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Implications of delayed diagnosis of infantile spasm in a child with Down syndrome

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Abstract

Trisomy 21, leading to Down syndrome (DS) is the most common genetic cause of intellectual disability. Approximately 1–13% of children with DS have co-morbid seizures, with infantile spasm being the most frequent type of seizure identified. Although the clinical and electroencephalography findings of infantile spasm are similar between children with DS and typically developing children, there is often a delay in the diagnosis of these seizures in children with DS. We present the case of a male infant with DS, where the diagnosis of infantile spasm was delayed by 5 mo. His case was associated with developmental regression and intractable seizure activity following diagnosis. The case highlights the implications of delayed diagnosis on treatment strategies and developmental outcomes. Keywords: Down syndrome, infantile spasm, delayed diagnosis

1. Introduction

Trisomy 21, leading to Down syndrome (DS), is the most common genetic cause of intellectual disability, with an incidence of 1 per 691 live births [1]. Approximately 1–13% of children with DS also have co-morbid seizures, which is a higher prevalence than the general population [2]. West syndrome, or infantile spasm, is the most frequent type of seizure identified in infants with DS. Although clinical and electroencephalography (EEG) features are similar between children with DS and typically developing children, the time from symptom onset to medical attention and/or diagnosis is often longer among children with DS [3].

Infantile spasm is a unique seizure disorder occurring in infancy, which is recognized by characteristic spasms associated with hypsarrhythmia on EEG and developmental regression. The spasms often occur in clusters and involve symmetric contractions of muscles of the neck, trunk, and extremities. The spasms can be extensor, flexor, or mixed, and are typically brief, with spasm clusters lasting from less than 1 min to 10 min. The incidence of the disorder is between 2 and 3.5 per 10,000 live births, with 90% of individuals presenting within the first year of life. Approximately 60–70% cases are associated with an underlying disorder and/or developmental delay, while 40% occur in typically developing children and have no identifiable underlying cause. The possible

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etiologies of infantile spasms are broad, and include brain malformation, metabolic disorders, and genetic syndromes [4].

Diagnostic evaluation begins with the identification of spasm episodes by caretakers and/or physicians. Once the spasms have been identified, an EEG evaluation is completed as soon as possible to confirm the diagnosis. If hypsarrhythmia is present, magnetic resonance imaging is recommended to help identify any possible underlying etiology. Current recommended treatment options include adrenocorticotrophic hormone (ACTH) and Vigabatrin, although there are no uniformly accepted dosage protocols for these medications [4].

Our case presents an example of delayed diagnosis of infantile spasms in an infant with DS, and highlights the challenges in treatment strategies and its implications on developmental outcomes.

2. Case report

Our patient was born by spontaneous vaginal delivery at 38 wk gestational age to a 29-year-old, Gravid 1 Para 0 mother, with apgar score of 8 and 9. He had a birth weight of 2775 grams (10th percentile), length of 48.8 cm (25th percentile), and a head circumference of 33 cm (10th percentile). Features of DS were noted at birth, including upslanting palpebral fissures with epicanthal folds, low set ears, flat nasal bridge, excess posterior nuchal skin, and hypotonia. Postnatal chromosomal karyotype testing confirmed a diagnosis of trisomy 21, 47, XY, +21.

The patient was progressing well in his developmental milestones initially. He was able to roll over at 2–3 mo of age and he lifted his head when placed in a prone position at 3–4 mo. He was fixating on objects, tracking, and smiling. He received physical therapy weekly since 1 mo of age. However, his parents noted regression of milestones at 5 mo of age, with poor head control, and loss in ability to roll over. He was not tracking objects with his eyes or responding to interaction. The parents also described intermittent contractions of arms and legs 5–7 times per day, which were later confirmed to be spasms. At that time he was also having significant arching of his back associated with feeding. He was subsequently diagnosed with gastroesophogeal reflux and prescribed Prevacid. The parents were reassured that the developmental profile of a child with DS waxes and wanes, and therefore the pattern of development for this child was considered appropriate for his chronological age.

At 9 mo of age, the patient was seen for the first time at the developmental pediatrics clinic, and was noted to have arching and drooling. With these findings, as well as the history reported above, there was concern for infantile spasm and the patient was immediately referred to the emergency room for an evaluation. All laboratory tests (e.g., complete blood count and metabolic panel) were normal, including a barium swallow. EEG was performed and demonstrated hypsarrhythmia, which is a finding consistent with infantile spasm. Magnetic resonance imaging of the brain was normal. He was given 100 mg IV Pyridoxine with no EEG changes. He was prescribed 0.125 mg Klonopin twice a day and ACTH injections.

When he developed intractable seizure activity, Klonopin and ACTH injections were discontinued, and he was started on Vigabatrin 375 mg twice a day, later increased to 500 mg twice a day. Seizure activity continued, and Klonipin was started again in conjunction with the Vigabatrin, but later discontinued due to lack of seizure control. Topamax was added with no improvement. Subsequently, the Klonipin and Topamax were discontinued, and he was started on high level ACTH injections and Vigabatrin, which was slowly titrated up to its maximum therapeutic level. No change was noted with the increased Vigabatrin, so this was weaned and Depakote was started. The infantile spasms resolved on this treatment regimen at age 14 mo. The ACTH was stopped due to an infection with respiratory syncytial virus, but he remained seizure free on Depakote for approximately 1 yr. He was weaned off all medication, and continued to be seizure free for approximately 3 mo, until he developed myoclonic seizures at age 28 mo. He was started on Depakote again, in conjunction with Onfi, and he regained seizure control approximately 2 mo later. He has had no seizure activity since that time, and currently takes Depakote 125 mg three times a day and Onfi 5 mg once a day. The most recent EEG was negative for seizure activity.

2.1. Developmental Outcome

The patient's development was assessed shortly after the diagnosis of infantile spasm, at the age of 10 mo 14 days. The results from the Bayley scales of infant and Toddler development showed cognitive developmental age of <16 days, receptive communication at <16 days, expressive communication at 20 days, fine motor at <16 days, and gross motor at <16 days. Following the control of his infantile spasms at an age of 14 mo, he began to make progress in his developmental milestones. He lifted his head when in prone position at ~16 mo, smiled at 18 mo, rolled over at 19 mo, and reached for toys at 19 mo. Repeat developmental testing at the chronological age of 19 mo 27 days showed cognitive development at 3 mo of age, receptive communication at 2 mo 10 days, expressive communication at 3 mo 20 days, fine motor at 4 mo, and gross motor at 3 mo 10 days.

3. Discussion

DS is an underlying cause in 3–5% of individuals with infantile spasms [3]. Infants with DS appear to show a better treatment response than the general population and a lower rate of persistent seizures later in life [3,5–7]. However, there is also a longer duration of time from spasm onset to diagnosis and treatment, as signs of spasm may resemble other features associated with DS (e.g. hypotonia, developmental delay, gastroesophageal reflux). As such, developmental regression is more subtle in children with developmental delay [3]. There have been several studies that correlate the length of time from diagnosis to spasm control with developmental outcome. These studies have included all etiologies of infantile spasm, and have had varied results [4]. A study by Eisermann et al. [6] focused specifically on children with DS and infantile spasm. The results indicated that longer spasm duration was strongly associated with a low developmental quotient and a high autistic features score. Additionally, when treatment was initiated greater than 2 mo after spasm onset, the response to treatment also took longer than in those who received treatment less than 2 mo after onset. Persistent seizures were consistently noted in those with a delay in treatment of over 2 mo.

In contrast, infants that received treatment within the first 2 mo of symptom onset were seizure free after 3 mo of treatment [6].

In our case, the delay from symptom onset to treatment was approximately 5 mo. The patient was displaying features typical of infantile spasms (developmental regression associated with cluster of spasm activity) but the diagnosis was delayed, with the symptoms being attributed to reflux and developmental progress consistent for a child with DS. The delayed diagnosis is consistent with previous case reports suggesting that symptoms infantile spasm are challenging to recognize in a child with DS [3,4]. Additionally, the developmental trajectory gain was minimal with overall scores of less than 1 mo of age and 2 mo for a chronological age of 10 mo and 19 mo, respectively.

As indicated in previous studies, our patient's delayed diagnosis of infantile spasms could be related to challenges in seizure treatment and worse developmental outcomes. Previous report has indicated that approximately 70–96% of children with DS respond to ACTH and 85% to Vigabatrin treatments [3,7]. However, when intractable seizures occur with ACTH, treatments become challenging as noted in our case. He continues to have intractable seizures with ACTH and Vigabatrin, and became seizure free with Depakote. There has been no reported cases of Depakote treatments for children with DS and infantile spasm.

Our case highlights the importance of having a high degree of clinical suspicion for infantile spasms among infants with DS, particularly if developmental regression is present. Early recognition and treatment of infantile spasm can prevent or decrease the likelihood of further insult to the developmental outcome.

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