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Phenomenology and disease progression of chorea-acanthocytosis patients in Spain

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1. Introduction

Neuroacanthocytosis (NA) comprises the association of movement disorders (MD) and spiny erythrocytes [1]. Autosomal recessive chorea-acanthocytosis (ChAc) is one of the core NA syndromes [2]. It is caused by mutations in the vascular protein sorting 13 homolog A gene (VPS13 A) [3,4] which encodes for the chorein protein [5]. Its prevalence is estimated to be around 1000 cases worldwide [6]. However, some areas such as the Japanese or the French-Canadian community [7] may have a higher prevalence.

Disease phenomenology is heterogeneous including psychiatric manifestations, seizures, neuromuscular involvement with myopathy and peripheral neuropathy as well as MD [8,9]. Some phenomena including head-drops, feeding dystonia and orolingual dyskinesias are especially characteristic [9,10] of ChAc.

Genetic testing is a cumbersome process due to the large size of the gene. Recent publications proved that diagnosis could also be established by detecting loss of chorein expression with Western Blot [11]. Due to its low prevalence there is a scarcity of literature regarding prognosis and treatment response. There are only few clinical series in which most of the reported cases lack molecular confirmation.

We here report a collaborative descriptive study of ChAc patients in Spain.

2. Materials and methods

We contacted Movement Disorders specialists across Spain potentially involved in the treatment and management of patients with ChAc. A standardized questionnaire with demographics, phenomenology, ancillary testing, treatment and disability scales (UHDRS independence scale) were requested, as well as video recordings and MRI images when available. All the participants gave their informed consent to participate in the study, videotaping and publication.

3. Results

We describe twelve patients from nine different families, of which seven subjects came from the Spanish region of Extremadura. Mean age at disease onset was 24 years (range 6–34) and diagnosis was made at a mean age of 34 (26–42). Mean follow-up was 18 years since disease onset.

The diagnostic process included in all the cases a detailed anamnesis and a neurological examination revealing a characteristic phenotype consistent with a ChAc syndrome, including motor, psychiatric and cognitive manifestations (see Table 1). Ancillary testing supporting the diagnosis included in most cases determination of acanthocytosis in peripheral blood smears, brain MRI, serum CK determinations and electrophysiological studies of the peripheral nerves. When available, chorein determinations [11] and a confirmatory DNA analysis of the large VPS13A gene were performed (http://www.mgz-muenchen.de). (See Table 2).

3.1. Clinical presentation(Tables 1 and 2)

Nine patients developed seizures during follow-up. All but one patient remained seizure-free with a single antiepileptic treatment. One patient experienced disease debut with status epilepticus. Ten patients experienced psychiatric symptoms, preceding movement

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Table 1
MD: Movement disorder; OCB: Obsessive compulsive behaviour; ADHD: Attention deficit, hyperactivity disorder. NA: Information not available.

Patient	Area	Age at last follow-up	Sex	Age at diagnosis	Age at onset	First symptoms	Seizures	Psychiatric symptoms	Dysphagia	Dysarthria	Main MD at last examination	MD age at onset	Chorea	Dystonia	Parkinsonism	Tics	Death
1a	Extremadu-ra	49	Female	unknown	19	Psychiatric	+ (36)	Depression (19)	–	+	Parkinsonism	36	–	+ (39)	+ (36)	–	–
1b	Extremadu-ra	41	Male	unknown	30	Tics and chorea	+ (30)	Depression (30)	+	+	Dystonia	30	+ (34)	+ (NA)	–	–	–
1c	Extremadu-ra	48	Male	unknown	33	Tics and corea	+ (33)	OCB (42)	+	+	Chorea	37	+ (36)	–	–	+ (33)	–
1d	Extremadu-ra	34	Male	34	25	Psychiatric	+ (29)	OCB (25)	–	+	Chorea and dystonia	29	+(29)	+ (29)	–	+ (34)	+ (35)
2	Castilla la Mancha	41	Female	unknown	25	Chorea	+ (33)	–	–	+	Chorea and tics	25	+ (25)	+ (25)	+ (33)	–	–
3	Extremadu-ra	32	Male	29	15	Psychiatric	+ (28)	OCB (15)	+	+	Chorea	30	+ (30)	+ (31)	–	+	–
4	Extremadu-ra	49	Female	36	26	Chorea	–	Depression and OCB (35)	+	+	Parkinsonism	32	+ (32)	+ (38)	+ (42)	+ (37)	–
5	Catalonia	39	Male	33	27	Tics	–	Depression and OCB (28)	+	+	Tics and Chorea	27	+ (29)	+ (37)	–	+ (27)	–
6	Basque Country	38	Male	33	6	Orolingual dyskinesias	–	ADHD (6)	–	+	Chorea	33	+ (33)	+ (34)	–	+ (6)	–
7	Puerto Rico	43	Male	42	34	Seizures	+ (42)	–	+	+	Chorea	NA	+ (NA)	+	–	+	–
8	Asturias	39	Male	36	27	Seizures	+ (26)	Depression, anxietyand OCB (25)	+	+	Dystonia and tics	33	–	+ (33)	+ (36)	+ (33)	–
9	Extremadu-ra	40	Female	26	20	Chorea	+ (25)	Depression (30)	+	+	Dystonia	20	+ (25)	+ (25)	+ (25)	–	NA

disorders (MD) in all but two patients, with a mean age at onset of 25.5 years (6–42). Six suffered depression and four obsessive compulsive behaviours. Remarkably one patient was diagnosed with attention deficit and hyperactivity disorder when aged six.

The most prevalent MD during follow up were chorea and dystonia. Parkinsonism was the most tardive and least frequent MD. Early and severe dysarthria was present in all. Dysphagia was also evident in the vast majority of patients suggesting bulbar involvement in early stages of the disease. Only one patient did not present any of ChAc characteristic phenomena (feeding dystonia, head-drops, orolingual dyskinesias/mutilations) (See Table 2).

3.2. Ancillary testing & diagnosis(Table 3)

All but one patient presented peripheral neuropathy with altered conduction velocity studies. All had elevated creatinine phosphokinase indicating the presence of myopathy.

MRI was performed in 11 patients. Major caudate atrophy was present in five patients, caudate and putamen atrophy in two and basal ganglia hyperintensities in another two patients.

Acanthocytes were tested in 11 patients and were found to be elevated in 8. Five patients were diagnosed after finding an absence of chorein on Western Blot analysis. On the other hand, 8 patients were found to have a mutation in the VPS13A gene. In one case molecular analysis did not reveal any mutation in the VPS13A gene and chorein could not be tested due to loss of follow-up, but patients' phenotype was highly suggestive of ChAc and acanthocytes were elevated. (see video, patient 9).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2017.10.016

Different pharmacological treatment approaches were used. Most frequently prescribed drugs were antiepileptics, atypical antipsychotics and benzodiazepines all taken by nine patients. Seven patients received selective serotonin reuptake inhibitors either for irritability or depression. Seven patients were receiving antichoreic treatment with tetrabenazine. Five typical antipsychotics, two anticholinergics and one levodopa. Response was generally poor regarding MD and psychiatric symptoms, but all had significant improvement in seizure frequency with antiepileptics.

Three patients underwent deep brain stimulation of GPi for the treatment of chorea (2 patients) and dystonia (1 patient). Mean follow-up after surgery was 6 years (2–10). Despite an excellent initial response, progressive lack of efficacy was observed in all cases. One patient experienced malfunction of the deep brain stimulation device due to Twiddler's syndrome [12] secondary to severe chorea, requiring lead replacement. When aged 47; seven years after surgery, the device had to be switched off after emergence of progressive akinesia and gate deterioration while the stimulator was on [13].

3.3. Prognosis

One patient committed suicide when he was 35 years old, nine years after of disease onset. Progressive disability was invariably seen. Five years after disease onset 50% of the patients maintained self-care abilities. Six years after disease onset mean score on independence scales was 70% and after 10 years every patient needed 24-h supervision (Fig. 1).

3.4. Literature review

A total of 40 confirmed cases with clinical descriptions have been reported so far [2,6,7,14–18]. Age at onset ranged from 15 to 42 years. Seizures were the most common symptom at onset (16 patients) followed by MD (14 patients) while only a 3 patients