Case report/Kazuistyka

West syndrome associated with Down syndrome: Case report and literature review

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ABSTRACT
West syndrome is the most frequent cause of epilepsy in Down syndrome. West syndrome is often associated with poor long-term prognosis in most of children. We report a girl with West syndrome associated with Down syndrome which occurred at 8 months of age for repetitive flexor spasms and electroencephalography (EEG) showed hypsarrhythmia. She had Down syndrome facies, microcephaly, psychomotor development delay and axial hypotonia. Computed tomography of the brain was normal. Her karyotype was 47, XX, +21. Phenobarbital therapy was immediately effective with good clinical control of seizures, while the EEG monitored after one month was unchanged. At 2 years of age, the patient had hypertonic status epilepticus following a lung infection. The EEG showed a persistence of hypsarrhythmia. Sodium valproate and hydrocortisone therapy was effective with good seizure control but her psychomotor development was severely impaired. After a follow-up of 7 years, the patient presents growth retardation, microcephaly, severe psychomotor development delay, generalized hypotonia and tetraparesis. Knowledge of West syndrome in Down syndrome allows the early detection and prompt management of this neurological complication in order to optimize psychomotor development and improve the quality of life of these children.

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Introduction

West syndrome or infantile spasms are a rare form of severe epilepsy, described for the first time by West in 1841. Epileptic spasms must be associated with a psychomotor regression and electroencephalography (EEG) hypsarythemia to make the diagnosis of West syndrome [1, 2]. It is well known that the incidence of major forms of epilepsy is higher in children with Down syndrome than in the general population, and West syndrome is the most frequent and most severe form of epilepsy in these children [3, 4].

In the general population of children, the incidence of West syndrome ranges from 2.2 to 4.5 per 10 000 live births.
[5, 6]. However, this incidence is much higher in children with Down syndrome. It has been reported that 6.4 to 8.1% of patients with Down syndrome had epilepsy, and 12.8–32% of these epileptic patients with Down syndrome had West syndrome [2, 7]. The West syndrome begins during the first year of life in 90% of those affected children. The peak age of onset is usually between 3 and 7 months. However, onset after 18 months is rare, though onset up to 4 years of age has been reported [8].

The association of infantile spasms with Down syndrome is considered a symptomatic form because of preexisting psychomotor development delay. However, the prognosis seems to be better in this association than in cryptogenic forms. This prognosis is linked to early diagnosis and rapid initiation of adequate treatment, but the long-term prognosis is often very poor in most of these children [1, 4]. We report a case of West syndrome in a girl with Down syndrome and we discuss the clinical characteristics, management and prognosis of this association.

Case report

An 8-month-old girl developed repetitive flexor spasms associated with fever, and was referred to the department of pediatrics. She was the first child of healthy non-consanguineous parents. Her mother was 46-year-old, and pregnancy was not followed. She was born at term with vaginal delivery without incident and neonatal period was unremarkable. Her psychomotor development was abnormal with hypotonia and disability of head control. At 8 months, she had flexor spasms several times a day, occurring in series. At admission, she was fever to 38.4°C, Down syndrome facies, microcephaly, short neck with skin folds, brachydactyly and single crease in the palm, psychomotor development delay and axial hypotonia. The following laboratory tests were normal: complete blood counts, serum chemistry results, and serum electrolytes. The fever was linked to a viral infection, but no viral studies were performed. The thyroid function was normal. The transfontanellar ultrasound was normal. Computed tomography of the brain did not demonstrate any abnormalities. The karyotype showed 47, XX, +21. The initial EEG showed hypsarrhythmia and she was diagnosed as having Down syndrome associated with West syndrome. She was treated with phenobarbital before the result of EEG at a dose of 3 mg/kg/day and her seizures disappeared immediately with good control of these seizures for 16 months, while the EEG monitored after one month of admission was unchanged.

At 2 years of age, the patient was readmitted for hypertonic status epilepticus following a lung infection. The EEG showed a persistence of hypsarrhythmia. Thus, she was treated with Sodium valproate at a dose of 30 mg/kg/day and hydrocortisone at a dose of 2 mg/kg/day and her seizures disappeared immediately. Thereafter, hydrocortisone was stopped after 3 months and sodium valproate was continued at the same dose. At long-term, valproate therapy was effective with good seizure control but her psychomotor development was severely impaired. After a follow-up of 7 years, the patient presents growth retardation, microcephaly, severe psychomotor development delay, generalized hypotonia, tetraparesis and epilepsy well controlled by sodium valproate.

Discussion

Down syndrome is the most common genetic cause of mental retardation with a reported prevalence of epilepsy of 6.4–8.1%. Infantile spasms or West syndrome is the most frequent epilepsy syndrome in children with Down syndrome. West syndrome occurs in 0.6–13% of children with Down syndrome, representing 12.8–32% of seizures in these children [2, 7].

The mechanisms that raise susceptibility to infantile spasms in patients with Down syndrome have yet to be thoroughly uncovered. However, several authors suggest a potential epileptogenic role for the interaction of various Down syndrome-specific structural abnormalities of the brain, such as lower rates of inhibitory interneurons, decreased neuronal density, abnormal neuronal lamination, persistence of dendrites with fetal morphology, primitive synaptic profiles or altered membrane potassium permeability [1, 2].

The diagnosis of West syndrome is often easy when the infantile spasms are associated with arrest or regression of psychomotor development, and a specific EEG pattern of hypsarrhythmia [1, 5]. The clinical symptoms of infantile spasms are very different than any other type of seizure because of the absence of paroxysmal motor phenomena, such as convulsions or loss of consciousness. This lack of more typical seizure phenomena may lead to initial misdiagnosis of infantile spasms by pediatricians at the first medical consultation. Recently, it was reported that approximately one third of infants with infantile spasms were not suspected of having epilepsy during the first medical consultation [9, 10]. Infantile spasms in infants are usually symmetrical and manifested by a repetitive flexor, extensor or flexor–extensor spasms with sudden and brief axial contraction, predominating in the upper limbs, with upper deviation of the eyes [11].

It is estimated that approximately 60–90% of children with West syndrome have an associated with a brain abnormality such as brain injury or cortical and subcortical malformations of the brain due to abnormal development, present in isolation or associated with other diseases such as Down syndrome [8, 12]. The magnetic resonance imaging is required to study the brain with great precision and detect brain malformations in some children [12]. In our case, the computed tomography of the brain did not demonstrate any abnormalities but magnetic resonance imaging of brain has not been made because this magnetic resonance imaging is not available in our hospital and parents do not have the means.

Medical treatment of infantile spasms should be effective and initiated as early as possible. Evaluation of treatment effectiveness includes cessation of spasms, a resolution of hypsarrhythmia on the EEG and reduction the cognitive decline associated with epilepsy. Currently, vigabatrin and adrenocorticotropic hormone (ACTH) are the only drugs whose effectiveness was approved to suppress clinical spasms and abolish the hypsarrhythmia on the EEG. In the literature, different treatment protocols were used, but the
large majority of children with infantile spasms received vigabatrin as first line treatment and ACTH as second line treatment [8, 13, 14].

The vigabatrin dose should begin at 50 mg/kg/day and be escalated up to 100–150 mg/kg/day in those patients requiring escalation. The vigabatrin used alone may be effective to suppress spasms and correct EEG abnormalities. However, in case of failure of vigabatrin, the combination of ACTH at dose of 0.01–0.015 mg/kg/day (0.4–0.6 IU/kg/day) may be more effective [14, 15]. Other corticosteroids, such as high-dose oral hydrocortisone or prednisolone may be associated with vigabatrin for a variable duration depending on the case. [14] Whatever the drug chosen, the effectiveness of treatment should be assessed within 2 weeks following dose titration. This efficiency is controlled by regular EEG. Other antiepileptic drugs such as topiramate, felbamate, sodium valproate or lamotrigine can be used in case of spasm resistant to previous treatments, as well as some benzodiazepines [13, 16].

Infantile spasms in children with Down syndrome were described in the literature as particularly sensitive to treatment than children with cryptogenic infantile spasms. The response rate was measured at 96% of cases treated with hormoneotherapy (adrenocorticotropic hormone or corticosteroids), 85% of cases treated with vigabatrin, and 73% of cases treated with conventional antiepileptic drugs [2, 17, 18]. In our patient, Phenobarbital was temporarily effective with a complete resolution of clinical spasms during the first two years. In our protocol Phenobarbital is the first-line treatment pending the results of the EEG. However, the recurring spasms at the age of two years were treated using the combination of sodium valproate with hydrocortisone. This therapy was effective with good control of clinical spasms without recurrence until the age of 7 years.

Despite early diagnosis and rapid initiation of effective treatment, West syndrome is still associated with a poor long-term prognosis. After an initial response, 12–57% of children relapse within 6 months. Thereafter, spasms tend to disappear before 5 years of age, but relapses are possible, as in our patient. The long-term follow-up showed that 60% of the children had drug-resistant epilepsy and that 75% of the children had a delay in their psychomotor development [18, 19]. It is generally accepted that children with West syndrome who have evidence of pre-existing developmental delay or neurological abnormalities have a worse prognosis with a poorer response to treatment and less favorable developmental outcome [4]. However, children with Down syndrome and West syndrome seem to have a better prognosis compared to other patients with symptomatic infantile spasms with a better control of clinical spasms, and early initiation of appropriate treatment may contribute to the prevention of late seizure development and better developmental outcome [1, 2, 20].

Conflicting results have been published regarding the role of diagnostic delay and/or treatment lag in the outcome of infantile spasms [9]. It was reported in a study that in children with Down syndrome, a time less than 2 months prior to diagnosis of infantile spasms is associated with rapid control of spasms and better psychomotor development [17], while another study including infants with cryptogenic infantile spasms reported that a delay less than one month in diagnosing infantile spasms was important for the outcome [21]. Recently, it has been shown that the response to treatment was significantly better when treatment was initiated less than 6 weeks after the diagnosis of infantile spasms [10]. These results suggest the importance of early diagnosis and rapid treatment to improve long-term prognosis of infantile spasms in children with Down syndrome.

### Conclusion

This case study leads us to conclude that the initiation of Phenobarbital therapy is not the adequate treatment for patients with Down syndrome associated with infantile spasms and psychomotor development delay. In the short-term, this treatment was effective immediately with a good clinical control of seizures. But in long-term, we observed an unfavorable progression with persistence of hypsarrhythmia on EEG and severely impaired psychomotor development. The better knowledge about this association by physicians and parents would reduce the time to diagnosis and delay to treatment in order to optimize psychomotor development and improve the quality of life of these children.

### Authors’ contributions/Wkład autorów

According to order.

### Conflict of interest/Konflikt interesu

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### Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

### REFERENCES/PIŚMIENNICTWO