Case Report

Chorea-acanthocytosis: Report of Three Cases from Iran

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Abstract

Chorea-acanthocythosis (ChAc) is an inherited neurodegenerative disorder characterized by movement disorders, neuropsychiatric disturbances, neuropathy, myopathy, seizures and acanthocytosis accompanied by an elevated serum creatine kinase (CK) level. Its causative gene (*VPS13A)* produces chorein which is absent in ChAc patients as evaluated by Western blot assay. We report the first three Iranian patients whose disease has been confirmed by chorein Western blot. Our cases presented with heterogeneous courses of ChAc. A high sense of clinical awareness in approaching patients with deteriorating and/or multiple abnormal movements that are accompanied by other neurological signs such as neuropathy, myopathy, seizures and high serum CK level will support an early diagnosis of this disease. We also emphasize on the presence of axial flexion/extension spasms as a good clinical sign for narrowing differential diagnosis.

Keywords: Acanthocytosis, chorea-acanthocytosis, feeding dystonia, trunk flexion

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Introduction

Chorea-acanthocytosis (ChAc) is a rare autosomal recessive neurodegenerative disorder caused by mutations in the *VPS13A* gene that codes for chorein.[1,2] It is characterized by chorea, neuropathy, seizures, neuropsychiatric disorders and cognitive decline in association with acanthocytosis.[3,4] The course of the disease consists of heterogeneous manifestations during its early stages,[5] such as dystonia and psychosis,[6] and may take many years to evolve into its classic features.[7] Laboratory investigations commonly reveal elevated creatine kinase (CK) and lactate dehydrogenase (LDH) levels.[1] As the causative gene is very large (73 exons) and has no specific hot spot, genetic confirmation of ChAc is difficult.[1,8] Thus, evaluation of chorein levels in the erythrocyte membranes by Western blot is a useful alternative.[9,10] Absent or reduced levels of chorein are highly suggestive of ChAc.[9]

Case Reports

Case 1

This 48-year-old man referred to our clinic for abnormal gait, bruxism and tongue biting. He was born to unrelated parents. The early years of his life were unremarkable. At the age of 37 years, this patient experienced his first generalized seizure while asleep, for which he received a variety of antiepileptic drugs [sodium valproate (1200 mg/d), carbamazepine (1200 mg/d), and topiramate (200 mg/d)]. Despite treatment, he had poor seizure control. Additionally, he noticed difficulty in walking and abnormal posturing of his right leg at age 45. Soon after, he developed involuntary tongue and jaw movements. Cheek and tongue biting forced him to wear gum shields. These abnormal movements generalized over the next three years. His speech became slurred and gradually unintelligible. His wife reported intermittent motor tics, impulsivity and memory decline. At age 48, he had generalized chorea, dysarthria, dysphagia, feeding dystonia and bruxism. Muscle strength was normal and tendon reflexes were elicitable with normal touch and position sensations. During the last follow up at age 50, the patient was hypokinetic with hesitation in walking, postural instability and falls. Saccades were hypometric and pursuits were fragmented, but in full range. Speech was dysarthric and difficult to understand. Tongue protrusion dystonia was seen occasionally and he frequently pushed out the gum shields during examination. Although muscle strength remained normal, deep tendon reflexes were reduced. Laboratory investigation revealed a regular level of acanthocytes in routine wet preparations, elevated CK to 220 U/L (normal < 177 U/L) and bilateral caudate atrophy on a brain CT scan. Chorein Western blot revealed an absence of chorein (Figure 1).

Case 2

This 41-year-old man (P1 in Figures 1 and 3) reported his first generalized seizure during sleep at age 17 years, after which he remained seizure-free without antiepileptic treatment. At the age 38, he developed abnormal gait and dyskinesia in his right leg. Over the next two years, symptoms progressed rapidly and he had difficulty in talking, swallowing and walking with frequent falls. Meanwhile, he experienced two generalized seizures that were controlled successfully with sodium valproate. At age 39, he was seen for the first time in our clinic with generalized chorea, abnormal wide-based gait, generalized hypotonia and areflexia, dysarthria, dysphagia, tongue protrusion and feeding dystonia without tongue biting. In the last follow up at age 41, his chorea and dysarthria worsened. In oculomotor examination, pursuits were normal and saccades had intermittent initiation delay and gaze palsy to the right side. In the sitting position, frequent trunk and head backward extensions resulted in the patient knocking his head on the wall. Gait was severely unstable with sudden knee and trunk flexions.

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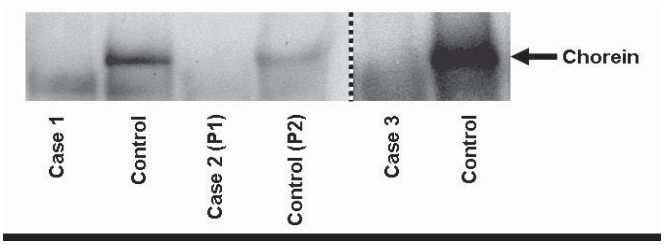

Figure 1. Chorein Western blot analysis. Arrow indicates the expected height of a normal full length chorein band at 360 kDa. The dotted line separates two independent Western blots.

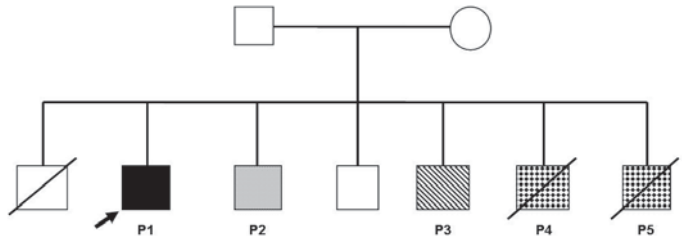

Figure 3. Pedigree of case 2. P1 (index patient) = chorea + epilepsy + flexion/extension; P2 = asymptomatic + reduced chorein; P3 = epilepsy; P4, P5 = progressive epilepsy + encephalopathy.

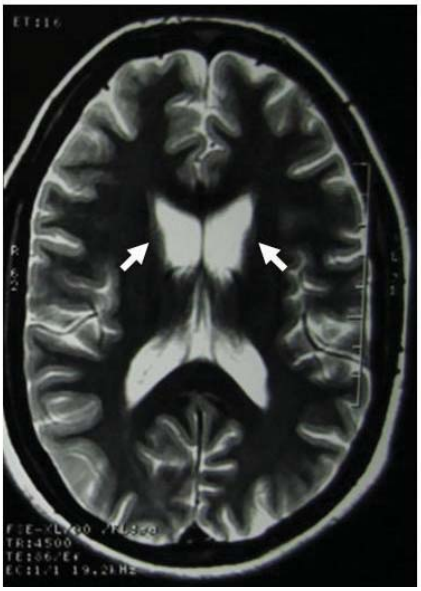

Figure 2. T2 weighted brain MRI of case 3 displaying bilateral caudate atrophy (white arrows) and ventricular enlargement.

Laboratory investigations revealed acanthocytosis, elevated LDH and CK levels and bilateral caudate atrophy on the brain MRI scan. An electrophysiological study demonstrated sensory-motor axonal polyneuropathy. Chorein was absent (Figure 1). The patient and his six brothers were born to healthy unrelated parents (Figure 3). His elder brother was normal until he drowned in the sea at age 12. One asymptomatic brother (P2) was also tested by chorein Western blot and a reduction of chorein was confirmed (Figure 1). Another brother (P3) was diagnosed with epilepsy at the age of 30. He had no chorein according to Western blot assay. The last two siblings developed epilepsy at age 1 year with progressive mental and physical regression (P4, P5). Both became bedridden and died during sleep at age 6, most likely as a consequence of seizure-induced asphyxia.

Case 3

A 28-year-old woman referred to our clinic for evaluating her phonic and motor tics and tongue biting. She was born to consanguineous parents and her childhood development was unremarkable. Her symptoms began at age 15 with phonic tics (chicken like sounds). During a period of approximately one decade, her symptoms progressed slowly with mild motor tics and choreic movements. At age 25, she developed dysarthria and dysphagia with hypersalivation and drooling. One year later, feeding dystonia and tongue biting worsened. She lost 30 kg of weight in three years due to dysphagia. Between ages 26 and 28, she experienced two generalized seizures that were completely controlled with lamotrigine and phenobarbital. Gum shields and botulinum toxin type A (Dysport; Ipsen, UK) injections into the genioglossus muscle moderately improved self-mutilation. At last follow up, examination revealed normal gait, mild choreic movements in her face, mild phonic tics, generalized hypotonia and hyporeflexia, postural instability and mild kyphosis with intermittent head drops in the sitting position. Speech was slurred with marked drooling. As seen in Table 1, laboratory investigations showed elevated levels of acanthocytes, CK (233 U/L) and LDH (533U/L; normal: < 350 IU/L). Brain MRI showed bilateral caudate atrophy (Figure 2) and an EEG revealed bitemporal polyspike paroxysms. Chorein was absent in Western blot analysis (Figure 1).

Discussion

The combination of chorea and other movement disorders, seizures, neuropathy and neuropsychiatric symptoms in association with elevated CK levels is strongly suggestive of ChAc.

Seizures are common in ChAc and appear in approximately 40% of patients,[7] though they may appear late, even after abnormal movements[6,7] or very early as presenting signs.[11,12] Al-Asmi et al. have reported two French-Canadian families who had temporal lobe epilepsy as an early manifestation of ChAc.[11] All were adults when seizures began and the gap between seizure and involuntary movements was less than 15 years. On the other hand, Scheid et al. described two cases of young onset ChAc with one 14-year old patient initially presenting with temporal lobe epilepsy.[12] In cases 1 and 2 described here, seizures were the presenting symptoms. Notably, in case 2 the first seizure occurred 21 years before the appearance of abnormal movements. Two of the brothers of case 2 (P4, P5) had progressive epilepsy and encephalopathy with psychomotor retardation at very young ages which most likely led to their demise in early childhood. Whether they suffered from another disease or died as a result of ChAc remains unsolved as no material for genetic or chorein Western blot analysis was available. However, it was possible that homozygous or heterozygous mutations in *VPS13A* were the underlying causes for this very early clinical manifestation as heterogeneity within the same family has also been described.[5]

Axial symptoms such as head drops, truncal flexions and backward extensions have been reported previously in patients with ChAc.[13] In a recently published article, Schneider et al. emphasized that sudden axial flexion/extension movements were features strongly suggestive of ChAc.[14] Case 2 described here showed severe axial symptoms with position dependency and pattern shift-

ing during walking and sitting. In the sitting position, backward extension of the neck and trunk were predominant while standing and walking were marked by sudden knee and truncal flexions. Despite lack of definite phenomenology, forward movements appeared similar to negative myoclonic atony while backward extensions had a dystonic appearance. Chorea or positive myoclonic jerks could be responsible for axial symptoms due to muscle contractions.

Absence of acanthocytosis in the first case might be the result of a non-standardized methodology in preparing and evaluating blood smears. Using the recommended method by Storch et al. increases the chance of finding acanthocytes.[15,16] However, determining chronically elevated CK levels in serum independent from recent seizures is a more reliable method.

For rare disorders with clinical heterogeneity and variable course of disease, a high sense of clinical awareness is necessary. Distinctive clinical features such as tongue protrusion and feeding dystonia, axial flexion/extension, chorea, multisystem involvement and elevated CK are strong clues for ChAc in particular or neuroacanthocytosis in general.[17,18] In such cases, chorein Western blot assay should be performed. Harirchian et al.[19] reported the first case of ChAc in Iran, followed by two other reports by Nikkhah et al. and Ghoreishi et al.[20,21] In the latter report, Ghoreishi et al. pointed out to paroxysmal oromandibular dyskinesia in their patient that was unmasked by Botulinum toxin injection, however they neither defined nor described the condition precisely. Then, presence of such phenomenon in ChAc is in doubt and more observations are needed for its confirmation. In addition, in all above reports diagnosis was based on clinical features and certain laboratory tests without molecular and genetic confirmation. Our report is the first case series from Iran with molecular confirmation of the clinical diagnosis.

Acknowledgments

Chorein Western blot is available free of charge. Please see more information at http://www.euro-hd.net/html/na/submodule or inquire by E-mail: bbader@med.lmu.de. *The diagnostic test is supported by the Advocacy for Neuroacanthocytosis Patients, London, UK and the Center for Neuropathology and Prion research (Prof. H. Kretzschmar), Munich, Germany.*

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