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Risk and Correlates of Autism Spectrum Disorder in Children with Epilepsy: a Community-Based Study

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Abstract

The prevalence of autism spectrum disorders for children with epilepsy in the general population is unknown. In a prospective community-based study of newly diagnosed childhood epilepsy, autism spectrum disorder was determined from parental interviews, medical records and expert review by a child psychiatrist. Twenty-eight (5%) participants had autism spectrum disorders. West syndrome (prevalence ratio =4.53, $p=0.002$), and intellectual impairment (prevalence ratio=4.34, $p=0.002$), were independently associated with autism spectrum disorder. Absent West syndrome, male gender was associated with autism spectrum disorder (prevalence ratio=3.71, $p=0.02$). For participants with overall normal cognitive abilities, 2.2% had autism spectrum disorder which is substantially higher than estimates from the general population (0.5-0.9%). In addition to West syndrome, which has repeatedly been shown to have a special relationship with autism spectrum disorder, the most important determinants of autism spectrum disorder in the general population (intellectual impairment and male sex) are also important in young people with epilepsy.

Keywords

Autistic Spectrum Disorders; Epilepsy; Epidemiology

Introduction

Autism spectrum disorder refers to a group of developmental disorders characterized by a wide range of impairments in social and communicative abilities, stereotyped behaviors, and restricted range of interests with onset of initial symptoms present prior to three years of age¹. The term autism spectrum disorder is used to include children with autistic disorder, Asperger disorder and those with Pervasive Developmental Disorders-not-otherwise-

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Author Contributions:

Dr. Berg is the principle investigator of the study, designed the analysis, performed the analysis, and drafted the first draft of the manuscript. Dr. Plioplys reviewed clinical data on cases and made a determination regarding the likely diagnosis of autism spectrum disorder and reviewed and revised drafts of the manuscript. Dr. Tuchman provided advice that assisted in guiding the analysis, drafted sections of the manuscript, and reviewed and revised the manuscript.

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specified 2. The epilepsies are also a heterogeneous group of disorders and similarly to autism spectrum disorder with multiple etiologies, a wide range of symptoms, and complex associations with cognitive and behavioral difficulties³. In its benchmarks for epilepsy research, the National Institute of Neurological Disorders and Stroke emphasizes the importance of understanding these social, cognitive, and behavioral (including autism spectrum disorder) problems associated with the epilepsies⁴.

Despite decades of recognition that autism spectrum disorder commonly co-occurs with epilepsy, the magnitude and nature of the association between the epilepsies and the autism spectrum disorder remain poorly understood⁵. Based on a meta-analysis, the prevalence of epilepsy in people with autism spectrum disorder was estimated to be 8% in the absence of intellectual disability and 20% in those with intellectual disability⁶. Children already diagnosed with autism spectrum disorder have a high risk of subsequently developing epilepsy, especially in the presence of significant intellectual impairment⁷. Relative to the study of epilepsy in autism spectrum disorder, there are few studies that have attempted to address the prevalence and risk factors for autism spectrum disorder in people with epilepsy.

In series of children with epilepsy and moderate to severe intellectual impairment, a high prevalence of autism spectrum disorder has been reported^{8,9}. In one prospective study of children with onset of epilepsy in the first year of life a large proportion of children developed autism spectrum disorder overall (14%), particularly those with West syndrome (46%) and whose seizures were associated with brain insults (69%)¹⁰. In a recent retrospective study of a prevalent sample of individuals identified in a pediatric neurology clinic and with onset of epilepsy up through 18 years of age, the investigators found 15% of patients met Diagnostic and Statistical Manual criteria for autism spectrum disorder¹¹.

Providing an estimate of the overall risk in the population for young people with epilepsy and identifying the main correlates of that risk would be beneficial for planning services, targeting those at highest risk, providing clues to factors that may explain any association between autism spectrum disorder and epilepsy, and providing estimates for the frequency of between autism spectrum disorder and its correlates that would be needed in designing future studies and shed further light on the nature of this association. The purposes of this study were to estimate the prevalence of ASD in a representative, prospectively identified, community-based cohort of children with epilepsy and provide information about the main factors associated with ASD in this context.

Methods

Data are from a community-based prospective long-term follow-up study of children enrolled when first diagnosed with epilepsy by pediatric neurologists throughout the state of Connecticut from 1993-1997. Details of the recruitment procedures and of the cohort have been described previously¹². When children were first enrolled in the study, parents completed a standard interview in which they responded to questions about several developmental disorders that their children might have including autism. Parents were re-interviewed at 5 and at 9 years after their child's recruitment into the study. Questions in both interviews specifically asked if the child had ever been diagnosed with or described as having autism or pervasive developmental disorder (5 and 9 year) or Asperger syndrome (9 year). Other questions addressed language disorders, developmental delay, and specific psychiatric diagnoses. Each subject's overall level of cognitive function designated as either within the normal range (estimated $IQ \geq 80$) or impaired ($IQ < 80$). Level of cognitive function was estimated based on the treating neurologist's assessment, special education reports, clinical neuropsychological assessments and research cognitive evaluations¹³.

To ensure accuracy and validity of the parental reports, we reviewed all information available for children whose parents had endorsed autism, pervasive developmental disorder, or Asperger syndrome on any interview or for whom autism spectrum disorder was mentioned in the medical record. After review of all records, decisions regarding autism spectrum disorder diagnoses were made based on standard Diagnostic and Statistical Manual criteria¹⁴ by an experienced child psychiatrist (SP) with specialized expertise in diagnosis of psychiatric disorders in children with epilepsy and developmental disabilities. Particular attention was given to clinical behavioral descriptions and observations, school reports, types of special educational services provided to the child, co-morbid developmental disabilities and psychopathology, available psychological and speech/language evaluation reports. The investigators examined alternative explanations for reported autistic-like behavioral features and the clinical interpretations of the developmental and behavioral problems provided by the treating child neurologist. To ensure that we did not miss any individuals who might have undiagnosed and therefore unreported autism spectrum disorder, we also reviewed the files of all children for whom developmental delay, language or anxiety disorders were endorsed as a diagnosis or concern on any interview. Only study participants who had participated in at least one or both follow-up interviews were included in the analyses. This assured that the question regarding autism had been asked at least once after the child had reached five years of age.

All study subjects were classified as (a) definitely or probably having autism spectrum disorder according to Diagnostic and Statistical Manual criteria and (b) not having autism spectrum disorder. A third group was identified as (c) having individual autistic-like features (e.g. hand flapping, echolalia, poor eye contact) which, in the proper clinical context, might be considered as symptoms of autism spectrum disorder but which in that particular child were not. Others have made this distinction before⁹. In two children, the diagnosis of autism spectrum disorder could not be fully determined due to inadequate records. These two cases have been included in this third category (potentially positive features but not meeting criteria).

Analysis was performed in Statistical Analysis Systems (SAS Institute, Cary NC). For multivariable analysis, we used multiple logistic regression with a binary response function to reflect relative proportions or prevalence ratios¹⁵.

At the beginning of the study, all parents participated in an informed consent process and provided written consent. Children, if able, provided informed assent and were later invited to participate as adults when they reached the age of majority. The Institutional Review Boards at all involved institutions approved the procedures used in this research.

Results

Of the original 613 children enrolled in the study, 555 (90.5%) were included of whom 542 had a five year interview, 502 had a nine year interview, and 489 had both. Fifty-eight (9.5%) had neither interview and were excluded from further analysis. The excluded subjects were more likely to have age at onset <2 years (31% vs. 20%, $p=0.05$), to be intellectually impaired (41% vs. 25%, $N=0.007$), and were more likely to have died (19% vs. 1% $p<0.0001$). Five children with West syndrome were excluded by the interview criteria. West syndrome represented 9% of the excluded group and 4% of the included group ($p=0.12$). Almost all of the differences in clinical characteristics between the two groups went away when children who had died were removed from the comparisons (included vs. excluded: age <2yrs 20.0% vs 21.3% $p=0.84$; intellectually impaired 24.4% vs. 31.9%, $p=0.25$; West 4.0% vs. 6.4%, $p=0.44$).

In the included cohort, 287 (51.7%) were male. The mean age at onset of epilepsy was 5.9 years (range 1 month – 15.6 years) and the mean age at last contact was 19.9 years (range 6 to 33 years). Three-hundred thirty seven (60.7%) had received special education services or had received services through the Department of Mental Retardation or Birth-to-Three.

Figure 1 provides a breakdown of the derivation of the analyzed cohort and the diagnosis of autism spectrum disorder. A total of 56 children were identified by parent report (N=42 yes and N=8 possible) and by medical records alone (N=6) as having or possibly having autism spectrum disorder.

Based on our review of these children, 28 of them could be classified as definitely or probably having autism spectrum disorder, including 26 who were identified by parent interview and two identified through the medical records only. Of the 28 children with definite or probable autism spectrum disorder, one carried the diagnosis of confirmed Rett syndrome. Four of the 28 children had been identified as having autism spectrum disorder prior to the onset of their epilepsy at age 3.5 to 10 years. In the other 24 children, the diagnosis of autism spectrum disorder, although not necessarily the initial onset of autistic symptoms, was identified after the children had been recognized as having epilepsy.

Another 28 children, whom we did not consider to have autism spectrum disorder, were identified by the parent or medical records as having or possibly having autism spectrum disorder. Seventeen had no specific clinical evidence of autism spectrum disorder, including 13 with moderate to severe intellectual impairment. The four other children in this group had primary psychiatric or neurocognitive conditions that better explained their symptoms. An additional 11 other children exhibited autistic-like features (echolalia, hand flapping, poor eye contact). In nine of these children, the behaviors were considered better explained by other primary cognitive or behavioral conditions, and the child's overall clinical profile was not characteristic of autism spectrum disorder. In fact, specialist behavioral reports often provided a different diagnosis or specifically rejected the previously reported diagnosis of autism spectrum disorder. In the remaining two children, the diagnosis of autism spectrum disorder was suspected but available information was inadequate either to confirm or to reject the diagnosis. Reasons for not considering these children to have autism spectrum disorder are further described in appendix 1.

In the process of reviewing the behavioral descriptions in the neurological records, we also identified additional 10 children with behaviors of concern for autism spectrum disorder (e.g. hand-flapping, echolalia, poor eye contact, poor socialization) but for whom the diagnosis of autism spectrum disorder was not mentioned either by the parents or in the records (see appendix 1). No additional cases of probable or definite autism spectrum disorder were identified that had not already been reported by parents or explicitly mentioned in the medical records.

The overall prevalence of autism spectrum disorder was 5.0% (95% Confidence Interval =3.2 %, 6.9%). In participants whose cognitive function was estimated to be within the normal range ($IQ \geq 80$), the prevalence was 2.2% (95% Confidence Interval =0.8%, 3.6%), while in those with evidence of cognitive impairment ($IQ < 80$), the prevalence was 13.8% (95% Confidence Interval= 8.0%, 19.5%). All individuals with either autism spectrum disorder or autistic-like features had received special education or related services.

In the bivariate analysis (Table 1), male gender, young age at onset, $IQ < 80$, presence of an underlying structural-metabolic cause were all associated with both autism spectrum disorder and with autistic-like features. West syndrome was associated with autism spectrum disorder but, based on this table, was not associated with autistic-like features only. These

associations did not appreciably change after exclusion of the child with confirmed Rett syndrome.

All of these factors were strongly inter-related. We used multiple logistic regression to determine which factors independently correlated with autism spectrum disorder. In the multivariable analysis, we excluded the child with Rett syndrome and compared the remaining 27 children with autism spectrum disorder to the 506 with no autistic-like behaviors.

A history of West syndrome (prevalence ratio = 3.43, 95% Confidence Interval = 1.36, 8.65, $p=0.009$) and intellectual impairment (prevalence ratio = 5.08, 95% Confidence Interval = 2.15, 12.00, $p=0.0002$) were the strongest independent correlates of autism spectrum disorder. After adjustment for the first two variables, male sex was associated with a prevalence ratio of 2.22 (95% Confidence Interval 0.97, 5.07, $p=0.06$). Young age at onset and underlying cause were not significantly associated with autism spectrum disorder after adjustment for these first three factors. The original bivariate association between autism spectrum disorder and young age at onset was almost entirely explained by West syndrome.

In children with no history of West syndrome, intellectual impairment (prevalence ratio = 4.46, 95% Confidence Interval = 1.93, 11.25, $p=0.0006$) and male sex (prevalence ratio = 3.71, 95% Confidence Interval = 1.24, 11.11, $p=0.02$) were independently associated with autism spectrum disorder. Young age at onset, although associated with intellectual impairment was not associated with autism spectrum disorder in this non-West group (table 2).

We also performed analyses to determine which factors were independently associated with autistic-like features only ($N=21$). Intellectual impairment (prevalence ratio = 8.57, Confidence Interval = 4.39, 16.74, $p<0.0001$) was strongly associated with autistic-like features. After adjustment for this factor, male sex was associated with a prevalence ratio of 1.85 (95% Confidence Interval = 0.97, 3.51, $p=0.06$), and West syndrome was not associated with these features (prevalence ratio = 0.59, 95% Confidence Interval = 0.14, 2.46, $p=0.47$ after adjustment for the first two factors).

Discussion

Our findings suggest that, conservatively, ~5% (5/100) of all young people with childhood-onset epilepsy have autism spectrum disorder. This is substantially higher than the overall prevalence of autism spectrum disorder in the general population of 1/110^{16,17}.

Children with intellectual disabilities account for up to 3/4s of all children with autism spectrum disorder in the general population^{18,19}. Intellectual disability is also the primary determinant of epilepsy in children with autism spectrum disorder⁶. Our findings are certainly consistent with these observations and emphasize the relationship between impaired cognitive function and autism spectrum disorder.

In children from the general population who do not have intellectual disability, the prevalence of autism spectrum disorder as measured at age 3 years is on the order of 4/1000¹⁹. Among those in our study whose cognitive abilities were within the normal range, the proportion with autism spectrum disorder (22/1000, 95% CI = 8 to 36/1000) was slightly higher than the overall estimates from the general population of 1/110 and certainly higher than from a cognitively normal population¹⁹. These findings suggest there may be some increased risk of autism spectrum disorder in children with epilepsy even in those with overall normal cognitive function.

The relation between autism spectrum disorder and epilepsy is the focus of another literature concerning the occurrence of epilepsy in children with autism spectrum disorder^{7,20-22}. There is relatively little known about this problem from the perspective of epilepsy and specifically the proportion of all children with epilepsy who also have autism. The available studies tend to focus on selected samples: very young epilepsy patients (<1 year at onset) ¹⁰; tertiary referral clinic patients ⁸; and children already identified as intellectually disabled⁹. A recent study of over 500 individuals with childhood onset epilepsy provided an estimate of the prevalence of autism spectrum disorder in epilepsy on the order of 15%¹¹. This study included a much broader range of ages at onset and types of epilepsy than did previous studies; however, the group still represented a prevalent sample. Further, no information was provided regarding the nature of the epilepsy in the overall sample and features that distinguished those with autism spectrum disorder from those without. To the best of our knowledge, we have presented one of the only estimates of the burden or frequency of autism spectrum disorder in a prospectively identified and followed cohort of young people with childhood-onset epilepsy who are representative of epilepsy in the general community and who have been included regardless of severity of epilepsy or presence of other neurological disorders.

A recent population-based study estimated the risk of autism spectrum disorder in children with epilepsy of onset in infancy as 14% overall, 46% for West syndrome and 5% for other epilepsies. Our results for the comparable groups follow a similar pattern with autism spectrum disorder present in 10% of children with onset of epilepsy at less than two years of age and 30% in those with West syndrome.

Not surprisingly West syndrome, cognitive impairment, underlying etiology were all associated with autism spectrum disorder and also strongly inter-correlated with each other. Young age at onset of epilepsy is repeatedly associated with an increased vulnerability for cognitive impairment²³⁻²⁵, including in this cohort¹³ (also see table 2), and autism spectrum disorder is strongly correlated with intellectual disability. Despite this, we found no clear, independent association between young age at onset and autism spectrum disorder in our cohort. If young age at onset is a marker of particular brain vulnerability, then our findings suggest that the increased risk of autism spectrum disorder associated with younger age at onset of epilepsy observed in the bivariate analysis largely manifests itself in the presence of intellectual disability. Autism spectrum disorder does not seem to be a major independent consequence associated with younger age at onset of epilepsy.

Our study has several strengths as well as weaknesses. On the positive side, our cohort is representative of epilepsy in the community. The characteristics of the cohort are highly comparable to other population-based or representative samples particularly the Nova Scotia study²⁶. The Connecticut cohort was prospectively identified and followed from initial diagnosis of epilepsy. Families were contacted 3 to 4 times every year, with permission, all relevant medical records were reviewed, and two additional parent interviews were performed which included specific questions about autism spectrum disorder and related diagnoses. Sixty-percent of the entire analyzed cohort had received special education services. This entails a variety of evaluations, and while it cannot be assumed that all behavioral concerns were identified, it would be reasonable to infer that this cohort was under fairly heavy behavioral and developmental surveillance by virtue of being under the care of pediatric neurologists and by virtue of the educational and related interventions received by over half the cohort members. Information from schools, physician's notes, parents' reports, and for many, neuropsychological testing was reviewed and final decisions regarding diagnoses were made by an experienced child psychiatrist. Children included in the analysis were all old enough (≥ 6 years) that concerns about autism spectrum disorder should have been fully apparent.

Potential concerns include that a standardized screener or assessment was not used and we did not perform assessments early in life. This is true of some of the other studies as well as of national surveillance programs. In fact, autism spectrum disorder is a difficult disorder to study epidemiologically, especially in the context of a disorder such as epilepsy which has a broad range in age at onset. Good screeners usually have specific age ranges outside of which their validity is questioned. Screeners also need careful interpretation, especially in developmentally disabled children²⁷. All of the children in this cohort were under the care of pediatricians and pediatric neurologists. Over half received special education or related services. Thus the level of behavioral and cognitive surveillance in this group was relatively intensive and reflects medical and educational standards of practice in the region where the study was conducted.

Autism spectrum disorders start early in life and are life-long disorders, thus assessing study participants when they were older (>6y) should not have resulted in any true autism spectrum disorder cases having been missed, although any early “false-positives” such as childhood language disorders, may have resolved or been more accurately diagnosed by the time we considered their information.

The 58 children excluded from analysis because their parents did not participate in either the 5-year or 9-year interview were somewhat younger at onset and more likely to have intellectual disability than those included. Further, a disproportionate number of those excluded had died early in the course of their participation in the study, some before a diagnosis of autism spectrum disorder could have been reasonably made. This could raise concerns about potential bias or lack of representativeness of the analyzed cohort. Because only ~10% of the entire cohort was excluded, we can confidently say that their exclusion is unlikely to have altered our estimates by more than one or 2 patients).

Future steps in studying autism spectrum disorder in epilepsy may include testing and refining available autism spectrum disorder screening instruments in epilepsy populations, particularly in children with other neurodevelopmental disorders, and longitudinal application of such measures to determine their utility and stability over time, especially if first administered in the very young and in children during the active phase of their epilepsy. Additional investigation into the relation between autism spectrum disorder and intellectual disability in epilepsy and their relationship to aspects of brain development is needed both in laboratory models and in clinical samples.

In the meantime, our results provide an initial estimate of the prevalence of autism spectrum disorder in young people with childhood onset epilepsy and an initial assessment of the key clinical correlates of autism spectrum disorder in this group. The results further suggest that aside from West syndrome, which appears to have a very strong and specific association with autism spectrum disorder, the main risk factors for autism spectrum disorder in children with epilepsy are the same as in the general population. Even in the absence of significant cognitive compromise, however, there may still be a small increased risk of autism spectrum disorder associated with childhood onset epilepsy.

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Appendix 1: Description of children identified as having autism spectrum disorder by parents or medical records but who were excluded from the diagnosis

autism spectrum disorder was identified as a diagnosis or possible concern; however, this diagnosis was not considered by the authors' review and specific autism spectrum disorder criteria could not be identified (N=17)

(N=2) The parent indicated a questionable concern only and no definite autism spectrum disorder diagnosis. In both cases, other specific psychiatric and cognitive diagnoses were evident.

(N=12) The parent endorsed the diagnosis of autism spectrum disorder.

Nine of the children's parents endorsed the diagnosis of "pervasive developmental disorder" but not "autism" at 5 years. Of the 8 who later participated in the 9 year interview, none endorsed the diagnosis of autism at nine years. All 9 children had moderate to severe intellectual disability. There was no evidence in fairly extensive neurological records to support the diagnosis of autism spectrum disorder. This suggests that parents may have interpreted the term "pervasive developmental disorder" as meaning global developmental delay or that patients with intellectual disability often present with pervasive features in early development that later crystallize as intellectual disability only.

Three parents endorsed the diagnosis of autism spectrum disorder but a distinct other psychiatric diagnosis was provided instead by a treating physician (e.g. oppositional defiant disorder, anxiety disorder) and there was inadequate evidence to support the diagnosis of autism spectrum disorder.

(N=3) The only evidence was a questionable concern noted in the medical records without supporting clinical or diagnostic information, and the diagnosis was not endorsed by the parent.

Of these 17 children, 13 had moderate to severe intellectual disability often accompanied by vision or hearing impairment or both, and some had motor impairments as well. Of the other 4, intellectual function was in the normal to mildly impaired range, and a specific other psychiatric diagnosis or diagnosis of nonverbal learning disorder could be made.

Evaluations by psychiatrists, neuropsychologists, or service-based developmental-educational specialists were available for six of these children. In only once case was autism spectrum disorder mentioned as a possible diagnosis among others; however, the diagnosis was never confirmed nor did it carry forward.

Autism spectrum disorder was identified as a diagnosis or possible concern, and features that could be construed as relevant to autism spectrum disorder were mentioned; however, the diagnosis was not considered as applying to the child by the authors' review or by any other evaluators who saw the child (N=11)

(N=2) The parent indicated a questionable concern only. In one case, the child was severely intellectually disabled and the clinical behaviors did not represent autism spectrum disorder symptoms. .

(N=8) The parent endorsed the diagnosis of autism spectrum disorder; however, there was no evidence in the record to support the diagnosis. In one of these cases, it was not clear whether the child had autism spectrum disorder or not.

(N=1) The question of autism spectrum disorder was raised in the medical record only.

In 7 of these cases, a detailed report from a neuropsychologist or school psychologist was available in which the cognitive and behavioral profile of the child was clearly described and diagnoses were made. Autism spectrum disorder was not diagnosed in any of these evaluations nor was any child referred for further evaluation of possible autism spectrum disorder based upon the psychologist's assessment. In some instances, the report mentioned that the possibility of autism spectrum disorder had been raised by others and was then explicitly discarded. In one case, good descriptions from the treating neurologist and an account (but not actual records) of the treating psychiatrist's diagnosis were available. In the last two cases good behavioral descriptions were provided by the pediatric neurologist (one for a child with what appeared to be Rett syndrome and one for a child with some early echolalia but who later outgrew that and had no further behavioral concerns).

7 of the 11 children in this group had intellectual function in the normal to mildly impaired range. The other 4 had function in the moderately to severely impaired range.

Autism spectrum disorder was not endorsed by the parents or raised in the medical records; however, red flag behaviors for autism spectrum disorder were present or other concerns with record arose (N=10).

(N=9) In these cases, individual features such as hand-flapping, head banging, perseverative behaviors, or other such behaviors commonly associated with autism spectrum disorder were described, usually in isolation. Other available information did not suggest that the child had autism spectrum disorder.

(N=1) There were some developmental concerns; however, the medical record was too sparse to determine the nature of the concerns.

3 of these ten children had moderate intellectual disability. The others had no or mild intellectual disability.

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Figure 1.
Derivation of analyzed sample and determination of autism spectrum disorder (ASD).

Table 1

Association between autism spectrum disorder and autism spectrum disorder -like features and clinical characteristics in the children

	N (555)	No autism spectrum disorder (506, 91%)	Definite-Probable autism spectrum disorder (28, 5%)	autism spectrum disorder -like features only* (21, 4%)	P-value***
Gender					
Female	268	252 (94.0%)	9 (3.4%)	7 (2.6%)	0.07
Male	287	254 (88.5%)	19 (6.6%)	14 (4.9%)	
Age at onset					
< 2	112	93 (83.0%)	11 (9.8%)	8 (7.1%)	0.003
2-15	443	413 (93.2%)	17 (3.8%)	13 (2.9%)	
Cognitive status					
Within normal	417	402 (96.4%)	9 (2.2%)	6 (1.4%)	<0.0001
Impaired	138	104 (75.4%)	19 (13.8%)	15 (10.9%)	
West syndrome					
No	532	491 (92.3%)	21 (4.0%)	20 (3.8%)	<0.0001
Yes	23	15 (65.2%)	7 (30.4%)	1 (4.4%)	
Nature of underlying cause					
Genetic/Unknown	438	411 (93.8%)	16 (3.7%)	11 (2.5%)	<0.0001
Structural-Metabolic	117	95 (81.2%)	12 (10.3%)	10 (8.6%)	

* e.g. hand flapping, echolalia, perseverative behaviors, poor eye contact, etc which were attributable to other conditions (intellectual impairment, nonverbal learning disorder, etc).

** Diagnosis of autism spectrum disorder had already been made prior to or at the time of onset of epilepsy 4 children; three children were >5 years old at onset of epilepsy.

*** Based on chi-square test with 2 degrees of freedom

Table 2

Association between young age of onset, intellectual impairment, and autism spectrum disorder in 511 children with no history of West syndrome

Group *	Factor	N	Definite-Probable autism spectrum disorder N (%)	p-value
Overall	Onset < 2 y	82	4 (4.9%)	0.62
	Onset ≥2y	429	16 (3.7%)	
Overall	Cognition – impaired	104	11 (10.6%)	<0.0001
	Cognition – within normal	407	9 (2.2%)	
With impaired cognition	Onset < 2y	26	3 (11.5%)	0.85
	Onset ≥2y	78	8 (10.3%)	
Cognition within normal	Onset <2y	56	1 (1.8%)	0.82
	Onset ≥2y	351	8 (2.3%)	

* Subjects with autism spectrum disorder -like behaviors but not meeting criteria for autism spectrum disorder are excluded as is a child with Rett disorder.