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Neurodevelopmental outcomes in children with Down syndrome and infantile spasms

Sarah Tapp*, Tovi Anderson, and Jeannie Visootsak

Department of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA

Abstract

Down syndrome (DS) is the most common genetic cause of intellectual disability in the United States. The prevalence of seizure in individuals with DS is 1–13%, and infantile spasm (IS) occurs in 6–32% of those with seizures. Since IS is relatively common in children with DS, it is important to understand the impact IS has on the neurodevelopmental outcomes in order to provide appropriate anticipatory guidance to help maximize the potential of these children. Our study is the first to compare the neurodevelopmental outcomes of children with DS and IS (DS + IS) to children with DS and no history of seizures (DS – IS). Using the Bayley Scales of Infant and Toddler Development III, we assessed the neurodevelopment of 29 subjects (eight DS + IS and 21 DS – IS). Neurodevelopmental outcome was poor in the DS + IS cohort, but the delay in treatment does not appear to contribute to any differences in their developmental scores. However, when compared to children with DS – IS, the DS + IS cohort scored approximately 20 points less in all domains including cognitive, motor, and language ($P < 0.05$). Our results indicate that IS may impact the neurodevelopmental outcomes of children with DS + IS; thus, it is important to provide ongoing developmental and educational assessments and potentially additional therapies for children with DS + IS.

Keywords

Down syndrome; infantile spasms; neurodevelopmental outcomes

1. Introduction

Trisomy 21, leading to Down syndrome (DS), is the most common genetic cause of intellectual disability in the United States, with an incidence of one in 691 live births [1]. The expression of DS-associated congenital and acquired medical conditions vary greatly, but it is typically higher than that of the general population. For example, the prevalence of seizure in individuals with DS is 1–13% compared to 1.5–5% in the general population [2]. Infantile spasm (IS), or West syndrome, is the most common type of seizure in infants with DS, occurring in 6–32% [3,4]. When IS is diagnosed shortly after the onset, children with DS and IS (DS + IS) have generally shown to be quite responsive to treatment with rates of long-term seizure control reported as high as 90% [3,5,6].

*Corresponding author: Sarah Tapp, Emory University School of Medicine, 1648 Pierce Dr. NE, Atlanta, GA 30322, USA, Tel.: 404-778-8590; Fax: 404-778-8562; Sarah.caitlin.tapp@emory.edu.

Studies on neurodevelopmental outcomes associated with IS have been focused on typically developing children, despite the increased prevalence of IS in children with DS [7–11]. These studies indicate that children with IS have increased risk of cognitive disability, persistent seizures, and early mortality [7–11]. Notably, research focusing on the neurodevelopmental outcomes in children with DS + IS has been limited to case reports which revealed that neurodevelopmental outcomes are compromised despite good seizure control [3,5]. These studies also revealed that it is difficult to determine the degree of neurodevelopmental impact since there is no comparison group consisting of children with DS without IS (DS – IS). The present study compares the neurodevelopmental outcomes of children with DS + IS and children with DS – IS.

2. Materials and methods

2.1. Participants

With the approval of the institutional review board, we conducted a retrospective chart review of 13 patients with DS + IS evaluated at the DS specialty clinic at Emory University for routine follow-up. For the DS – IS group, the data was obtained from our neurodevelopmental research study focusing on the impact of medical issues in children with DS. In both groups, the subject had a confirmed trisomy 21 diagnosis based on chromosomal karyotype, was delivered 34 wk gestational age, had vision and hearing within normal limits based on medical records, with or without corrections and parents spoke English as the primary language. For this study, we defined cases as children with DS and IS (DS + IS). IS is confirmed by a waking electroencephalography (EEG) evidence of hypsarrhythmia. Hypsarrhythmia is a disorganized brain electrical activity with no recognizable pattern indicative of IS. Controls were subjects with DS who met the same eligibility criteria and had no history of any type of seizures (DS – IS) as confirmed by their medical records.

2.2. Assessment procedures

Our Master's level psychometrician administered the Bayley Scales of Infant and Toddler Development III (Bayley-III) to 29 subjects (eight DS + IS and 21 DS – IS) at the DS clinic at Emory University. For the DS + IS cohort, the Bayley-III was administered at least 3 mo after subject has been seizure-free. The Bayley-III is one of the most commonly used instruments for assessing developmental function of infants and children between 1 mo and 42 mo of age and has well-documented construct validity [12]. It typically takes ~ 30–45 min to complete depending on the children's age and level of functioning. The Bayley-III test results were expressed as cognitive, language, motor developmental indexes, with a mean of 100 and a standard deviation (SD) of 15. Composite scores (cognitive, language, and motor) between 70 and 84 (–2 to –1 SD) are considered abnormal and composite scores of less than 69 (<–2 SD) indicate severe developmental delay.

Because infants with DS had global developmental delay and were unable to perform tasks at their chronological age, we adjusted the Bayley-III testing by starting the test items that were usually appropriate for children younger than the chronological age of our subjects

(e.g., 9 mo instead of 24 mo). Parents were present during the testing administration and children were given breaks when necessary.

2.3. Statistics

Summary statistics were given as the mean $\pm$ SD. Descriptive analyses were conducted to examine the distributions of outcome measures. Based on the modest sample size and the fact that the outcome measures were not normally distributed, group-wise comparison was performed using the Mann-Whitney U two-sample test to compare the two groups. Statistical analysis was performed using Statistical Analysis Software, version 9.1 (Cary, NC).

3. Results

As indicated in table 1, the age of IS onset for the DS + IS group ($n = 13$) was approximately 3–10 mo of age with a delay in starting treatment of 2 days – 5 mo. The total time experiencing seizures vary widely from 1–10 mo.

For the neurodevelopmental assessment, cases with DS + IS ($n = 8$) received the Bayley-III testing at approximately the same age as controls ($n = 21$), 28.5 ± 6.3 mo compared to 25.4 ± 5.6 mo, respectively. We were unable to conduct the developmental assessments on five subjects because they did not return to clinic for their appointment. The composite scores in all domains for the DS + IS cases were compared to the DS – IS controls as described in figure 1. The DS + IS cohort scored approximately 20 points less than the DS – IS group in all domains including cognitive, gross motor, fine motor, receptive language, and expressive language ($P < 0.05$).

4. Discussion

IS presents with certain characteristic spasms, hypsarrhythmia on EEG, and developmental regression. The spasms typically involve the neck, trunk, and extremities; they can be flexor, extensor, or mixed flexor-extensor in nature. While the spasms themselves generally last for less than 5 sec, they tend to occur in clusters that can have a duration ranging from less than 1 min to more than 10 min [13]. These spasm clusters can be infrequent, brief, and subtle. For these reasons, there is often a diagnosis delay and/or misdiagnosis of IS in children with DS [5,14].

In our cohort, the age of IS onset ranges from 3–10 mo of age with a delay in starting treatment of approximately 2 days – 5 mo (Table 1). Treatment lag was contributed by several factors including delay in seeking medical attention by parents as the symptoms were subtle. Furthermore, in several cases treatment lag was attributed to the medical professionals as signs of spasm may resemble other features typically associated with DS (e.g., hypotonia, developmental delay, gastroesophageal reflux). Children with DS + IS with treatment delay ≥ 2 mo experienced a longer course of seizure ($n = 5$, 7–10 mo) compared to those with treatment delay < 1 mo ($n = 8$, 1–8 mo). Of note, in the group with treatment delay < 1 mo, one patient died due to cardiac and respiratory complications and another patient experienced seizures for 8 mo despite starting treatment 14 days after the onset of IS.

It was not possible to determine the impact of treatment responses and its relationship to neurodevelopmental outcomes as our subjects required several medication changes for intractable seizures.

Our results are consistent with findings from previous neurodevelopmental outcome studies of children with DS + IS [3,5] which revealed that neurodevelopmental outcome was poor, but the delay in treatment did not seem to contribute to any differences in their developmental scores as noted in table 1. However, when we compared the neurodevelopmental outcomes of children with DS + IS to the DS – IS group, children with DS + IS had greater developmental deficits in all domains (cognitive, gross motor, fine motor, receptive language, expressive language), compared to children with DS – IS (Fig. 1). Based on our results, it is likely that IS impact the neurodevelopmental outcome of children with DS + IS. Our findings have implications in emphasizing the needs for ongoing developmental and educational assessments in children with DS + IS. Additionally, children with DS + IS may need ongoing intensive therapies in areas of physical, occupational, and language to ensure that they continue to make progress after they are seizure-free.

It is also important to consider the needs of parents of children with DS + IS. Although our study did not evaluate the family psychosocial factors, we speculate that the diagnosis of IS in addition to the diagnosis of DS may provide increased stress to the parents. Parents of children with DS + IS are likely to encounter extra follow-up appointments with specialists, medical procedures (e.g., EEG) and medications for their child.

Limitations of this study include a small sample size that may limit our statistical significance, and may not be representative of the spectrum of individuals with DS + IS. We also did not collect parental socioeconomic status which may play a role in a child's neurodevelopmental outcome. We also recognize that our DS + IS group may not be homogeneous in terms of the onset of seizure, medications, and duration of seizure. The small sample makes it impossible to examine any of these factors.

In general, our preliminary results confirm that there is greater neurodevelopmental deficits in children with DS + IS compared to the DS – IS group. Children with DS + IS should receive ongoing developmental surveillance even after they are seizure-free. Consideration for initiating physical, occupational, and speech therapies early is important as their developmental course may differ from their peers with DS – IS. In addition, clinicians should provide support to the parents of children with DS + IS as they may be encountering additional stress and other challenges at home associated with IS, which may put their child at even greater risk for developmental deficits. Although our study is cross-sectional, we hope that further studies with a larger sample size will evaluate the neurodevelopmental trajectory of children with DS + IS, and will consider the family psychosocial functioning in its contribution to the developmental profiles as well.

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Fig. 1.

Bayley scales of infant and Toddler development III composite scores of Down syndrome + infantile spasm compared to Down syndrome and no history of seizures ($P < 0.05$). Bayley scales of infant and Toddler development III composite scores have means of 100 and standard deviations of 15 in samples of typically developing children. Composite of < 69 indicate severe developmental delay.

Table 1
Neurodevelopmental and seizure outcomes in children with Down syndrome and infantile spasms (n=13)

Patient number	Age at onset of spasms (mo)	Sex	Treatment	Treatment Lag	Total time experiencing seizures (mo)	Cognitive	Receptive communication	Expressive communication	Fine motor	Gross motor
1*	6	Male	Topamax, Vigabatrin	2 days	2					
2*	4	Female	ACTH, Topamax, Vigabatrin	2 days	deceased					
3	6	Male	ACTH, Topamax	2 wk	8	40	40	40	40	40
4	7	Male	ACTH	2 wk	1	41	41	40	40	58
5*	8	Male	Keppra, Prednisone	2 wk	3					
6	10	Female	Topamax, Prednisone	2 wk	2	53	42	46	49	53
7	7	Female	Zonegran	2 wk	1	40	40	40	40	40
8	7	Female	Topamax, Klonopin	1 month	3	45	53	53	40	42
9	5	Female	ACTH, Vigabatrin, Lamictal	2 mo	8	40	40	40	40	40
10	4	Male	ACTH, Klonopin, Topamax	3 mo	10	51	51	55	46	40
11*	4	Male	ACTH, Vigabatrin, Depakote, Zonegran	3 mo	7					
12*	3	Male	ACTH	5 mo	7					
13	4	Male	ACTH, Klonopin, Vigabatrin	5 mo	10	40	40	40	40	40

*Bayley - III not administered to these subjects

ACTH = Adrenocorticotrophic hormone