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Research Article

Epilepsy in Children with Down Syndrome: An Observational Study in a District Epilepsy Centre in South of London

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Abstract

Objectives: To assess the presence and type of epilepsy in children with Down syndrome attending a child development centre in the south of London, U.K.

Methods: We retrospectively reviewed the case notes of 225 patients with Down syndrome (121 males and 104 females) at Child Development Centre, London, between 2006 and 2020. Follow-up period was 13.6 years, with examinations once per year.

Results: In our cohort of 225 patients with Down syndrome, only two patient presented with epilepsy (prevalence 0.08%) and they had Infantile epileptic spasms syndrome. Response to treatment was favourable. Only one patient was misdiagnosed with epilepsy.

Conclusion: Infantile epileptic spasms syndrome (IESS) was the most common epilepsy syndrome in patients with Down syndrome. Electroclinical features of IESS resemble those of idiopathic West syndrome, with a favorable response to treatment. Prospective studies that provide accurate estimates of the lifetime prevalence of epilepsy in patients with Down syndrome are needed.

Keywords: *Down Syndrome, Epileptic Seizures, Epileptic Spasms*

Introduction

Down syndrome (DS) is the most frequent genetic cause of intellectual disability, with an incidence of 1:1000 live births.[1] Approximately 95% of individuals with DS have an extra chromosome 21. Of the remaining 5%, less than 1% show somatic mosaicism, and the rest experience chromosome 21 translocations. [1,2] The first case of a child with DS was described in 1836 by a French psychiatrist, Jean-Etienne Dominique Esquirol, but John Langdon Down provided a detailed clinical description in 1866. The cause of this phenomenon has remained unknown for nearly 100 years. In 1959, Lejeune and Gautier reported that an extra copy of the human chromosome 21 causes DS.[3]

The clinical phenotypes of DS can be broadly divided into two major groups: the presence of invariable clinical signs such as hypotonia and mild-to-profound levels of intellectual disability and the presence of variable clinical signs such as cardiac abnormalities and respiratory, autoimmune, gastrointestinal, vascular, metabolic, and neurological diseases, including epileptic seizures.[2,3]

Although epilepsy is not mentioned in the original descriptions of DS, the prevalence of epilepsy in this population is known to be higher than that in the general population, but lower than that in patients with other chromosomal abnormalities. According to some studies, the prevalence of epilepsy in patients with DS can be up to 13%.[4,5]

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Epilepsy can develop at any age but shows a bimodal distribution, with seizure onset either in childhood or in older adults.[6,7] However, there are some limitations to previous studies, as the definitions of epilepsy are inconsistent and there is no detailed information about how and from where the data were collected; the follow-up period is also not mentioned.[4,5,7]

Susceptibility to seizure in patients with DS is attributable to inherited genetic differences in the brain structure and secondary complications such as hypoxic-ischaemic brain injury, congenital heart diseases, or cardiac surgery, and perinatal asphyxia, but the mechanisms underlying epilepsy in DS patients remain unclear.[8,9] However, neuronal structural abnormalities (e.g., decreased neuronal density, decreased inhibitory interneurons, abnormal neuronal lamination, and persistent foetal dendritic morphology) have been examined in previous studies.[10]

Infantile epileptic spasms syndrome (IESS) is an age-dependent epilepsy that frequently occur in the first 2 years of life.[10,11] It is characterised by epileptic spasms, often in clusters, developmental delay, and a high-voltage interictal electroencephalography (EEG) pattern called hypsarrhytmia.[12] The ictal and interictal changes in DS are similar to those in idiopathic West syndrome.

The prevalence of IESS in children with DS is 1–3%, and it is accepted that DS is a "cause" of IESS, but brain imaging studies are not usually conducted for this patient population.[4,12,13] According to data from the literature, IESS tends to be easier to control in these patients using conventional treatment.[13,14] However, the response to treatment may vary, and the condition can become intractable if not contained within a few weeks after treatment.[14] In a few studies that reported on the early responses to corticosteroids or conventional antiepileptic drugs (AED), the condition appeared to be controlled in a partial and transient manner.[15,16] The optimal therapeutic strategies (e.g. choice of AED, dose, duration, side effects, or treatment of IESS relapse in this population) have yet to be elucidated.[17] Treatment lag can also be attributed to a lack of recognition of unusual events or developmental regression in children with an underlying learning disability. The presence of comorbidities or autistic features has also been reported as an essential prognostic factor.[18,19]

Lennox–Gastaut syndrome (LGS) is a rare condition that has been well documented in patients with DS.[19] As per the data from five European epilepsy centres collected for over 30 years, LGS was diagnosed in 13 (eight males and five females) patients with DS with late seizure onset after the age of 8 years, and West syndrome did not precede the onset of LGS in any of them. All patients presented with LGS symptoms, multiple seizure types, psychomotor regression, or behavioural disturbances. The interictal and ictal findings were typical of LGS, and all were drug resistant.[7,19]

Other types of seizures, such as focal and generalised tonic-clonic seizures, have also been described in patients during childhood and adolescence.[4,19] Most patients with DS have well-controlled epilepsy with sodium valproate or carbamazepine monotherapy.

The prevalence of epilepsy in older individuals with DS is higher compared to younger ones. One explanation is that the onset of Alzheimer's disease is caused by the overexpression of the amyloid precursor protein (APP) gene due to triplication of chromosome 21.[14] A particular type of epilepsy has been observed in older people with this syndrome called late-onset myoclonic epilepsy, which should be differentiated from other types of myoclonic epilepsy in adults.[21,22]

Methods

We retrospectively reviewed the case notes of 225 patients with DS aged 0–19 years (median age 8.75 years; 121 males and 104 females) at Child Development Centre, London, between 2006 and 2020. The inclusion criteria were diagnosis of DS and follow-up at the district epilepsy clinic at least once per year. Excluded were those who were lost in follow-up. The diagnosis of DS was confirmed at the molecular level, with trisomy 21 being the most frequent chromosomal abnormality. The mean follow-up period was 13.6 years (SD +/- 4.3). This study was approved by the hospital's internal audit committee. Because this was a service evaluation project, informed patient consent was not required.

Results

Two male patients were diagnosed with IESS at 4 and 9 months of age. Both patients underwent a comprehensive diagnostic workup, including baseline blood tests, metabolic screening, and cerebrospinal fluid analyses. Brain magnetic resonance imaging (MRI) did not reveal any other causes of IESS (stroke or cardiovascular factors). Their EEG findings were consistent with hypsarrhythmia, but it resolved subsequently in 4 weeks, as confirmed by a repeat EEG.

Regarding treatment, both were started on prednisolone, as per the International Collaborative Infantile Spams Study (ICISS) guidelines, and sodium valproate.[22] Four weeks of spasm cessation indicted a clinical response to treatment, and the response was sustained at the 18-month follow-up.

Misdiagnosis of epilepsy was observed in one patient who had been started on targeted treatment for childhood absence epilepsy, which was later excluded by paediatric neurologist.

We focused only on comorbidities that may have influenced the prevalence of epilepsy. In all, 40% of our cohort was diagnosed with atrial ventricular septal defects and 35% had obstructive sleep apnoea. None of the patients had a history of asphyxia.

Discussion

The incidence of epilepsy in children with DS is higher than that in the general population and its prevalence increases with age and intellectual disability. IESS is the most common epileptic syndrome in patients with DS. IESS can be subtle and may be mistakenly attributed to gastroesophageal reflux, hypotonia, pain, or repetitive mannerisms, sometimes leading to delayed recognition. Therefore, IS should be considered in any infant with DS who presents with a developmental plateau or regression.

The only seizure type in our cohort was IESS, consistent with the data from the literature. Comorbidities did not contribute to the development of IESS in our study. The low prevalence of IESS (0.08%) in our cohort and favourable response to treatment was too small to confirm the effectiveness of the provided treatment. Sustained cessation of epileptic spasms was achieved in 4 weeks. Children with DS and idiopatic West syndrome are thought to respond better to treatment than other children with IESS but without DS.

Early detection of epilepsy is essential for successful treatment and avoidance of cognitive decline. Labelling the genetic disease as the “cause” of IS may be inaccurate and misleading. Therefore, detailed semiology and full diagnostic workup, including brain imaging studies, are essential for differentiating epilepsy from other non-epileptic events.

The main limitation of this study is its retrospective nature. Assessing developmental outcomes was difficult because of pre-existing developmental delays and the retrospective nature of the study. The developmental trajectories of patients with DS are variable, and evaluating the subsequent impact of IS on development is challenging. However, IS in patients with DS is associated with poor developmental outcomes, increased risk of autism spectrum disorder, and high levels of intellectual disability.[23] Only patient was misdiagnosed with epilepsy and started on ethosuximide. Subsequently, the patient was examined by a paediatric neurologist, and the diagnosis of epilepsy was excluded. It is essential to recognise that there are many potential causes of abnormal movement disorders in DS, and clinicians should be vigilant in investigating any symptoms suggestive of IS or epilepsy and decrease the prevalence of symptomatic epilepsy compared to previous studies.

Conclusion

Down syndrome is the most frequent chromosomal abnormality, usually detected by antenatal diagnosis, and IESS was the most common epilepsy syndrome in patients with DS with favorable response to treatment. Prospective studies that provide accurate estimates of the lifetime prevalence of epilepsy in patients with Down syndrome are needed.

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