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Differential Diagnosis in Progressive Infantile Spastic Tetraparesis

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Abstract
Progressive infantile spastic tetraparesis spans a wide spectrum of partially rare differential diagnoses. Based on a clinical example the differential diagnostic thoughts are discussed in detail. Though juvenile motor neuron disease is a rare entity, it has to be kept in mind for differential diagnostics in cases of slowly progressive spastic tetraparesis, especially when a pseudobulbar palsy or distal amyotrophies add to the clinical picture. Electromyography can be helpful for early detection of lower motor neuron involvement. The glutamate antagonist riluzole slows the disease progression, but a causal treatment is not available, yet. Therefore symptomatic treatment of disturbing symptoms like muscle cramps, spasticity, pseudobulbar affect, dyspnea or dysphagia are of major interest.

Key words: Progressive spastic tetraparesis, ALS2, juvenile motor neuron disease

Introduction

Movement of voluntary muscles is controlled by several interacting systems within the central and peripheral nervous system. Primary control is through the upper motor neurons in the motor cortex, which send their axons via the corticospinal tract to connect to lower motor neurons in the spinal cord. Spasticity is a characteristic clinical sign caused by a damage of upper motor neurons. Symptoms may include increased muscle tone, clonus, exaggerated tendon reflexes, muscle spasms, scissoring (involuntary crossing of the legs), and fixed joints. The degree of spasticity varies from mild muscle stiffness to severe, painful, and uncontrollable muscle spasms. Infantile spastic tetraparesis is a well known symptom in cerebral palsy [1], but it spans a wide spectrum of partially rare differential diagnoses. In this paper the differential diagnostic thoughts are described and discussed based on a clinical example.

Case Description

After an uncomplicated pregnancy and birth a Turkish boy grew up as the second of three male children. His consanguineous parents were first cousins once removed. Except for an acute high febrile intestinal infection at the age of 3 months, the early childhood was uncomplicated. At the age of 6 months the boy learned to sit, but the ability to walk was reached delayed at the age of 22 months. His gait was primarily spastic with mild hip flexion, hip adduction and inward rotation and plantar flexion of the feet. Clinical examination revealed bilateral positive Babinski's signs and brisk tendon reflexes. From the age of 2.5 years on he was tiptoeing without touching the ground with the sole of his feet. Claw toes and a weakness of dorsiflexion of the feet were documented. The spastic gait worsened in the course and spasticity of the upper limbs added at the age of 12. From this time on, a progressive pseudobulbar palsy developed with dysphagia, dysarthria and pathological laughing and crying. Since the age of 18 a linguistic communication was impossible, only inarticulate sounds could be produced and he communicates either by writing letters with the right hand or nodding, shaking the head or closing the eyes to aimed questions or via personal computer with mouse control. In the course, the whole facial muscles were affected (Fig. 1 a) with a positive *Signe de cils*, impossibility to frown and reduced elevation of the soft palate. Jaw movements were aggravated and since the age of 20 years mouth could not be closed completely due to spasticity and contracture of the masseter muscle. The patient suffered from severe siallorhea and difficulty swallowing as tongue motility was extremely compromised. The tongue could not be moved over the row of teeth. In spite of increasing difficulties chewing and swallowing due to incomplete mouth closure no changes of food composition were necessary and weight was still constant at 66 kg (height 175 cm). Choking appeared occasionally, especially on liquids. At the age of 15 distal muscular atrophies of the upper and lower extremities were described for the first time. From this time on the patient was wheelchair-dependent. At the age of 20 he suffered from an asymmetric spastic tetraparesis with distal muscular atrophies (Fig. 1b-d). His mobility was severely compromised due to the spasticity which included the muscles of the spine. At the age of 31 sitting without support became impossible. The patient had to be turned once a night, but sleep was reportedly undisturbed. There were no signs of nocturnal hypoventilation. In the recent years painful cramps of proximal muscle groups emerge. Although inten-

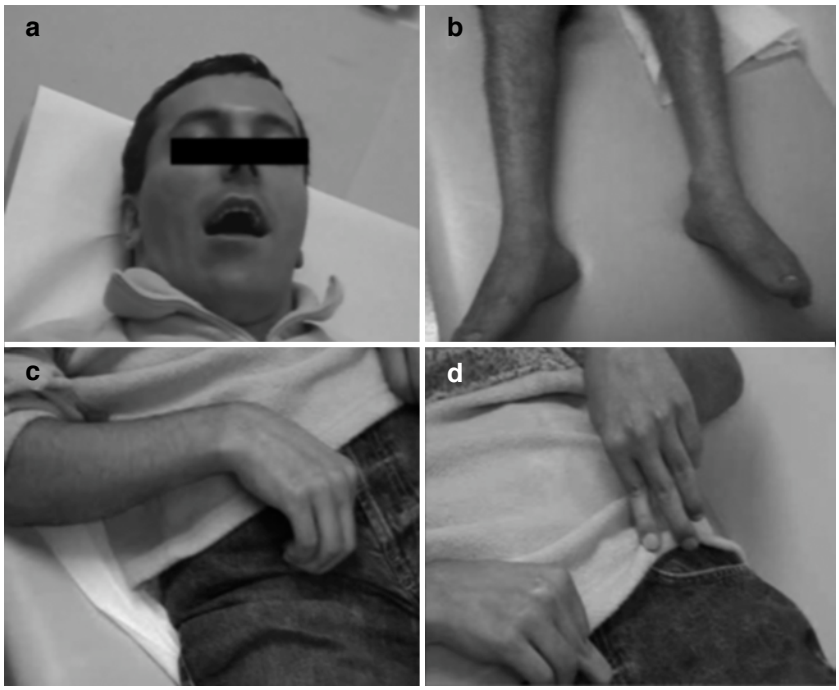

Fig. 1. a: Involvement of facial muscles, b: Amyotrophies of the distal lower extremities, c and d: Severe spasticity of both hands with joint contractures.

sive physiotherapy was carried out regularly twice a week joint contractures of the shoulder, elbow and fingers in flexion, hip in adduction and the feet in pes equinovarus position could not be avoided. At the age of 33 years an urge incontinence developed. However, cognitive functions remained impaired during the complete disease course.

Diagnostics and Differential Diagnostic Thoughts

As the ability to walk was reached delayed and gait was primarily spastic, initially a cerebral movement disorder was suspected. Twelve years later the patient presented in a neurological clinic with a progressive spastic tetraparesis accentuated in the lower limbs and additional pseudobulbar symptoms. At this point of time, he showed mild distal muscular atrophies. Cerebral and cervical magnetic resonance imaging (MRI) were repeatedly normal. Routine laboratory tests including creatine kinase were also regular. An *infantile brain damage* was favoured as the patient had an acute intestinal infection with temperatures up to 40 degrees centigrade for 5 days at the age of 3 months, though the progression of the symptoms was admittedly not explained by this diagnosis. The differential diagnosis of an autosomal recessive *hereditary spastic paraplegia* was discussed as in complicated forms both distal atrophies and pseudobulbar symptoms are frequent additional clinical signs [2]. An *inflammatory disease of the central nervous system* could be excluded by repetitively normal CSF findings. Abnormalities of the cranio-cervical region including *syringobulbia/syringomyelia* were excluded by cerebral and cervical imaging. *Funicular myelosis and folate deficiency* were unlikely as vitamin B12 und folic acid blood levels were regular [3]. Furthermore, pseudobulbar palsy has never been described in these disorders. *Neuronal ceroid-lipofuscinoses*, the biggest group of neurodegenerative diseases in childhood and adolescence with autosomal-recessive inheritance, have been considered, but none of the typical symptoms like dementia, loss of vision and epileptic seizures [4] were present and electroencephalography was repeatedly normal. Hereditary *lipidoses* have also been discussed. *Niemann-Pick's disease type C* was clinically unlikely because except for dysarthria none of the typical clinical signs like peri- or postpartal icterus, spleno- and hepatomegaly, vertical gaze palsy, dementia, cataplexy, or epileptic seizures could be found [5]. An infantile form of *metachromatic leukodystrophia* [6] seemed to be clinically possible as the disease onset was at the age of about one year with progressive changes in gait with spasticity and pyramidal signs, however, psychomotoric regression, ataxia and bulbar paralysis were not evident. The diagnoses was made unlikely by normal levels of the arylsulfatase A, which is characteristically elevated and an inconspicious cranial MRI. *Gangliosidoses* could be excluded as beta-galaktosidase (GM1 gangliosidosis) and beta-hexosaminidase A and B levels (GM2 gangliosidosis M. Tay-Sachs, M. Sandhoff) were normal and none of the typical clinical signs like cherry-red spot, hepato-/splenomegaly, spinocerebellar degeneration, extrapyramidal signs, encephalopathia or epileptic seizures were observed [7]. *Louis-Bar-syndrome (Ataxia teleangiectatica)* [8] was excluded by laboratory tests of alpha-feto-protein, immunoglobulines and total number of lymphocytes. Clinically, our patient showed dysarthria and muscle weakness but none of the other typical symptoms like ataxia, teleangiectasia, choreoathetosis, abnormalities of eye motility and nystagmus or recurring infections. *Wilson's disease* [9] was ruled out by analysis of copper ions and coeruloplasmine levels. Affect lability, dysphagia and pyramidal signs as possible symptoms of Wilson's disease were presented by our patient, but neither basal ganglia nor cerebellar signs (dystonia, hyperkinesias,

Table 1. Symptomatic treatment options in motor neurone disease.

Symptom	Therapy
Pain	Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids (WHO pain ladder)
Constipation	Hydration, food with high fiber content, laxatives
Urge incontinence	Oxibutynin
Spasticity	Physical therapy, baclofene, tizanidine, benzo-diazepines, local injections of botulinum toxine
Muscle cramps and fasciculations	Physical therapy, magnesium, quinine sulphate, carbamazepine
Drooling, siallorhea	Glycopyrrolate, amitryptiline, atropine, clonidine, transdermal scopolamine or hyoscine patches, intraglandular injections of botulinum toxine
Thick mucous secretions	Adequate hydration, ambroxole, N-acetyl-cysteine, beta blockers, insufflation-exsufflation devices
Laryngospasm	Reassurance, protone pump inhibitors, prokinetic drugs (e.g.domperidone, metoclopramide)
Depression	Counselling, selective serotonine reutake inhibitors (SSRI), amitriptyline
Anxiety, panic	Reassurance, benzodiazepines
Pseudobulbar affect	Amitriptyline, selective serotonine reuptake inhibitors, lithium carbonate
Dysphagia, malnutrition	High calory diet, speech and language therapy, enteral nutrition
Dyspnea, respiratory insufficiency	Physical therapy, non-invasive ventilation, invasive ventilation (tracheostomy)

parkinsonian-syndrome, ataxia, intention tremor) nor psychiatric abnormalities or the pathognomonic Kayser-Fleischer-ring were apparent. Also discussed, though quite unlikely was the *pantothenatkinase associated neurodegeneration (formerly Hallervorden-Spatz syndrome)*. For this rare hereditary disease in more than 50% mutations of the pantothenat-kinase-gene 2 (PANK2) can be found. Mutations lead to a pathological accumulation of iron in the brain causing extrapyramidal symptoms like parkinsonism, dystonia, choreoathetosis, tremor but also spasticity, hyperreflexia, pyramidal signs, dysarthria, impaired vision and sometimes psychomotoric regression [10]. The pathognomonic tiger-eye sign could not be seen in cerebral MRI.

Diagnosis

The pathbreaking diagnostics in this case was the electromyography of the atrophic musculature of the upper and lower limbs which demonstrated acute and chronic denervation. By reason of a combination of upper and lower motor neuron involvement and exclusion of differential diagnoses a juvenile amyotrophic lateral sclerosis type III (jALS) according to Ben Hamida and colleagues [11]. Blood was examined for mutations in the *ALS2* gene located on chromosome 2q33, which was isolated by positional cloning by the groups of Yang and Hadano and found to be mutant in families with recessive juvenile amyotrophic lateral sclerosis or primary lateral sclerosis [12, 13]. The genetic examination revealed one nucleotide deletion at nucleotide position 553 (553delA) in exon 4, of the ALSIN gene resulting in a frame shift and premature stop of translation at amino acid position 189. This homozygous change was detected in the heterozygous state in both parents and in both brothers [14].

Discussion

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive degeneration of upper and lower motor neurons in cortex, brainstem and spinal cord. Clinical hallmarks are progressive muscular atrophy and weakness, fasciculations and muscle cramps, and spasticity, brisk tendon reflexes, pyramidal signs and pseudobulbar affect. A bulbar onset with dysarthria and dysphagia is found in about 20-30 % of cases. Respiratory failure is typically the disease limiting factor. The estimated incidence of ALS is 1.5-2/ 100,000/year and the prevalence is approximately 6-8/100,000. The mean age at onset is between 50-70 years, however, an early disease onset in childhood and adolescence is possible. Disease duration varies from a few months to up to ten or more years with a mean of 3-5 years. About 90 % of ALS cases occur sporadically, whereas just 5-10 % are familial (fALS). Mutations of different genloci causing fALS have been described so far (ALS 1–8, ALSX, ALS-FTD) and some of them account for specific phenotypes. About 10 % of autosomal dominant fALS cases are due to mutations in the Cu/Zn superoxide dismutase gene (SOD1) located on chromosome 21 [15, 16]. Mutations in the *ALS2* gene cause an autosomal-recessive juvenile motor neuron disease. The phenotypical spectrum covers juvenile amyotrophic lateral sclerosis type 2 and primary lateral sclerosis (PLS), which encompasses a group of motor neuron diseases with isolated degeneration of the upper motor neuron. Furthermore, infantile-onset ascending hereditary spastic paraplegia (IAHSP) can be caused by mutations in the *ALS2* gene [17, 18]. The presented case of *ALS2* with an very early disease onset in childhood and rapid progression rate differs from other reported cases with an onset between 3 and 23 years

and inability to walk between 40 and 50 years [11, 19, 20]. So far, 10 *ALS2* gene mutations have been described. An obvious genotype-phenotype correlation does not exist and it remains unclear why similar mutations can result in three distinct clinical pictures.

Though juvenile ALS is a rare entity, it has to be kept in mind for differential diagnostics in cases of slowly progressive spasticity with pseudobulbar palsy with an onset in early childhood, even if family history is negative. Distal amyotrophies and paresis might appear late in the second decade of life. Electromyography can early detect lower motor neuron involvement. So far, no causal treatment is available. Besides a neuroprotective treatment with the glutamate antagonist riluzole [21] symptomatic treatment of symptoms like muscle cramps, spasticity, pseudobulbar affect, dyspnea or dysphagia, an adequate provision with adjuvants like wheel-chair or communication devices, and a consistent physiotherapy and speech therapy are of major interest [22] (Table 1).

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