Seizure 45 (2017) 184–188

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Diagnosis, treatment, and outcomes of infantile spasms in the Trisomy 21 population

Christopher W. Beatty[a,*], Joanna E. Wrede[a,b], Heidi K. Blume[a]

[a] Department of Neurology, University of Washington, Division of Pediatric Neurology, Seattle Children's Hospital, 4800 Sand Point Way NE, MB.7.420, Seattle, WA, 98105, USA
[b] Department of Pediatrics, Division of Pulmonary and Sleep Medicine, Seattle Children's Hospital, 4800 Sand Point Way NE, OC.7.720, Seattle, WA, 98105, USA

ARTICLE INFO

Article history:
Received 1 March 2016
Received in revised form 29 June 2016
Accepted 16 December 2016

Keywords:
Infantile spasms
Epileptic spasms
Trisomy 21
Down syndrome
West syndrome
Idiopathic infantile spasms

ABSTRACT

Purpose: To determine if there are differences in the timing of diagnosis and response to treatment between infants with infantile spasms (IS) and Trisomy 21 (T21) and those with idiopathic IS.
Method: This was a retrospective study evaluating the time from onset of IS to diagnosis, treatment of IS, time from treatment to resolution of IS, and development of epilepsy in children with T21 and IS compared to children with idiopathic IS.
Results: Thirteen children with T21 and IS were identified over a 10 year period and compared to 32 children in the control group. There was no significant difference in age of onset, time between onset and diagnosis, or acute response to treatment. However, the children with idiopathic IS were more likely to go on to develop epilepsy than those with T21 and IS (41% vs. 0, p = 0.006).
Conclusion: The children with T21 and IS were diagnosed and treated similarly to those patients with idiopathic IS. There were no significant differences in the age of onset, time between the onset and diagnosis of IS, or acute treatment response of IS between the T21 and control groups. However those with T21 and IS had a lower risk of subsequent epilepsy following IS than those with idiopathic IS. IS in the T21 population appears to be inherently different from IS of unknown etiology.

1. Introduction

Trisomy 21 (T21), or Down syndrome, affects approximately 13 out of every 10,000 children in the United States [1]. Epilepsy is a common problem in this population and affects up to 2–13% of those with T21 [2]. Infantile spasms (IS) is also a significant manifestation of epilepsy in this cohort as 2–5% of children with T21 develop the characteristic spasms and electroencephalogram (EEG) changes [3,4].

The classification of IS is difficult and various diagnostic systems have been proposed. The West Delphi Group proposed a classification of "idiopathic" (unknown etiology without other neurologic signs or symptoms), "cryptogenic" (unknown etiology but suspected symptomatic), and "symptomatic" (an identifiable cause of IS is present or an unequivocal developmental delay precedes IS) [5]. Those that fall into the category of idiopathic IS have a better chance of achieving positive outcomes with resolution of IS, lower likelihood of developing epilepsy, and higher likelihood of normal cognition than those with symptomatic IS [6,7]. Recently the International League Against Epilepsy (ILAE) has proposed a change to the categorization of these children to better reflect our understanding of the causes. Children would be categorized by the underlying etiology of their IS: structural/metabolic, genetic, or unknown etiology [8,9]. The classification of "unknown etiology" does not differentiate between idiopathic and cryptogenic IS. This distinction is important given the differences in prognosis for these two subgroups. For this reason, the West Delphi classification will be used as it is more appropriate for the focus of the current study.

First line treatment for IS is controversial. Adrenocorticotropin hormone (ACTH), high dose prednisolone, and vigabatrin have all been used as first line therapy in various studies with data suggesting that ACTH or prednisolone are superior in those children without tuberous sclerosis [10–14]. Early treatment within 30 days of spasm onset has been shown to improve outcomes, with some suggestion that a delay of a week could result in worse performance on the Vineland Adaptive Behavior Scales [6,15–18]. Data in the T21 population suggests that treatment

* Corresponding author. Fax: +1 206 987 2649.
E-mail addresses: Christopher.Beatty@seattlechildrens.org (C.W. Beatty), Joanna.Wrede@seattlechildrens.org (J.E. Wrede), Heidi.Blume@seattlechildrens.org (H.K. Blume).

http://dx.doi.org/10.1016/j.seizure.2016.12.016
1059-1311/

initiated within 2 months of onset of IS is associated with faster resolution of IS, improved development, and fewer autistic features [19].

Despite appropriate therapy, there is a risk for relapse once IS has resolved. Those children with idiopathic IS have a relapse rate of 10–20% [6,16]. The relapse rate in the T21 population was noted to be 57% in a recent study; however, the median time to treatment initiation was 3.3 months [20].

Approximately 20% of infantile spasms are categorized as idiopathic [6,12,21]. While this group is thought to have a higher likelihood of favorable outcomes than symptomatic IS; there remains a risk in this population for very poor outcomes, with many developing refractory IS, epilepsy, and/or significant intellectual disability [6,7]. In contrast, those children with T21 who develop IS appear to be very responsive to treatment with most having resolution of IS and are less likely to go on to develop epilepsy despite similar characteristics of their clinical spasms and EEGs [19,20,22].

One possibility may be that the T21 population seeks care earlier in the course of the disease process, obtains earlier treatment, and thus has faster resolution of IS given that many families of children with T21 are already familiar with the medical system and may have received anticipatory guidance with regards to the possibility of IS. The purpose of this study was to determine if IS were more quickly identified in the T21 population, using time from spasm onset to diagnosis as the primary outcome. We also examined the time from treatment to clinical and EEG resolution of IS as a secondary outcome measure.

2. Methods

We conducted a search of ICD-9 codes for all patients treated at Seattle Children's Hospital from 1/1/2003 to 10/31/2013 for infantile spasms with or without intractability (ICD-9 345.6, 345.60, 345.61). In order to be included in the study, a child had to be diagnosed with IS at Seattle Children's Hospital after 1/1/2003. IS was defined as a clinical history of spasms and an EEG demonstrating hypsarrhythmia, modified hypsarrhythmia, or electroclinical spasms captured on EEG. The child had to initiate treatment of IS at Seattle Children's Hospital and be followed until either IS resolved or the patient reached 2 years of age. A cut off of 2 years was chosen as there is evolution of the epileptic encephalopathy and alteration of treatments after this age.

Children were then further stratified by the etiology of their IS: structural, metabolic, genetic, or unknown etiology. Genetic etiology was further subdivided to examine those children with a diagnosis of T21 (n = 18). Unknown etiology was then subdivided into idiopathic or cryptogenic IS. Children with idiopathic IS were chosen as the control group as these children have the better outcomes, thus making them a more "rigorous" comparison for T21 patients than other cohorts.

"Age of spasm onset" was determined based on parental report of onset of clinical spasms. "Age at diagnosis" was based on EEG confirmation of IS. "Clinical resolution" of spasms was determined by parental report. "EEG resolution" was defined as resolution of clinical spasms and an EEG showing resolution of hypsarrhythmia. Relapse of infantile spasms was defined as 2 weeks without reported clinical spasms followed by return of clinical infantile spasms or a return of hypsarrhythmia after resolution. This time period was chosen as the ACTH protocol used suggests treatment with ACTH for 2 weeks prior to the decision to wean, and as such is a routine time period for contact with families for management decisions.

The data were analyzed using a Pearson x^2 and Fisher's exact test for categorical variables and Mann–Whitney U test with unequal variances for the continuous variables using Stata Version 12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: Stata Corp LP). A two-sided p value of less than 0.05 was considered statistically significant.

This study was approved by the Seattle Children's Hospital Institutional Review Board.

3. Results

We initially identified 161 children with IS who met inclusion criteria. There were 102 children who had structural, metabolic, or genetic etiologies consistent with symptomatic IS and were excluded from analysis. Eighteen children had a diagnosis of T21; however 5 of these children had other insults such as hypoxic ischemic encephalopathy or a perinatal infarct which lead to a classification as symptomatic for structural reasons as opposed to solely T21. Further analysis of these children was not completed due to associated epilepsy at the time of IS onset or goals of care that altered treatment decisions. Thirteen had T21 as the primary etiology for spasms (8% of the total IS population) and comprised our study group. Of these, 7 had neuroimaging that did not demonstrate any other underlying etiology for their infantile spasms, 6 did not undergo neuroimaging. One child with T21 did not develop hypsarrhythmia and was not included in the analyses for EEG resolution, but was included in all other analyses.

Forty-one children had no known etiology for their infantile spasms. Of these children, 9 were excluded from analysis as they had other features of an underlying disease (such as movement disorder or microcephaly) consistent with cryptogenic IS. This allowed for inclusion of 32 children into the control group, consistent with idiopathic IS. Two of these children did not have hypsarrhythmia on the EEG recording and were excluded from the analysis of EEG resolution. One of these children never had resolution of their infantile spasms and was excluded from the analysis of clinical resolution. These children were included in all other analyses.

The 32 children with idiopathic IS had varying levels of investigation. All 32 underwent neuroimaging with magnetic resonance imaging (MRI) of the brain. Investigation for metabolic disease varied, and was unremarkable for the controls: 30 (94%) plasma amino acids, 27 (84%) urine organic acids, 24 (75%) venous lactic acid, 14 (44%) pyruvate, 15 (47%) ammonia, 7 (22%) alpha-aminoadipic semialdehyde, 25 (78%) acylcarnitine profile. Genetic testing was completed in some children with 10 (31%) undergoing karyotype and 9 (28%) with single nucleotide polymorphism array as part of the initial evaluation.

There was not a significant difference in the male/female distribution between the two groups (p = 0.372). The median age of onset of spasms was similar in the T21 and control groups (6.6 versus 5.6 months respectively, p = 0.12). The median time delay between clinical spasm onset and IS diagnosis was 6.9 days in the T21 cohort versus 19.5 days in those with idiopathic IS (p = 0.35) (Table 1).

Time from diagnosis to initiation of treatment was similar in the two cohorts. Mean duration in the control group was 1.07 days (SD 1.83) and 1.00 day (SD 1.78) in the T21 cohort (p = 0.91). This data was reported as mean duration as the median of both cohorts was zero with initiation of treatment on the day of diagnosis. Two patients had initiation of treatment with zonisamide based on clinical suspicion prior to confirmation of IS on EEG and were excluded from this analysis.

All children received treatment for IS. Treatment in our study varied based on provider preference. However, ACTH was the treatment of choice at our institution with 84.6% of the T21 group and 84.4% of the control group receiving treatment with ACTH (p = 0.98). Routinely, children were started on low dose ACTH of 75 units/m^2 per day to minimize side effects. If clinical spasms