practice approaches.[12]

The same study by Wirrell found that remission was significantly more likely in cases in which initial antiepileptic drug treatment was successful than in cases in which initial antiepileptic drug treatment had failed.[12] That study also suggested that patients who had generalized tonic-clonic seizures prior to treatment had less success with controlling their absence seizures.[12] Another study found that; "poor initial response to treatment, myoclonic jerks or generalized tonic-clonic seizures before or during the active phase of absences and photo-sensitivity are associated with unfavorable prognosis".[13] Unfortunately, these findings could not be validated in this report as there was not a sufficient number of patients in Group 2 that had undergone over two years of treatment (the minimal amount of time required to try to discontinue treatment) and there was not a sufficient number of patients in either group who had experienced generalized tonic-clonic seizures prior to treatment intervention.

Although control of the typical absence attacks themselves is eventually attained in about 90% of cases,[3] there has not been enough documented research to support the identification of predicting factors in patients in whom seizure control is sub-optimal with a single appropriate medication. Successful distinction of the subgroup of typical childhood absence epilepsy requiring two medications for control would ideally provide treating physicians with the capability to identify this subgroup at the time of initial diagnosis. Identification of predisposing factors for this subgroup of typical childhood absence epilepsy will reduce the duration of possibly ineffective treatment, thus lessening the burden of this particular epilepsy. Since even brief generalized spike-and-wave discharges and their resulting absences can affect cognitive function, it is therefore important to begin proper and efficacious drug therapy as soon as the diagnosis is assured.[14] This will undoubtedly benefit the patients' quality of life, as determining the need for an additional medication is frequently a time-intensive process. Furthermore, the establishment of such a subgroup based on specific predisposing factors also may suggest the need for further research leading to a clearer understanding of the pathogenesis and management of this disorder.

While our study possess limitations due to its retrospective design and small number of individuals requiring two medications for seizure control, it has been shown in this report that younger boys can be identified at initial assessment as having an increased risk for sub-optimal seizure control with one medication and appear to be more at risk to require a second medication. This observation requires prospective validation on a larger number of children and may suggest the need for more intensive early programmatic follow-up for young males with newly diagnosed absence epilepsy to effect more rapid attainment of seizure control. These observations may also provide insights into pathogenesis and variable pharmacologic responsiveness in this common childhood epilepsy syndrome.

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