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Phenotypic Variability of a Distinct Deletion in McLeod Syndrome

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Video 

Abstract: The X-linked McLeod neuroacanthocytosis syndrome strongly resembles Huntington's disease and has been reported in various countries world-wide. Herein, we report two Chilean brothers with predominant psychiatric

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features at disease onset including schizophrenia-like psychosis and obsessive compulsive disorder. Molecular genetic analysis revealed a small deletion in the *XK* gene (938-942delCTCTA), which has been already described in a North American patient of Anglo-Saxon descent and a Japanese family, presenting with seizures, muscle atrophy or chorea yet absence of psychiatric features. These findings argue against a founder effect and indicate a profound phenotypic variability associated with the 938-942delCTCTA deletion. Our report supports the inclusion of McLeod syndrome in the differential diagnosis of Huntington's disease as well as acute psychosis in male subjects. © 2007 Movement Disorder Society

Key words: McLeod syndrome; neuroacanthocytosis; chorea.

McLeod syndrome (MLS) is an X-linked multisystem disorder with central nervous system (CNS) features similar to Huntington's disease with a mean onset age ranging from 30 to 40 years.¹⁻⁴ Hematologically, MLS is characterized by absent Kx red blood cell (RBC) antigen and weak expression of Kell RBC antigens (the so-called McLeod blood group phenotype), acanthocytosis, and compensated hemolysis.^{5,6} Carriers of the McLeod blood group phenotype have elevated serum creatine phosphokinase (CK) levels.¹⁻³ Neuromuscular manifestations usually are subclinical or mild and include myopathy, cardiomyopathy, and sensory-motor axonal neuropathy.^{3,7,8} CNS manifestations comprise a choreatic movement disorder, psychiatric symptoms, cognitive decline, and generalized epileptic seizures.¹⁻³

MLS has been reported from Europe, North America, Australia, Japan, and Brazil.^{1-3,9,10} We report a Chilean McLeod family of German descent with predominant psychiatric manifestations at disease onset. They harbored a distinct disease-causing mutation already known from patients differing in clinical presentation as well as in geographical and ethnical background.

PATIENTS AND METHODS

The two brothers reported herein had nonconsanguineous parents and grew up in Chile. Their ancestors immigrated in the mid 19th century from South West Germany. No alliances with Hispanic or indigenous persons were known. Based on the statements of the brothers and her mother, there was no family history of neurological or psychiatric disorders in both parents, in particular. The two brothers were assessed by means of neurological and neuropsychological examination, laboratory evaluations, computed tomography (CT), electromyography, and cardiological examinations. A part of these observations had been reported previously in a Chilean review.¹¹ The study was approved by the local ethical committee and all subjects gave written informed consent.

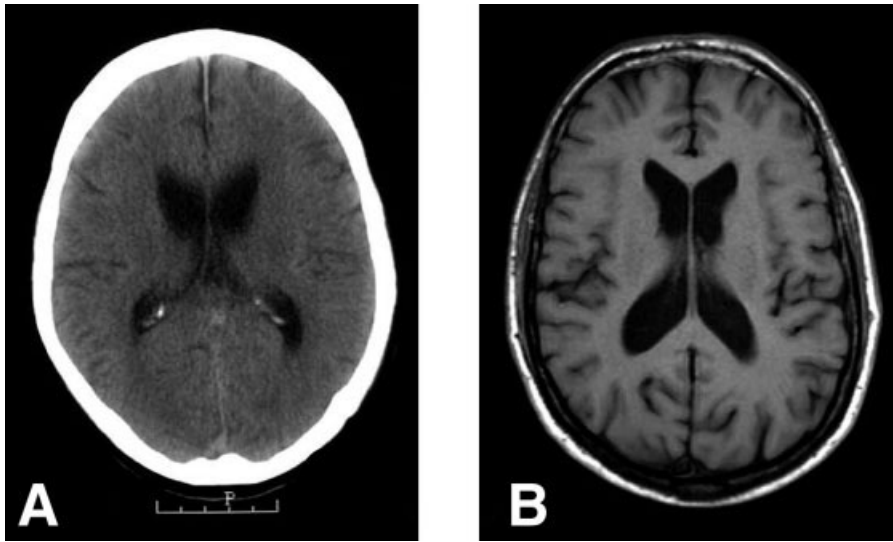


FIG. 1. Neuroradiology Brain CT scan of Case 1 (A) and T1-weighted cerebral MRI of Case 2 (B) showing pronounced caudate atrophy with consecutive enlargement of the anterior horn of the lateral ventricles.

CASE REPORT AND RESULTS

Case 1

The younger brother presented at our department at the age of 54 years. He had a normal childhood psychomotor development and school performance, and became a merchant. At the age of 23 years he presented with a psychotic disorder characterized by paranoid delusions with auditory hallucinations and social withdrawal necessitating a psychiatric hospitalization. Based on the clinical notes from that time, there was no evidence for a mood disorder or neurological abnormalities. Diagnosis of paranoid schizophrenia was made and he was discharged on chlorpromazine 200 mg daily. Three years later, he discontinued medical treatment. He experienced another acute psychosis and haloperidol 5 mg was started. At the age of 29 years, choreatic movements were noted for the first time but thought to be drug-induced. During the following years, his psychiatric condition and the movement disorder remained stable despite the medication has been discontinued. In the last years before admission, however, paretic gait developed. At age 54 years, a first neurological examination was performed. He was alert and fully oriented. Cognitive testing demonstrated moderate cognitive deficits with predominant frontal lobe dysfunction. There was a reduced score in the Mattis Dementia Rating Scale (117/144 points; normal 142 ± 2), impairments on trail making tests (Test A 74 seconds, Test B stopped after 4 min with six faults), false recognition in the Grober-Buschke test, impairments on the Controlled Oral Word Association Test (8, 8, and 6 words), a pathological Wisconsin card sorting (two mistakes, failure to keep criteria and

numerous perseverations), and a poor performance on the frontal assessment battery test (FAB; 7/18 points; normal; normal 17.3 ± 0.8). Psychiatric evaluation by a psychiatrist revealed no hallucinations or delusions, normal formal thoughts and ideation, slightly depressed mood but no evidence for anxiety, obsession, or compulsion. There were mild choreatic movements of trunk and limbs but no facial dyskinesias. Cerebellar or pyramidal tract dysfunction was absent. There was marked atrophy of all four limbs, moderate paresis (MRC Grade 3–4), and paretic gait. Deep tendon reflexes were absent. There were no sensory disturbances and vegetative functions were normal. Laboratory evaluation showed increased serum CK (400 U/L; normal <200). Analysis of the Huntington's disease gene revealed no abnormal CAG expansion. In a conventional blood smear, less than 2% acanthocytes were seen. However, dilution of the blood with heparinized isotonic saline solution following the protocol of Storch et al.¹² resulted in acanthocytosis of 23%. Electromyography of proximal upper and lower limb muscles revealed a myopathic pattern. Cardiological evaluation including electrocardiogram and transthoracic echocardiogram were normal. Cerebral CT showed pronounced caudate atrophy (Fig. 1A).

Case 2

The elder brother, a chemical engineer, presented at the age of 57 years. He also had a normal childhood psychomotor development and school performance. He reported a 9-year history of a choreatic movement disorder associated with episodic major depression. He noted reduced ability to concentrate at work and diminished ability to control his emotions in the every-day life. In addition, he showed

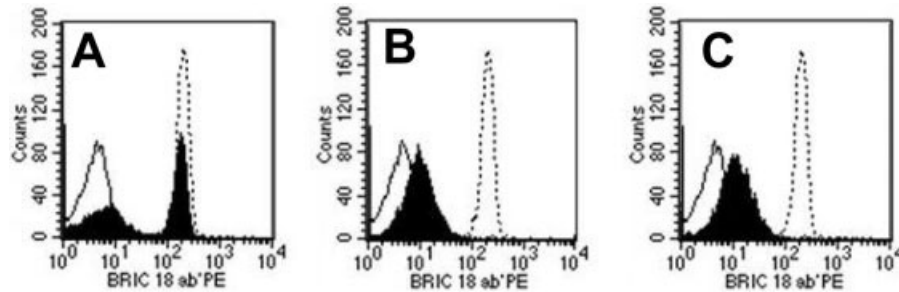


FIG. 2. Flow Cytometry Flow cytometry of fresh red blood cells from the mother (A), Case 1 (B), and Case 2 (C) using anti-BRIC18. Blood donor cells expressing normal Kell phenotype (dotted line) were used as positive control and ZZAP treated blood donor cells mimicking K_0 cells (solid line) were used as negative control. The heterozygous mother (A) had red blood cells with suppressed Kell protein as found in their sons as well as red blood cells with normal expression of the Kell protein. Case 1 (B) and case 2 (C) showed severe suppression of BRIC18 expression. Stainings with anti-BRIC68 and anti-BRIC203 gave identical results (data not shown).

compulsive checking and ordering in symmetry and exactness as well as stockpiling of various goods. Psychiatric evaluation by a psychiatrist revealed no hallucinations or delusions, slightly narrowed formal thoughts, normal mood, no anxiety but an obsessive-compulsive disorder according to the DSM-IV (32/64 points Yale-Brown obsessive compulsive disorder evaluation scale). Upon neurological examination, he was alert and fully oriented. Cognitive testing demonstrated a mild impairment. There was a slightly reduced score in the Mattis dementia rating scale (137/144 points, normal 142 ± 2), and an abnormal Wisconsin card sorting test (failure to keep criteria and perseverations). There were normal values for Stroop test, digital span reversal, Grober-Buschke test, normal verbal fluency, and FAB score. Upon neurological examination, there was mild facial masking and monotonous speech (Video). In addition, generalized chorea, tic-like grimacing, shoulder shrugging and sniffing were observed. There was moderate atrophy of all limbs with mild paresis (MRC Grade 4). Deep tendon reflexes were absent. There were no sensory disturbances and vegetative functions were normal. A conventional blood smear revealed 2% acanthocytes whereas after dilution with heparinized isotonic saline 29% acanthocytes were seen.¹² Cardiac assessment including electrocardiogram and transthoracic echocardiogram was normal. Cerebral MRI revealed pronounced caudate atrophy (Fig. 1B). Cerebral ^{99m}Tc -HMPAO SPECT demonstrated severe striatal hypoperfusion (data not shown).

Immunohematological and Molecular Analysis

Immunohematological examination of Kell and Kx antigens was performed as previously described.¹³ The McLeod blood group phenotype was present in both patients ($K1-$, $K2+$, $K3-$, $K4-$, $Kx-$). The mother displayed a normal pattern of Kell and Kx antigens ($K1-$, $K2+++$, $K3-$, $K4++$, $Kx++$). Fresh RBCs from Case 1, Case 2, and their mother were assessed by

flow cytometry using the Kell protein specific antibodies anti-BRIC18, anti-BRIC68, and anti-BRIC203 as previously described.¹³ Blood donor cells expressing normal Kell phenotype were used as positive control and ZZAP treated blood donor cells mimicking K_0 cells were used as negative control. The two brothers (Case 1 and 2) showed severe suppression of Kell protein expression on their RBCs with identical expression pattern of the three epitope specificities (Fig. 2B,C). In contrast, the heterozygous mother had RBCs with suppressed Kell protein as found in their sons as well as RBCs with normal expression of the Kell protein (Fig. 2A).

Molecular genetic analysis of the *XK* gene was performed as described previously.² Sequence analysis demonstrated a 5 bp deletion in exon 2 of the *XK* gene (938-942delCTCTA) in both patients.

DISCUSSION

The diagnosis of MLS in the two brothers was suggested by the characteristic clinical triad of choreatic movement disorder, muscle atrophy, and areflexia as well as the laboratory findings of elevated CK levels and erythrocyte acanthocytosis. Reliable determination of acanthocytosis was only feasible using the validated method of Storch et al.¹² Final confirmation of the diagnosis was achieved by detecting the McLeod blood group phenotype and the causative mutation in the *XK* gene. Both brothers had significant psychiatric morbidity including schizophrenia-like psychosis or obsessive compulsive disorder at onset, and there was a remarkable delay of 10 and 30 years, respectively, until the diagnosis of MLS was made. Predominant psychiatric manifestations have been observed in other McLeod patients, including acute psychosis at disease onset.^{2,14} More than 80% of McLeod patients develop psychiatric manifestations during the disease course, thus necessitating the

inclusion of MLS in the differential diagnosis of acute psychosis in young males.³

MLS has been observed in patients originating from the United Kingdom, Germany, Switzerland, the United States, Australia, Japan, and Brazil and was associated with major deletions and different nonsense mutations in the *XK* gene.^{1-3,9,10} The 938-942delCTCTA deletion has been found in three other McLeod patients originating from the United States with Anglo-Saxon descent (Patient 22 in³) and Japan, respectively.^{3,9} Although an extended haplotype analysis was not feasible, the geographical and ethnic distribution of the 938-942delCTCTA mutation strongly argues against a founder effect. In addition, analysis of the clinical data does not reveal a common phenotype associated with this deletion. The North American patient presented with seizures at the age of 49 years. Neurological examination revealed cognitive impairment, limb chorea, involuntary vocalizations, dysarthria, areflexia, and reduced vibrations sense at the ankles.³ No major psychiatric manifestations were reported. However, no detailed data of psychiatric signs and symptoms were provided. Since the initial report, he had developed progressive muscle wasting, gait impairment, falls and dysphagia. Mainly confined to his bed, he experienced repeated episodes of pulmonary edema, probably due to congestive heart disease, and died at age 77. The two Japanese brothers manifested with progressive leg weakness at the age of 37 years and a choreatic movement disorder at the age of 62, respectively. Neurological examination of the first brother at the age of 50 years revealed sensory-motor neuropathy with severe weakness and atrophy in both calves with diminished deep tendon reflexes. Involuntary movements or cognitive decline were not noted. The second brother had limb chorea and mild leg weakness without cognitive symptoms. No psychiatric manifestations were evident, although no detailed data were provided as well.

In conclusion, these observations indicate a profound phenotypic variability in line with previous reports.^{3,15} Our observations emphasize the importance of McLeod syndrome in the differential diagnosis of a choreatic movement disorder with psychiatric features. A simple, validated technique for acanthocyte determination¹² facilitates the diagnosis where immunohematological analysis and molecular genetic testing are not readily available.

LEGENDS TO THE VIDEO

Segment 1. Shows one of the brother (Case 2) with McLeod syndrome in a sitting position while he is interrogated about the disease history. There is mild facial masking and monotonous speech. In addition, frequent choreatic movements of the hands, arms, and shoulders were observed. Less frequently, choreatic leg move-

ments and tic-like grimacing are observed. In addition, there are tic-like movements such as sniffing and stamping with the feet, and some voluntary arm movement have a manneristic aspect.

Segment 2. Shows a normal finger-to-nose test on the right but slightly dysmetric movements on the left side. The palm-wrist test is slightly slowed on the right and moderately slowed and dysmetric on the left side.

Segment 3. Shows moderate atrophy of the shins, absent deep tendon reflexes and negative plantar responses. In addition, infrequent choreatic movements of the feet are observed.

Segment 4. Shows moderate leg muscle atrophy and a paretic gait. In addition, pronounced gonarthrosis can be observed contributing to the gait difficulties.

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