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Stiff-Person Syndrome masking an atypical Chorea-Acanthocytosis-like syndrome

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Dear Editor,

Chorea-acanthocytosis (CA) is a rare autosomal recessive inherited neurodegenerative disorder caused by a loss-of-function mutation in the VPS13A gene, which codes for chorein.[1] It is a complex movement disorder characterized by involuntary movements, chorea, tics and dystonia. The onset is slow and progressive, often subtle, and occurs mainly in adulthood. Clinical manifestations are widely including temporal lobe epilepsy, peripheral neuropathy, myopathy, behavioral and psychiatric disorders.[1] Laboratory findings show elevated blood CK and liver enzyme levels, as well as increased numbers of acanthocytes in the peripheral blood smear. [1,3] it is very well-known that it's crucial for diagnosis to demonstrate the absence of chorein in erythrocytes and to reveal the VPS13A mutation to the diagnosis of ChAc, the diagnosis often remains presumptive due to the high cost and limited availability of these techniques.[1] Brain MRI is not specific but it can show caudate atrophy and additional findings such as hippocampal sclerosis and cortical atrophy. Although, differential diagnosis should exclude Huntington syndrome type 2, Mc Leod syndrome, pantothenate kinase-associated neurodegeneration, abetalipoproteinemia, cases of confounding Stiff person syndrome (SPS) have never been described. [1,2,3,4]

SPS is an autoimmune disorder associated with stiffness and muscle spasms, often caused by emotional or environmental triggers. The pathophysiology of this disorder remains poorly understood. Several case reports and literature reviews describe that SPS is more typical in women than in men, especially between the ages of 30 and 50, with disabling symptoms that are typically progressive and fluctuating. Major criteria for making a diagnosis of SPS include rigidity of axial and limb muscles, painful spasms precipitated by emotional stress or tactil stimuli, confirmed on EMG by continuous motor unit activity in agonist and antagonist muscles, absence of other neurological disorders or cognitive impairment that could explain the stiffness; minor criteria include anti-GAD positivity and clinical response to benzodiazepines.[5] The diagnosis of SPS is based on clinical manifestations, EMG, presence of antibodies, and response to diazepam.[5]

In this case report we describe an intriguing case of a patient with a typical SPS masking a CA highlighting the importance to potential unusual manifestation among patients with CA.

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Case report

A 33-year-old woman was admitted to our department for reported widespread muscle pain associated with morning stiffness, difficulty holding objects in both hands and exercise intolerance. At the age of 7, she underwent cardiac surgery for a Foramen Ovale Pervious (PDA). At the age of 20, she developed a slow and progressive exercise intolerance, described as difficulty walking for long periods, and later complained of hip pain, frequent fall injuries, and 'difficulty getting out of bed'. At the age of 28, she was diagnosed with polycystic ovary syndrome and adenomyosis. Previous reported blood tests showed increased CK (up to tenfold), LDH and liver enzymes (slightly increased) with one brother showing elevated CK but clinically silent. Several antibodies were searched such as antinuclear antibodies, anti-smooth muscle antibodies, hepatic microsomal type 1 antibodies, anti-parietal cell antibodies, anti-neutrophil cytoplasmic antibodies, anti-mitochondrial antibodies, extractable nuclear antigen, anti-cardiolipin and antiphospholipids but all resulted normal, thus suspecting a serum negative polymyositis she was treated with oral corticosteroids, methotrexate and cholecalciferol with improvement in pain and muscle stiffness. However, a couple of weeks later the muscle biopsy performed in September 2018 showed no alterations for diagnosis of polymyositis. To roll out the suspicion of mitochondrial diseases, a genetic search was conducted without significant results. Few years later (at the age of 33) sporadic rapid involuntary movements of the arms and legs started to appear during walking and the patient started tetrabenazine therapy suddenly withdraw because of intolerance. Very recently she displayed balance disorders with a tendency to fall, widespread paresthesias, insomnia, restlessness, clumsiness in fine movements (such as writing or holding tools), fatigue, weight loss, ecchymosis, dysmenorrhoea and amenorrhoea in the last 6 months.

On admission to our department, the neurological examination showed: attention deficit, restlessness, vocalisations (sighs), tongue protrusion for less than 10 seconds, unstable gait impaired by the presence of rapid involuntary movements in the lower limbs, whereby the patient often needed bilateral support, at the Pull test she took a step backwards, sporadic hyperkinetic movements, sometimes with choreiform features in the limbs which were also present at rest, normal eye movement; slight hypertonia with rigidity at axial level and at all four limbs, restlessness and muscle spasms in the lower limbs; no significant weakness; slight doubtful left hypoesthesia; reduced reflexes at all four limbs, plantar reflex in bilateral flexion. There were no signs of tongue biting; on general examination there was diffuse thinning of the hair over the scalp. Blood examination showed: high levels of CK (1749 U/L), low levels of ceruloplasmin (17 mg/dL) and cupremia (62 µg/dL); multivitamin deficiency with reduced levels of vitamin B1, vitamin B9 (folic acid), vitamin E, vitamin B1 and vitamin B12 (after discharge); absence of acanthocytes and presence of platelet aggregates on the blood smear; the expression of the Kell blood group antigen was normal. In addition, the X-linked inheritance and the female gender allowed to exclude pattern of McLeod syndrome. The diagnostic workup included neurophysiological examinations such as Electromyography (EMG), Motor Evoked Potentials (PEM), Somatosensory Evoked Potentials (SEPS), Auditory Evoked Potentials (PEA) which were normal except for the visual evoked potentials which showed a cortical evoked response P100 reduced in amplitude bilaterally. Therefore, idiopathic hyperCKemia not associated with metabolic or inflammatory disorders was initially considered on the basis of the clinic and the examinations performed. The cardiological examination and echocardiogram were normal. In addition, she underwent psychiatric counselling that showed the tendency towards orderliness and

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precision and the dysphoric mood. Neuropsychological tests carried out over several sessions due to the patient's reported fatigue, showed the presence of slight temporal disorientation, fluent speech even if slight stumbling in the production of words and the presence of slight anomic disturbances. The patient also showed regressive attitudes and numerous motivational disturbances, impaired attentional and executive cognitive functions, deficits in verbal anterograde memory, both long and short-term, and in the ability to access vocabulary according to semantic and phonological criteria. Subsequently, the patient underwent brain MRI, which showed a reduction in the volume of the head region of the caudate nucleus bilaterally, focal signal changes with hyperintensity in FLAIR and a reduction in the volume of both putamen. On slit-lamp examination by the ophthalmologist (for suspected Wilson's disease) but no Kayser-Fleischer rings were found.

In suspicion of a genetic disorder, she performed genetic counselling to search for mutations concomitant with Wilson's disease or Neuroacanthocytosis and the patient was discharged pending the results.

Two months later her neurological examination was unchanged; blood tests still showed a deficiency of vitamin B and D complexes and still high CK levels (1800 U/L). B complex and vitamin D supplements and low-dose pimozide (2 mg/day) were started. One month later, a telephone interview was performed to assess the response to treatment: the patient reported little improvement in pain and motor symptoms.

Finally, exon sequencing and multigenic analysis for neuroacanthocytosis, abetaliproteinemia, Wilson’s disease and other pathologies showed a deletion in exons 69 and 70 in the VPS13A gene.

Discussion

This complex case has failed to be associated with a specific diagnosis for more than 10 years, and the patient developed slowly progressive exercise intolerance, muscle pain, psychiatric symptoms, amenorrhoea with constantly elevated (up to 10-fold) CK blood levels. Inflammatory, metabolic and mitochondrial myopathies have been excluded for the past 15 years.

After admission to our department on neurological examination, a very subtle hyperkinetic movement disorder emerged, mostly with restlessness and muscle spasms in the lower limbs, which made us consider first a metabolic or endocrine-based hyperCKemia, dystothyroidism or acute liver failure. Thyroid hormones and TSH appeared normal, ruling out an underlying thyroid pathology. Apolipotreins A and B were in the reference range, which led us to exclude Bassen-Kornzweig disease. In addition, there was evidence of B-complex hypovitaminosis, particularly of thiamine, which could suggest gastrointestinal pathology or malabsorption or alcohol abuse, which the patient denies.[2]

Despite low levels of ceruloplasmin and cupremia, no Kayser Fleischer rings were found at the slit lamp and no specific signs of Wilson's disease on brain MRI. Brain MRI also exclude pantothenate kinase-associated neurodegeneration (PKAN) due to the absence of the characteristic 'eye of the tiger', hypointensity reflecting areas of iron deposition in T2-weighted sequences. But brain MRI showed severe bilateral hypotrophy of the caudate nucleus, characteristic of both Huntington disease (HD) and Neuroacanthocytosis (CA).[2,6]

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The neurological examination exhibited clinical manifestations not be correlated with Huntington disease, and the patient's progressive neurological manifestations associated with the psychiatric and cognitive disturbances made us suspect at first SPS in its early phase, supported firstly by the symptoms, patient response to the empirical immunosuppressive treatment carried out on rheumatological indication, and to the treatment with diazepam in the first few days in our department, which slightly improved the patient's symptoms. Although the symptoms were strongly related to SPS, negative EMG and the absence of anti-GAD led us to the necessity to perform further investigations and exclude other pathologies.

In the suspicion of a CA we performed a blood smear with no evidence of acanthocytes. Genetic tests were performed and showed a homozygous deletion mutation of exons 69 and 70 in the VPS13A gene, suggesting a CA-like syndrome. Regarding to the absence of acanthocytes, their presence is not mandatory for the diagnosis of CA and they can also appear later on follow-up.

Conclusion

There is a lack of literature regarding CA with only two cohort clinical studies and one meta-analysis. The remaining papers are reviews or case reports in which all patients presented severe involuntary buccal and perioral movements, even with self-mutilation of the tongue; symptoms of the neuromuscular and gynecological sphere are less described.

In the present case the diagnosis was made more than 10 years after the clinical onset, thus the incidence of CA might be underestimated and masked by other pathologies with which CA shares some symptoms. A better clinical, neuroimaging and genetic descriptions are necessary to better diagnose this rare condition. For this reason, it is essential to consider rare hypotheses and to suspect when dealing with a clinical presentation of SPS also a possible CA.

We are aware of the major limitation of this study, the lack of a western blot search for chorein or RBCs on muscle tissue that could have strengthened more the final diagnosis.

Author Contributions

F.L. contributed to the conception and design of the study. A.M., C.T., V.R., L.M., I.A. were responsible for data collection. A.L. (Laganà) was responsible for the drafting. F.G. was responsible of imaging acquisition. A.L. (Labate) and all authors contributed to the manuscript revision and approved the submitted version.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ISSN: 3035-062X
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