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Clinical variability of neuroacanthocytosis syndromes—a series of six patients with long follow-up

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ABSTRACT

Objective: To provide clinical clues to differential diagnosis in patients with chorea and other movement disorders with blood acanthocytes.

Methods: We present a long-term video accompanied follow-up of six Caucasian patients with neuroacanthocytosis from several centers, three diagnosed with chorea-acanthocytosis (ChAc): 34-y.o.(no.1), 36-y.o.(no.2), 43-y.o.(no.3), two diagnosed with McLeod Syndrome (MLS): 52-y.o.(no.4), 61-y.o.(no.5) and one 63-y.o.(no.6), a brother of no.5, with clinical suspicion of MLS. Additionally we report pathological findings of the mother of two brothers with MLS reported in our series with acanthocytes on peripheral blood smear

Results: The patients had an unremarkable family history and were asymptomatic until adulthood. Patients no. 1,2,4,5,6 developed generalized chorea and patient no. 3 had predominant bradykinesia. Patients no. 1,2,3 had phonic and motor tics, additionally patients no. 1 and 2 exhibited peculiar oromandibular dystonia with tongue thrusting. In patients no. 2 and 3 dystonic supination of feet was observed, patient no. 3 subsequently developed bilateral foot drop. Patients no. 2 and 4 had signs of muscle atrophy. Tendon reflexes were decreased or absent and electroneurography demonstrated sensorimotor neuropathy in patients no. 1,2,3,4,5, except no. 6. Generalized seizures were seen in patients no. 2,3,5,6 and myoclonic jerks in patient no. 1. Cognitive deterioration was reported in patients no. 1,2,3,5,6. Serum creatine kinase levels were elevated in all six patients.

Conclusion: We highlight the variability of clinical presentation of neuroacanthocytosis syndromes and the long time from the onset to diagnosis with the need to screen the blood smears in uncertain cases, however, as in one of our cases acanthocytes may even be not found.

Based on our observations and data from the literature we propose several red flags that should raise the suspicion of an NA syndrome in a patient with a movement disorder: severe orofacial dyskinesia with tongue and lip-biting (typical of ChAc), feeding dystonia, psychiatric and cognitive disturbances, seizures, peripheral neuropathy, elevation of creatine kinase, elevation of transaminases, hepatosplenomegaly, cardiomyopathy and arrhythmias, and an X-linked pattern of inheritance (McLeod Syndrome, MLS).

1. Introduction

Neuroacanthocytosis (NA) is a broad term that refers to a group of heterogeneous nervous system disorders that are associated

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Table 1
Summary of clinical and laboratory findings in our case series (ALT- alanine transaminase, AST- aspartate transaminase, Ch-Ac – chorea-acanthocytosis, GGT- γ-glutamyl transferase, MLS – McLeod syndrome).

	Patient no. 1	Patient no. 2	Patient no. 3	Patient no. 4	Patient no. 5	Patient no. 6
Age	34	36	43	died at age of 52	61	63
Diagnosis	Ch-Ac	Ch-Ac	Ch-Ac	MLS	MLS	clinical suspicion of MLS
Family history	unremarkable	unremarkable	unremarkable	positive for heart disease	mother (acanthocytosis)	mother (acanthocytosis)
Age of onset	20	24	Late 20's	45	early 20's	early 20's
Age at diagnosis	31	29	42	51	52	–
First symptoms	simple vocal tics	involuntary tongue movements and vocalizations	epileptic seizures	orofacial and limb dyskinesia, irritability, restlessness	choreiform movements (unspecified)	choreiform movements (unspecified)
Chorea	Generalized	Generalized	No	Generalized	Generalized	Generalized
Dystonia	oromandibular region, four limbs	oromandibular region, feet	mild tongue dystonia	present	no	no
Orofacial dyskinesias	present	present	no	present	present	present
Involuntary vocalizations	present	present	no	no	no	no
Tongue and lip biting	present	no	no	no	no	no
Dysarthria	present	present	present	present	no	no
Dysphagia	present	present	no	no	no	no
Parkinsonian features	no	no	bradykinesia	no	no	no
Tendon reflexes	areflexia of the lower extremities	areflexia of the four limbs	areflexia of the lower extremities	areflexia of the four limbs	areflexia of the four limbs	areflexia of the four limbs
Muscle weakness	no	no	bilateral foot drop	no	no	distal muscle weakness
Neuropsychiatric symptoms	present	present	present	present	present	present
Cognitive impairment	present	present	present	no	present	present
Seizures	myoclonic jerks	generalized	complex partial and generalized	no	generalized	generalized
Neuroimaging	hypointensity in the globi pallidi	mild subcortical atrophy	atrophy of putamina and caudate nuclei	atrophy of the heads of the caudate nuclei	data not available	data not available
Electromyoneurography	sensorimotor neuropathy	sensorimotor neuropathy	sensorimotor neuropathy	sensorimotor neuropathy	sensorimotor neuropathy	non-specific
Cardiomyopathy	left atrial dilation	no	data not available	present	no	no
Hepatosplenomegaly	data unavailable	present	data not available	data unavailable	data unavailable	data unavailable
Creatine Kinase	1200–3600 (U/l)	950–1100 (U/l)	27 microkat/l (ref. 0.80–6.7)	22.4 (ref. 0.16–1.33)	1600–3200 (U/l)	1600–3200 (U/l)
Transaminase levels	elevated ALT and AST; no data about GGT	elevated ALT and AST; GGT within the norm	elevated AST; ALT and GGT within the norm	elevated ALT, AST and GGT	elevated ALT, AST and GGT	elevated ALT, AST and GGT
Acanthocytes	detected	detected	detected	not proved	detected	detected

Table 2
"Red flags" that should raise the suspicion of NA in a patient with a movement disorder (Ch-Ac – chorea-acanthocytosis, CK – creatine kinase, MLS – McLeod syndrome).

Severe oromandibular dyskinesia with tongue-and lip-biting (typical of ChAc)
feeding dystonia
psychiatric and cognitive disturbances
Seizures
Peripheral neuropathy
Elevation of CK
Elevation of transaminases
Hepatosplenomegaly
Cardiomyopathy (MLS)
X-linked pattern of inheritance (MLS)

with spiny red blood cells (acanthocytes). These disorders may be divided into two main groups: NA syndromes affecting the basal ganglia and those consisting of decreased plasma lipoproteins.

The first group includes NA syndromes that primarily affect basal ganglia and manifest as movement disorders and cognitive impairments with psychiatric features, similar to Huntington's disease (HD), but also seizures in a half of patients, myopathy and axonal neuropathy. This group comprises the "core" NA syndromes, as autosomal recessive chorea-acanthocytosis (Ch-Ac) and X-linked McLeod syndrome (MLS) and is associated with mutations of the *VPS13A* and *XK* genes, respectively. Acanthocytosis is also seen in other genetic conditions such as panthotenate kinase-associated neurodegeneration (PKAN) and Huntington disease-like 2 (HDL2) syndrome. The second group of NA syndromes consists of disorders characterized by decreased plasma lipoprotein levels (primarily abetalipoproteinemia and hypobetalipoproteinemia) with concomitant peripheral neuropathy and ataxia due to dorsal column degeneration [1–5].

The prevalence of "core" NA syndromes, perhaps the second most common cause of hereditary chorea after HD [5], is very low. It is estimated that there are approximately one thousand patients with Ch-Ac and only a few hundred patients with MLS worldwide [3,6]. However, NA syndromes may be underdiagnosed due to the rarity of the disease and its high clinical variability.

In this report we present a long-term, video accompanied follow-up of six Caucasian patients with NA from different centers in Europe and USA (Table 1). We suggest clinical clues to the differential diagnosis of patients with chorea and other movement disorders that are associated with the presence of blood acanthocytes (Table 2).

2. Materials and methods

2.1. Case 1

A 34-year-old man was asymptomatic until the age of 20 years, which was when he developed simple vocal tics followed