The Chorea of McLeod Syndrome

A. Danek, MD, PhD, F. Tison, MD, PhD, J. Rubio, PhD, M. Oechsner, MD, W. Kalckreuth, MD, and A.P. Monaco, MD, PhD

1 Neurologische Klinik, Ludwig-Maximilians-Universität, München, Germany
2 Service de Neurologie, Groupe Hospitalier Sud, CHU de Bordeaux, France
3 Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom
4 Neurologische Universitätsklinik, Hamburg, Germany
5 Zentrum für Psychiatrie, Emmendingen, Germany

Abstract: Among the movement disorders associated with acanthocytosis, McLeod syndrome (McKusick 314850) is the one that is best characterized on the molecular level. Its defining feature is low reactivity of Kell erythrocyte antigens. This is due to absence of membrane protein KX that forms a complex with the Kell protein. KX is coded for by the XK gene on the X-chromosome. We present six males (aged 29 to 60 years), with proven XK mutations, to discuss the chorea associated with McLeod syndrome. The movement disorder commonly develops in the fifth decade and is progressive. It affects the limbs, the trunk and the face.

In addition to facial grimacing, involuntary vocalization can be present. In early stages there may only be some restlessness or slight involuntary distal movements of ankles and fingers. Lip-biting and facial tics seem more common in autosomal recessive choreoacanthocytosis linked to chromosome 9. This, together with the absence of dysphagia in McLeod syndrome, may help in differential diagnosis. Recent findings suggest a role for the endothelin system of the striatum in the pathogenesis of McLeod syndrome. © 2001 Movement Disorder Society.

Key words: McLeod syndrome; chorea; X-linked; neurogenetic disorder; acanthocytosis

Red blood cells that weakly express Kell antigens are said to be of the “McLeod” phenotype (named after the blood donor in whom it was detected 1). An association of the blood group variant with dysfunction of multiple organ systems was subsequently recognized. 2 This includes acanthocytosis, the presence of erythrocytes with multiple protrusions (“akantha”: Greek for thorn). 3 McLeod syndrome also affects the nervous system and thus is a subtype of “neuro-acanthocytosis.” The neuroacanthocytosis group of syndromes, in addition, comprises abetalipoproteinemia (Bassen-Kornzweig), autosomal recessive choreoacanthocytosis, 4 and neuroaxonal dystrophy (Hallervorden-Spatz 5 ). The relationship between their core features, neurological disease and abnormal red cell morphology, is not clear.

McLeod syndrome is the consequence of mutations of a recently identified gene on the X-chromosome. 6 This gene, XK, codes for the KX protein of 444 amino acids. KX is assembled with the Kell protein to form a disulfide bonded complex in the cell membrane. 7

Due to the potential transfusion hazards of low Kell antigen expression, most cases of McLeod syndrome are known to blood banks (at present approximately 100 cases). Their neurological features have received little attention or were regarded as accidental. 8–10

We present six males with proven XK mutations to discuss the spectrum of the movement disorder that develops in McLeod syndrome. We argue that progressive basal ganglia damage is an essential feature of KX protein dysfunction.
CASE REPORTS

Case 1 (Video Segments 1–3)

This man, an economist, presented at the age of 40 with cardiac arrhythmia and CK serum levels of up to 1,232 U/l (normal <80 U/l), with creatine kinase MB band (CK-MB) always less than 6%. In a peripheral blood film, approximately 3% acanthocytes were seen. The characteristic red cell McLeod phenotype was noted and a deletion of approximately 50,000 base pairs in the XK region was detected. Details concerning his associated cardiomyopathy, myopathy, axonal neuropathy, sleep apnea, slight neuropsychological impairment, and neuroimaging findings are on record.

Abnormal movements were first noted at the age of 51. A 20-minute video was taken while he was left alone to read a newspaper. He sat with crossed legs, which he switched approximately once a minute (17 times). He adapted the floor contact of his supporting foot 100 times, moved the free ankle 70 times, and slightly bent or extended the supported knee 20 times. We counted 23 movements of his arms and hands to touch or scratch the trunk and a similar number of shoulder and trunk movements (22 and 25, respectively). Apparently purposeless movements of fingers, hand, or the whole arm (12) were less frequent, as were movements of the head (6). The patient reported a permanent need to change body positions and described the movements as “semivoluntary,” claiming that he could temporarily suppress them. Video segment 1 shows typical examples.

The choreatic disorder remained unchanged until the age of 57 (segment 2), but then progressed dramatically. When seen the following year (segment 3), the proximal arm and leg movements were insuppressible and an irregular tremor of the right arm, involuntary facial contractions, and grunting had developed. There was some improvement under sulpiride 200 mg three times a day (tid).

A telephone interview at the age of 61 disclosed considerable dysarthria and the patient reported that he had suffered from fecal and urinary incontinence for more than a year. He was not interested in further investigations.

Neuroimaging had shown caudate atrophy and T2-signal inhomogeneity of the globus pallidus bilaterally. Striatal dopamine-D2-receptor binding and glucose metabolism were reduced on IBZM-SPECT and FDG-PET, respectively.

Case 2 (Video Segment 4)

This patient was the younger brother of case 1 and had lost jobs as a construction worker and stage hand. He originally presented at age 44 with recurring grand mal seizures since the preceding year. Muscle CK, independently, was elevated up to 1,000 IU/l. Three percent of his red cells were acanthocytic. They displayed the McLeod phenotype of Kell antigens. For several years, he had noted that he could hardly sit still and that pacing around relieved his restlessness. On examination, the patient displayed choreatic movements of all limbs distally and spontaneous movements of head, neck, and tongue. He could partly suppress them and tended to incorporate them into purposeful movements. His speech was unmodulated, slurred, and partly explosive. He had noted increasing forgetfulness. Memory, concentration and speed of thought were diminished on psychometric testing. There was an indication of delusions of persecution and external control.

A follow-up study was not possible until age 57, when he consented only to a clinical examination. Symptom progression in the interval of more than a decade was modest. Under continuous treatment with carbamazepine and phenytoin, he had experienced no more seizures. All tendon reflexes were absent and there was markedly reduced sensation of vibration distally, with pallanaesthesia at the ankles. Muscle weakness or wasting was not observed, but the patient was continuously in motion. The limb chorea was now proximally accentuated. There were dystonic trunk movements and the patient repeatedly adopted dystonic postures of the head. He displayed mannerisms of the face and vocalizations, often grunting. Dysarthria with slurring of speech had increased. He also showed motor impersistence (segment 4).

Case 3 (Video Segment 5)

This patient was a 51-year-old farmer who had fractured his T12 vertebra during woodcutting the previous year and was left with leg pareses. The chronic care facility transferred him for neuropsychiatric evaluation after he had developed increasingly disruptive behavior. Moving about hyperactively in his wheelchair, he was considered a danger to himself and to others. Retrospectively, it was noted that a dentist had commented about hyperkinesia of the tongue when the patient was 44 years old.

When he was admitted, a choreatic movement disorder was obvious. The patient showed facial, perioral, and periorbital as well as lingual hyperkinesias and displayed involuntary vocalizations. There were trunk movements of a dystonic and athetoid nature, a proximally pronounced limb chorea, motor impersistence of the tongue and dysarthria (video segment 5). Both arms showed some reduction in muscle strength and in vibration sen-
sation, with normal tendon reflexes. From his previous accident, there was a cauda equina syndrome distal to L5 bilaterally, sphincter function remaining intact. Electromyography and electroneurography were within normal limits.

He avoided contact with fellow patients, in keeping with previous descriptions of his personality as withdrawn and introverted. His collecting of toys such as cars and plastic animals but also of garbage seemed compulsive. He combined these objects into eccentric works of art. He neglected his hygiene and was restless at night.

Compared to his educational history (elementary and middle school, vocational training), his estimated IQ of 80 was considered reduced and mental speed was thought impaired. Clinically, there was no indication of memory impairment, thought disorder, or delusions. The patient’s mood was depressed. His conduct was inappropriate with frequent belching and passing of wind in public. Two generalized epileptic seizures were observed (none had occurred in the past). The electroencephalogram (EEG) showed some generalized slowing to 7–8 Hz. Neuroimaging demonstrated caudate atrophy on both sides as well as some T2-signal increase in the lateral putamen.

The CAG repeat length in the \textit{IT15} gene on chromosome 4, responsible for Huntington’s disease (HD), was normal for both alleles (9 and 20 repeats). Muscle creatine kinase was persistently elevated (93–337 IU/l). The patient’s blood showed acanthocytosis of 5–8% when diluted 1:1 with 0.9% NaCl. Lipoprotein electrophoresis was normal. His erythrocytes showed weak reactions with antisera against Kell antigens. Weak expression of K2 (k), K4 (Kp\(^{b}\)), and K7 (Js\(^{b}\)) was diagnostic for the McLeod erythrocyte phenotype. A point mutation in exon 2 of \textit{XK} was found, resulting in premature termination of protein \textit{KX} synthesis.

On examination, he showed mild limb and trunk chorea. He displayed facial grimacing and involuntary vocalizations due to smacking and grunting and clicking his tongue (video segment 6). He also showed lip-biting. Saccades and pursuit eye movements were normal. There was no buccofacial apraxia or motor impersistence of the tongue. Psychometric testing disclosed slight impairments in working memory, verbal fluency, and “frontal” subtests (Wisconsin Card Sorting, Stroop, Trail Making). There was no dementia, no psychopathological abnormality, and no history of seizures. He reported daytime somnolence. Polysomnography and multiple sleep latency tests demonstrated an excessive propensity to sleep, yet no sleep apnea syndrome. On neuroimaging there were caudate atrophy (Fig. 1A) and T2-abnormalities in the putamen on both sides (Fig. 1B).

The patient showed no muscle weakness or wasting, but displayed fatigue upon exercise. Tendon reflexes were abolished in the legs. Arm reflexes were present. Without further neuropathic symptoms or signs, neurography showed a mainly axonal neuropathy. On biopsy, there was moderate sural nerve demyelination with regeneration clusters and widespread Schwann cell hypertrophy in addition to axonal lesions with Büngner bands. Deltoid and peroneus muscle biopsies showed neurogenic changes. Staining for dystrophin was normal. Subclinical myopathy was deduced from increased plasma levels of CK (1,142–1,533 IU/l), of aldolase and of myoglobin. Reduced haptoglobin indicated a chronic compensated hemolysis. Acanthocytes accounted for 5% of the red cells. Cardiac and hepatic disease, splenomegaly, pigmented retinopathy, and granulocyte dysfunction were ruled out as appropriate (electrocardiogram, sonography, blood chemistry, fundoscopy, candida albicans phagocytosis, and destruction test).

In the course of the following 2 years, he developed progression of muscle weakness and was unable to continue at his job. When reexamined at age 44, slight progression was noted of chorea, involuntary facial movements, lip-biting, and grunting noises. Tiapride (50 mg tid) had no recognizable effect. There was a suggestion...
of slowed horizontal saccadic eye movements (video segment 7). So far, this could not be further analyzed. The neurological, cognitive, neuroimaging, and clinical neurophysiological findings were otherwise stable.

Case 5 (Video Segment 8)

The older brother of case 4 and a painter by profession, this patient was examined at age 45. He gave a history of unintended facial and shoulder movements, both known to him for a long time. He had had no seizures. On examination, excessive blinking and slight upper limb chorea were noted (segment 8). There was no dementia and psychometric examination showed no abnormalities (Mini Mental Status Examination, Benton Visual Retention Test, Isaac’s Set Test, Wechsler Memory, Stroop, Trail Making). Lower limb tendon jerks were abolished and clinical neurophysiology showed axonal sensory neuropathy. Three percent acanthocytes were found. Kell antigens were undetectable on his erythrocytes. Haptoglobin was low and CK (931 IU/l), myoglobin and aldolase were elevated. Splenomegaly was absent as was hepatic and cardiac disease. Neuroimaging showed caudate atrophy and T2-abnormalities in the putamen bilaterally. His condition remained stable over the course of 2 years.

This patient has the same XK mutation as his younger brother. In both, the CAG repeats of the IT15 gene were of normal length, thus excluding HD.

Their maternal uncle, according to the nephews, had shown a movement disorder identical to theirs. His CK was increased (343 IU/l). He had also suffered from dilated cardiomyopathy with atrial fibrillation and died from heart failure at age 67. An autopsy was not performed.

Case 6 (Video Segment 9)

This administration clerk presented at the age of 27 years with slight generalized weakness which was pronounced in the legs. Mild sensorimotor axonal neuropathy was found on clinical neurophysiological examination and there was some calf hypertrophy. Serum muscle CK was elevated (300–400 IU/l). Calf muscle biopsy showed both neuropathic and myopathic changes. Transaminases were slightly increased. Splenomegaly and cardiac disease were ruled out.

Blood smears contained 5% acanthocytes. Immunohematology showed the McLeod phenotype. Genetic analysis disclosed a two-base pair mutation in exon 3 of XK, resulting in premature termination of KX protein synthesis.

There was no history of seizures and the EEG was normal. Extensive psychometric evaluation disclosed no abnormality. A movement disorder was notably absent (video segment 9) and neuroimaging of the basal ganglia with magnetic resonance imaging (MRI) and IBZM-SPECT was normal. FDG-PET, however, demonstrated glucose hypometabolism in the caudate nuclei.12
DISCUSSION

XK is a gene expressed in a variety of tissues such as skeletal muscle, heart, and brain. Correspondingly, subjects with McLeod syndrome that is caused by XK mutations display multiple abnormalities. Two of our patients had initially complained of muscle fatigue (cases 4 and 6), one patient had presented with elevation of skeletal muscle CK and cardiomyopathy (case 1), and another presented with seizures (case 2). Behavioral changes were the presenting feature in one patient (case 3) whose accompanying hyperkinetic disorder had led to an initial working diagnosis of Huntington’s disease. In one of the cases (case 5), the movement disorder was the leading symptom, but it had not come to medical attention before our family investigation.

The systemic features of McLeod syndrome (apart from the defining red cell phenotype of depressed Kell antigens) are acanthocytosis, hemolytic anemia, splenomegaly, laboratory evidence of liver involvement, and a cardiomyopathy with arrhythmias. Of neurological interest are muscle weakness and wasting, related to both a myopathy with high serum levels of creatine kinase and an axonal neuropathy with areflexia. Sleep-related disorders such as sleep apnea have been noted, but are still not well characterized. Cerebral involvement is apparent from cognitive impairment, occurrence of seizures, and the movement disorder, which is the central topic of the present report.

Chorea in McLeod syndrome has been regarded as incidental or as an atypical finding. This view appears misleading due to the delayed clinical manifestation and the hematological preoccupation of the early reports. Although approximately 100 cases are known to blood banks worldwide, their neurological findings still receive insufficient attention.

The slow development of the movement disorder is well illustrated by the observations in our first patient (segments 1–3). Chorea associated with the McLeod phenotype could theoretically be attributed to a contiguous gene effect in cases of chromosomal deletions such as our cases 1 and 2. Genes in the vicinity of XK, however, can be ruled out as responsible since the movement disorder is seen with XK point mutations (cases 3–5). Case 6, in spite of clinically normal posture and movements, displayed basal ganglia dysfunction when cerebral glucose metabolism was examined with PET. In subjects at risk for HD, this observation was found to predict the future development of chorea. We conclude from these observations that basal ganglia dysfunction and the ensuing movement disorder are constitutive for McLeod syndrome.

Early manifestations of the McLeod movement disorder may be some motor restlessness with frequent changes of posture and shoulder shrugging (case 1) or increased blink rate and slight involuntary spreading of fingers (case 5). If more pronounced, all limbs, the trunk, and the face show unintended movements (cases 1–4). Involuntary vocalizations, some due to tongue movements (cases 1 and 4), a dysarthria (cases 1–4) and biting of lips (case 4) may develop as well as grimacing, mannerisms and dystonic movements (case 2).

In the present series, the movement disorder became manifest in the early forties. Single case observations in the literature show that onset may range from 27 to 57 years. All neurologically documented cases of McLeod syndrome have shared limb chorea. In some, similar to our observations, the authors noted dystonic movements, dysarthria, and facial and generalized motor tics.

Correct clinical diagnosis is difficult due to symptom overlap with choreoacanthocytosis. The latter label, for example, was applied to one case with a hyperkinetic disorder and acanthocytosis until closer scrutiny disclosed the McLeod phenotype.

Unfortunately, the terminology is confusing. In a loose sense, one might call the McLeod syndrome a “choreoacanthocytosis.” This term, however, should be reserved for those instances of acanthocytosis and movement disorder, where the McLeod Kell phenotype, neuroaxonal dystrophy, and lipoprotein disorders have been excluded.

A chromosome 9q21 gene with autosomal recessive transmission, CHAC, has been implied in such cases. Their movement disorder appears earlier than in McLeod syndrome, and habitual biting of tongue and lips is common. The nigrostriatal system seems regularly affected. Parkinsonism is not uncommon in choreoacanthocytosis but has not yet been observed in McLeod syndrome. The substantia nigra was basically intact in the two autopsies that have been reported for this syndrome. One, however, might be atypical, since it is from the single known female with systemic expression of an XK mutation. The second autopsy report of McLeod syndrome has not been extensively documented.

Oculomotor abnormalities have been noted in some cases of choreoacanthocytosis (limited upgaze and convergence; progressive supranuclear palsy and apraxia of eyelid opening) but not in McLeod syndrome. Slowing of horizontal saccades, however, was suggested by one observation in the present series (video segment 7) and would indicate degeneration of neurons outside of the basal ganglia.
Both McLeod syndrome and choreoacanthocytosis share prominent neuromuscular involvement with muscle weakness and wasting, muscle CK elevation ("hyperCKemia"), and depression of reflexes due to myopathy and axonal neuropathy.17,35 In both, cardiomyopathy has been noted.34 Such findings allow for the clinical distinction from HD, along with red cell acanthocytosis and family history. Age of onset and disease progression are delayed in McLeod syndrome.25,35. Chorea, “subcorticofrontal” cognitive impairment, and the associated neuroimaging abnormalities, however, are common to all three conditions: McLeod syndrome, choreoacanthocytosis, and HD.17,28,35–38 Comparative data on the three diseases are presented in Table 1.

On neuroimaging, McLeod patients have shown involvement of the basal ganglia and the cerebral cortex with some degree of atrophy and/or hypometabolism, particularly of the caudate nucleus and the frontal cortex.9–12,18,20 On postmortem, loss of neurons and astrocytosis were severe throughout the caudate nucleus, moderate in the putamen, and were less obvious in globus pallidus.8,26 The changes in the caudate nucleus were pronounced posteriorly. The claustrum, thalamus, and subthalamic nucleus were found unaffected.8

The overall course of McLeod syndrome and of its movement disorder must still be better delineated. Comparisons within families suggest the existence of disease-modifying factors. Case 1, for example, was only slightly affected until he developed rapid deterioration after age 57. In contrast, his brother (case 2) had a severe movement disorder from at least age 44 but showed no appreciable change when seen more than a decade later. Different clinical expression of identical mutations is obvious also from the second pair of siblings (cases 4 and 5).

There is no established treatment for McLeod syndrome. Particular attention must be paid to heart involvement, since it is repeatedly reported as a cause of death (see case report 5). Upon transfusion of erythrocytes that display full-strength Kell antigens, McLeod patients may form red cell antibodies. Therefore, they should have their blood collected prospectively in case of future surgery.39 This appears particularly important, as stereotaxic procedures on the basal ganglia may be performed in patients with neuroacanthocytosis.40,41

From the viewpoint of pathogenesis, it is a fascinating possibility that McLeod syndrome and choreoacanthocytosis, possibly even Huntington’s disease, might feed into one common final pathway of basal ganglia damage. The KX protein that is absent from McLeod red cells is regarded as a membrane transporter6 but is still not well understood. It forms a complex with the endothelin-3 processing Kell protein in erythrocytes but also in brain cells.7,42,43 One might therefore speculate about an interaction of KX with the endothelin system of central nervous system, which could be altered in disease.

### TABLE 1. Differential diagnosis of McLeod syndrome, choreoacanthocytosis, and Huntington’s disease (HD)

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<tr>
<th></th>
<th>McLeod syndrome (314850)</th>
<th>Choreoacanthocytosis (200150)</th>
<th>Huntington’s disease (143100)</th>
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<tbody>
<tr>
<td>Onset (range)</td>
<td>25–57 years</td>
<td>13–58 years</td>
<td>4–74 years (mean 35–44)</td>
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<td>Movement disorder</td>
<td>Chorea</td>
<td>Chorea with prominent oral</td>
<td>Chorea, Marked rigidity in</td>
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<td></td>
<td></td>
<td>dyskinesia/lip-biting,</td>
<td>juvenile subtype</td>
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<td>Atrophy of caudate</td>
<td>Yes</td>
<td>Yes, plus cell loss in</td>
<td>Yes, plus widespread cell</td>
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<td>and putamen</td>
<td></td>
<td>substantia nigra</td>
<td>loss</td>
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<td>Epileptic seizures</td>
<td>Possible</td>
<td>Common</td>
<td>Common in juvenile HD</td>
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<tr>
<td>Neuropathy</td>
<td>+</td>
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<td>Myopathy and high</td>
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<td>to variant Kell antigens</td>
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<td>Gene</td>
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<td>CHAC (chromosome 9)</td>
<td>IT15 (chromosome 4)</td>
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<td>X-linked, may manifest in</td>
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<td>autosomal dominant</td>
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<td>an endothelin-peptidase</td>
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neurons. Endothelins release dopamine in the rat striatum via specific receptors. As part of an endothelin-processing complex, XK might transport endothelins or their precursors across cell membranes, and its absence may lead to slowly accumulating toxic effects.

So far, XK has not been studied in basal ganglia cells. The recent identification of the XK homologue in the mouse should facilitate the description of its expression in specific brain areas as well as the search for possible interactions with transmitter peptides of the striatum.

Note added in proof: The gene responsible for choreoacanthocytosis has recently been cloned. Some of this new information was incorporated in Table 1. See: Rampoldi L, Dobson-Stone C, Rubio JP, et al. A conserved sorting-associated protein is mutant in chorea-acanthocytosis. Nat Genet 2001;28:119–120.


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LEGENDS TO THE VIDEOTAPE

Segments 1–3. The progressive nature of McLeod chorea is obvious from these video segments taken over the course of 6 years in this patient, case 1. At age 52 (segment 1), he displays motor restlessness while left alone to read a newspaper (clips from a 20-minute video). The slight repetitive, “semivoluntary” ankle and leg movements, some shoulder shrugging, body scratching, and throat clearing have changed little when filmed again at age 57 (segment 2). One year later (segment 3), leg movements and shrugging of the right shoulder are insuppressible. Facial involuntary movements on the left side have newly appeared.

Segment 4. Case 2, the brother of patient 1, at age 57 displays mannerisms of facial expression and head posture reminiscent of dystonic movements. His speech is slurred and hardly intelligible, some of its contents appear inappropriate. Motor impersistence is obvious when being asked to keep his arms elevated.

Segment 5. Case 3, 51 years of age, is wheelchair-dependent due to traumatic cauda damage. His speech is hardly intelligible, much more due to dysarthria than to his local dialect. While reporting about his siblings or extending his arms, he displays motor restlessness of his legs, more obvious on the right side. He extends the right knee repeatedly and shows almost continuous, albeit slight rotational hip movements, rarely also left hip rotations. Involuntary grimacing can be seen occasionally, but no involuntary movements of the arms. There is motor impersistence of the tongue.

Segments 6–7. This patient aged 42 years (case 4) shows slight trunk and limb chorea, particularly brought about by mental calculation (segment 6). Intermixed clicking sounds and utterances of an “explosive” nature (while the patient comments about infrequent unintended lip-biting) indicate a disturbance of tongue movement control and of airflow during speech. Left facial grimacing is particularly obvious during an imperfectly performed Luria-type movement sequence. These findings progressed little until a follow-up examination at age 44. Tongue motor impersistence now was evident also in this patient (segment 7). There was a suggestion of somewhat reduced horizontal saccade velocity.

Segment 8. Case 5, the brother of case 4, was filmed at age 45. He displayed increased eye blinking and slight involuntary finger spreading (ulnar side of left hand), particularly while holding his arms extended.

Segment 9. Case 6 shows no involuntary movements at age 28. He is sitting completely still while left alone to read a journal. Position emission tomography, imaging, however, detected caudate hypometabolism of glucose.