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An Unusual Triad in Pediatric Neurology: A Case Report on Cerebral Palsy, Epilepsy, and Duchenne Muscular Dystrophy

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Abstract

We present a case of an unusual triad in pediatric neurology: a currently 12-year-old boy with cerebral palsy and epilepsy who was later also diagnosed with Duchenne muscular dystrophy. We describe the clinical path that resulted in this exceptional diagnosis. This case report illustrates how different neurological disorders may overshadow each other. In addition, it demonstrates that every child with cerebral palsy and either an atypical clinical course or with inexplicable laboratory values—as well as every infant boy born to a theoretical Duchenne muscular dystrophy carrier—should be subjected to additional investigations.

Keywords

cerebral palsy, Duchenne muscular dystrophy, epilepsy, diagnostic overshadowing, dystrophin

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Introduction

Cerebral palsy (CP) is a nonprogressive disorder of movement and posture. It is attributed to a disturbed development of the fetal or infant brain, which can thus occur in the prenatal, perinatal, or postnatal period. Since cerebral palsy affects 1 in 400 children, it is the most common developmental disorder associated with lifelong disability.[1] Although the true pathophysiology of cerebral palsy has not yet been fully elucidated, it appears to depend on a complex interplay between genetic predisposition and multiple environmental triggers such as extreme prematurity, traumatic brain injury, or intrauterine infection. The clinical presentation of cerebral palsy can vary enormously and partly depends on the affected areas in the central nervous system. Children with cerebral palsy initially present with delayed achievement of motor milestones, abnormal muscle tone, disturbances in posture, and muscle weakness. Children with cerebral palsy also more often encounter problems with learning. Furthermore, seizures are common in these children, and up to one-third is diagnosed with epilepsy.[2]

A complete history and physical examination are of essential importance in diagnosing cerebral palsy. In addition, the diagnosis can be facilitated by imaging techniques such as brain ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT) that demonstrate central nervous system damage in 80% of children with cerebral palsy.[3]

Neuromuscular disorders constitute another frequent cause of aberrant development. Duchenne muscular dystrophy is the most common neuromuscular disorder and affects

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approximately 1 in 3500 to 5000 live male births. Patients with Duchenne muscular dystrophy carry a mutation in the DMD gene, located on the short arm of the X-chromosome in band 21 (Xp21), which arises either as a de-novo mutation or via inheritance. It is characterized by a progressive loss of muscle function and mass. The first presenting symptoms, which manifest around the age of 4, consist of pseudo-hypertrophy of the calf muscles, delayed motor abilities and milestones, frequent falls, and a typical way of getting in upright position, known as Gower's maneuver. Without adequate symptomatic management, boys with Duchenne muscular dystrophy become wheelchair dependent before their teens. At some point during the progression of the disease, cardiac and respiratory complications emerge; without interventions, the mean age at death is around 19 years. Clinical management of these complications is therefore of vital importance, since such management is able to extend both the ambulatory period and the average life expectancy.[4]

Over the last decades, it has become increasingly clear that Duchenne muscular dystrophy is more than a muscle disease, as there is also specific involvement of the brain, resulting in lower general intellectual capacities[5], and learning and neuropsychiatric disorders.[6,7] Moreover, it has been shown that epilepsy is more common in Duchenne muscular dystrophy populations.[8,9] These latter comorbidities constitute a group of additional brain-related disorders that also have been reported in cerebral palsy as mentioned earlier.

A boy, in whom the diagnosis of Duchenne muscular dystrophy is suspected, can subsequently be diagnosed by genetic testing, sometimes in combination with a muscle biopsy if a mutation cannot be identified.[4] Diagnosis is approximately made at the age of 5 years. Furthermore, prenatal diagnosis of Duchenne muscular dystrophy is possible if the mother is suspected to be a carrier.

In line with a case report by Rha and colleagues[10] who reported on a belated diagnosis of cerebral palsy in a patient with Becker muscular dystrophy, a milder form of Duchenne muscular dystrophy, we here report the case of a boy who was diagnosed with Duchenne muscular dystrophy during his follow-up for both cerebral palsy and epilepsy. The aim of the case report is to describe and demonstrate the possible concomitant appearance of Duchenne muscular dystrophy, cerebral palsy, and epilepsy, which has serious implications for diagnosis, therapy, and prognosis of the patient. Furthermore, we aim to show that pediatricians and pediatric neurologists, in particular, should remain alert if the course of cerebral palsy is evolving differently from what is usually expected (as based on medical history and MRI results) and should perform additional investigations such as a creatine kinase screening.

Case Report

A currently 12-year-old boy was born to a Dutch couple. There was a possible positive family history for Duchenne muscular dystrophy, as the mother of the patient had 2 uncles who presumably had a muscle disorder, most likely Duchenne muscular dystrophy. However, a diagnosis was never made, and the men died at the age of 17 and 27. Because of the family history, the mother had undergone genetic screening for Duchenne muscular dystrophy in 1992 by means of creatine kinase screening, DNA screening of both X-chromosomes, and a muscle biopsy. The DNA screening was performed by means of genomic DNA (gDNA) hybridization with dystrophin probes, which did not detect any deletions in the dystrophin genes. Since all 3 investigations yielded normal results, the mother of our patient was explained that she was probably not a carrier of Duchenne muscular dystrophy (the estimated risk of being a carrier was therefore 10%). However, it was mentioned that this possibility was not completely ruled out, since dystrophin expression and creatine kinase serum levels can be normal in carriers. Furthermore, the sequence of the possible DMD gene mutation in the family was unknown, thus impeding a fully accurate—that is, with 100% certainty—detection of possible DMD gene mutations in the maternal X-chromosomes.

The boy was delivered by a Cesarean section at the premature age of 32 weeks and 2 days because of fetal distress based on a maternal infection and asphyxia. His body weight was 1955 g. Despite that mentioned earlier, he initially obtained a high Apgar score of 8 over 9.

At day 8, he was admitted to a neonatal intensive care unit with a neonatal necrotic enterocolitis. He remained here for 4 weeks, after which he was discharged with a weight of 2400 g and a frontal occipital circumference of 33.1 cm. An initial ultrasound of the brain did not reveal any abnormalities. However, after 1 month, another ultrasound demonstrated cyst formation, particularly frontal and parietal (periventricular leukomalacia degree 3), with enlarged periventricular liquor space. Subsequently, an electoencephalography (EEG) was made, which showed a normal background pattern according to his age without epileptiform activity yet with moderate focal abnormalities. An MRI made at the age of amenorrhea duration + 40 weeks (AD+40) showed a PVL degree 4 with cyst formation, mainly temporally located and left more than right (Figure 1). The parents were informed about the prognosis, which likely included that their son would become spastic in his lower limbs. Additionally, it was mentioned that epilepsy and cognitive problems could possibly develop at a later age.

At the age of 3 months abnormal repeated general movements were present. After 6 months, cerebral palsy was diagnosed as he clinically presented with axial hypotonia while having hypertonia in his extremities. Moreover, he presented with hyperreflexia and general movement abnormalities at different moments during follow-up.

From the age of approximately 7 months, he developed Salaam spasms, and in a later stage absence seizures with head nodding followed by tonic rigidity as based on multifocal epilepsy. This was subsequently confirmed by EEG registration, which revealed the epilepsy was originating from left and right occipital areas. The clinical picture further deteriorated, and he lost his visual ability. He was then diagnosed with a

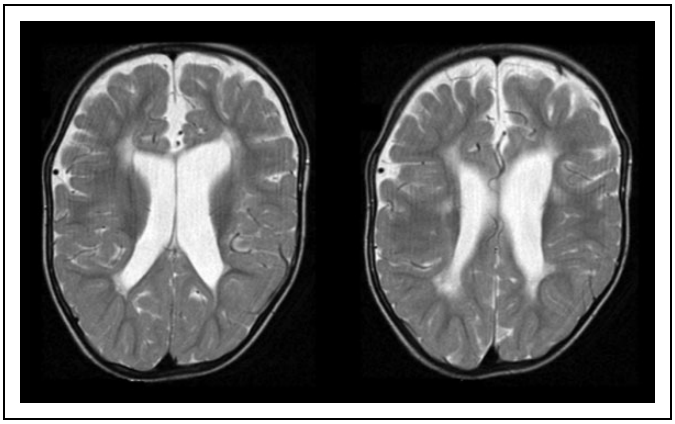

Figure 1. Transversal T2-weight magnetic resonance imaging sections revealing periventricular leukomalacia, mainly anteriorly, and posteriorly seen of both lateral ventricles, suggesting perinatal asphyxia.

symptomatic West syndrome, since the EEG did not show any signs of hypsarrhythmia.

In line with the clinical picture of PVL, the boy was, at the age of 3½, not able to stand and walk independently. At the age of 3 years and 10 months, he was evaluated by a pediatrician for constipation, probably as a side effect of the use of the antiepileptic drugs. An extensive hematological and biochemical workout revealed increased liver enzymes: aspartate transaminase, 299 IU/L; alanine transaminase, 206 IU/L; lactate dehydrogenase, 1644 IU/L; and creatine kinase, 13 485 IU/L (normal <200 IU/L). Initially, liver disease was considered and tested for (i.e. hepatitis A, B, and C-; Epstein Barr virus; and cytomegalovirus serology, which turned out to be all negative) and also the family history of the mother was taken into account. On physical examination, a boy with severe growth and mental retardation was seen. The frontal–occipital circumference was 48.0 cm. Furthermore, he was hypotonic, which was in sharp contrast to the past when he was initially hypertonic. Moreover, his reflexes were diminished or even absent, while they used to be vivid at the early stages of his life. Additionally, no (pseudo)hypertrophic calves were observed nor were contractures present.

Working out the differential diagnosis, some of the aforementioned signs, such as the family history and the increased creatine kinase levels, pointed in the direction of a neuromuscular disorder, whereas other features did not. This prompted, however, additional investigations at the age of 4; a muscle biopsy and genetic testing were initiated. The muscle tissue appeared to be devoid of dystrophin. The genetic testing also confirmed the suspected Duchenne muscular dystrophy, as exon 61 of the Duchenne muscular dystrophy gene was duplicated. The mother, who never had any complaints, subsequently decided not to get tested for this mutation, as it would not have consequences for her or her offspring. That is, her son born with Duchenne muscular dystrophy was her second child (the oldest son did not have Duchenne muscular dystrophy), and she and her husband did not have a desire for more children. Therefore, it cannot be ascertained whether the dystrophin mutation of our patient was inherited from the mother or whether it was a de-novo mutation. After the diagnosis of Duchenne muscular dystrophy was made, our patient was eventually able to stand up individually and walk a short distance at the age of 5½ years. It was noticed that for standing up, he pulled himself in upward direction, thereby resembling Gower's maneuver. At the age of 7, he lost the ability to walk again.

After having established the diagnosis for Duchenne muscular dystrophy, he was psychologically tested at the age of 8 years, which revealed a developmental age of 9 months (Kent Infant Development Scale), showing serious retardation. He started rehabilitation therapy, physiotherapy, and physical therapy. The parents eventually decided not to start prednisone treatment. The patient currently visits a day care center for mentally retarded children.

Discussion

We describe a patient with an atypical course of cerebral palsy, epilepsy, and also Duchenne muscular dystrophy. Although a concomitant diagnosis of cerebral palsy in Becker muscular dystrophy has already been documented, this report describes the first case with this unusual triad of neuropediatric disorders. Although these disorders most likely have a different etiology, the simultaneous presentation is highly uncommon and therefore particularly interesting. Most probably, the cerebral palsy and malignant epilepsy syndrome are the consequence of the pre- and perinatal asphyxia, especially since 50% of cases of cerebral palsy result from hypoxic events with irreversible cell death.[11] Also, in cerebral palsy, the prevalence of epilepsy is much higher than in the normal population, certainly when there are structural abnormalities visible on MRI. The dystrophin deficiency, which was later diagnosed at the age of four years, is the result of a duplication of exon 61 of the DMD gene, consequently disrupting the reading frame since this causes a frame-shift mutation.

In this particular case, the patient was initially diagnosed with cerebral palsy because he showed hypertonia, abnormal movement, and hyperreflexes. The clinical picture then slightly changed over time to a state of areflexia and hypotonia. Based on the delayed walking and motor milestones and especially the positive family history, one might have suspected the presence of a neuromuscular disorder. However, cerebral palsy is also characterized by delayed walking and delayed motor milestones, and these characteristics were therefore interpreted as a consequence of the motor and ambulatory problems associated with cerebral palsy. Moreover, on neurological examination, there were no other evident signs of Duchenne muscular dystrophy such as pseudo-hypertrophy. Since our patient was not able to stand up independently before the diagnosis of Duchenne muscular dystrophy was made, a Gower's maneuver could not be observed either. This has also impeded a straightforward diagnosis of Duchenne muscular dystrophy, as this maneuver provides clinicians often with an easy but valuable

tool that triggers further diagnostic investigation.[4] Thus, the spasticity overshadowed the Duchenne symptoms to a certain extent here. The atypical course of the clinical picture and the elevated creatine kinase levels prompted further analysis. This enabled the diagnosis of Duchenne muscular dystrophy at the age of 4 years and 1 month, which is nevertheless still below the average age of 4.9 years.[12]

One year and 4 months after the diagnosis Duchenne muscular dystrophy was made, our patient started to walk. Regarding walking in cerebral palsy, it is known that most children lose the ability to walk around puberty, mainly because of a so-called crouched gait as a consequence of a combination of factors including growth, weight gain, contractures, and paresis. In our case, the boy lost the ability to walk already at the age of 7 years, which was not due to crouched gait but rather weakness, the most important clinical characteristic of Duchenne muscular dystrophy.

The presence of Duchenne muscular dystrophy might have influenced the development of seizures: A lack of dystrophin can theoretically result in a larger susceptibility for the development of seizures (see Hendriksen et al[8]). The latter is clinically reflected by an increased prevalence of epilepsy in Duchenne muscular dystrophy.[9] The mutation of our patient in exon 61 would affect all 3 dystrophin protein (Dp) isoforms expressed in the brain (i.e. Dp427, Dp140, Dp71). As particularly the absence of Dp427 and Dp71 might lead to increased neuronal excitability (both by their own distinctive mechanisms), this specific mutation may result in an accumulated risk of hyperexitation.[8] Nonetheless, it is unclear to what extent the lack of brain dystrophin has contributed to the epileptogenesis of this patient. Although it seems far more likely that the epilepsy resulted from perinatal asphyxia, a combinational interplay between a predisposing dystrophin absence and a precipitating perinatal hypoxia could constitute a theoretical third explanation here.

In addition to epilepsy, cognitive problems are more often seen in Duchenne muscular dystrophy as well and can, again, partly be clarified by a lack of several brain dystrophin isoforms, particularly Dp71. Furthermore, it has been proposed several times that distal mutations, such as in this case, could result in more profound cognitive deficits.[7] Therefore, it would have been interesting to discern the cognitive level of the two maternal uncles in order to relate this to their DMD gene mutations. Since both are unknown, the latter is unfortunately not possible. However, it is, as stated above, more plausible that the cognitive deficits result from the oxygen deprivation, as this is more often encountered in cerebral palsy.

This is the second case report on a patient who was diagnosed with cerebral palsy and a neuromuscular disorder yet the first who was diagnosed with cerebral palsy and Duchenne muscular dystrophy. Making a clinical diagnosis of cerebral palsy and a concomitant neuromuscular disorder can be challenging, as signs from both disorders can overshadow each other.[10] Diagnostic overshadowing is an important phenomenon in clinical practice that should not be underestimated. This term was introduced in 1982 and has recently been described in a population study of children with diverse neurological disorders with respect to attention-deficit hyperactivity disorder as comorbidity.[13]

In conclusion, epilepsy, cerebral palsy, and Duchenne muscular dystrophy can be comorbidities, although they are not necessarily based on the same underlying pathology. Because Duchenne muscular dystrophy and cerebral palsy share clinical features, the diagnosis of each can be hampered. In line with the proposal of Ciafaloni and colleagues,[12] this case report illustrates the importance of creatine kinase screening in boys with unexplained developmental delay, as the increased creatine kinase levels, as part of general blood, prompted further analysis. Furthermore, as this case report also demonstrates, such creatine kinase screening (preferably in the first weeks of life) is highly indicated in infant boys who are born to a theoretical carrier of Duchenne muscular dystrophy, even if the probability of carriage is minor (ie, less than ten percent). Next to that, it underlines the importance of a multidisciplinary approach, as this approach allowed a timely diagnosis, despite the fact that Duchenne muscular dystrophy was initially barely visible. It is of vital importance to diagnose a concomitant disorder such as Duchenne muscular dystrophy next to cerebral palsy, since this affects not only therapeutic aspects such as timely initiation of (corticosteroid) therapy but also timely beginning of genetic counseling. Additionally, the prognosis of the diseases is different, and the health-related quality of life appears to be differently affected in both children with cerebral palsy and boys with Duchenne muscular dystrophy.[14,15] Therefore, clinicians working in the (neuro)pediatric fields should be aware of this uncommon triad. Although this triad rarely occurs, it shows that every child with cerebral palsy, either with an atypical course or with inexplicable laboratory values, should be subjected to additional investigations for possible comorbidities that might be overshadowed.

Author Contribution

RH and JV drafted the manuscript, MA, JH and GH critically revised the manuscript, CDS acquired the necessary genetic information.

Declaration of Conflicting Interests

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