A Case of McLeod Phenotype of Neuroacanthocytosis Brain MR Features and Literature Review

J.R. SHAH¹, D.P. PATKAR², R.N. KAMAT³

¹Gokuldas Tejpal Hospital Spectrum CT MRI Centre; Mumbai, India

²Dr. Balabhai Nanavati Hospital and Research Centre; Mumbai, India

³Department of Pathology, Nair Hospital; Mumbai, India

Key words: McLeod syndrome, neuroacanthocytosis, Huntington's disease, extrapyramidal system, MRI

SUMMARY – *Huntington's disease and neuroacanthocytosis may present similar clinical and MRI features. It is important to differentiate these findings since treatment and prognosis vary vastly between them. The aim of this article is to familiarize radiologists with the differentiating features of Huntington's disease and various diseases comprising neuroacanthocytosis. A 40-year-old Indian man with extrapyramidal symptoms was referred for MRI. The clinical diagnosis was Huntington's disease, but there were a few atypical clinical features such as a history of biting the tongue, tics, marked hyporeflexia and lower limb muscle wasting. MR showed atrophy of the caudate nucleus and putamen with iron deposition in the basal ganglia, which can be seen in Huntington's disease and in neuroacanthocytosis. An increased blood acanthocyte level was subsequently confirmed. Further work-up revealed increased serum creatine phosphokinase levels, normal serum lipoprotein levels and depressed K cell antigen activity on serological studies, confirming the diagnosis of McLeod syndrome. McLeod syndrome is one of the distinct phenotypes of neuroacanthocytosis. Neuroacanthocytosis is a group of disorders with increased serum acanthocyte counts and neurological involvement. Various causes of neuroacanthocytosis are discussed. It is important to consider the possibility of neuroacanthocytosis when features typical of Huntington's disease are encountered on imaging.*

Introduction

Neuroacanthocytosis is a progressive neurologic condition characterized by movement disorders, axonal neuropathy, personality changes, cognitive deterioration and seizures. Most patients have acanthocytosis on peripheral blood smear at some point during the course of the disease. Neuroacanthocytosis was first described by Levine in 1960 in a presentation to the American Academy of Neurology. Estes et al., Levine, and Critchley et al. published the first case descriptions^{1,2}. The term acanthocytosis is derived from the Greek word "acanthos" meaning "thorn" and is used to describe a peculiar spiky appearance of erythrocytes. Acanthocytosis is found to be associated with a group of hereditary neurological disorders generally referred to as neuroacanthocytosis

such as chorea-acanthocytosis, McLeod syndrome, abetalipoproteinaemia, hypobetalipoproteinaemia, Hallervorden Spatz disease, etc.³. We describe a case of McLeod syndrome/phenotype with MR features suggestive of Huntington's disease i.e. signal changes and atrophy of the caudate nucleus and putamen (i.e. neostriatum).

Case Report

A 40-year-old Indian man presented with a six-year history of abnormal generalized gradually progressive involuntary movements, mainly chorea. Initially, the movements occurred during walking and standing, but of late they were seen even at rest, interfering with daily activities. Involuntary movements

Figure 1 MR SE axial T1- (A) and T2-weighted (B) images show atrophy of the caudate nucleus and putamen (arrows) with a subtle increase in signal intensity changes on T2-weighted images causing minimal frontal horn dilatation bilaterally. Minimal cerebral atrophy is also observed.

were also seen involving the orofacial region, tongue, lips and facial muscles (e.g. grimacing). Swallowing difficulties had recently started due to abnormal tongue movements and repeated biting of the tongue. Tics were noted. The patient had become impatient. He had had a single generalized tonic clonic convulsion a year ago, which was treated with phenobarbitone. The patient was non-diabetic, non-hypertensive, a non-smoker and non-alcoholic. There were no features suggestive of abnormal higher functions, psychiatric disorder, hepatic or renal dysfunction, thyroid or parathyroid dysfunction, rash, arthralgias, exposure to toxins or any sensory complaints. He was born of healthy parents of a non-consanguineous marriage. The family history was negative up to the preceding two generations. He has one normal healthy son aged 13 years and a 15-year-old daughter.

On examination, generalized choreiform movements and orofacial dyskinesias were observed. An extrapyramidal type of dysarthria

was noted. There was minimal muscle atrophy in the calf muscles on both sides. However, tone and power were normal. Deep tendon reflexes were abnormal. Biceps, triceps, supinator and calf reflexes were depressed. Ankle reflexes were absent bilaterally. Plantars were bilaterally flexor. No sensory deficit could be elicited. Higher functions were normal. Other systems findings were within normal limits. No KF ring was found on slit lamp examination.

On investigations, haemoglobin was 11.5 gm%. Renal and hepatic function tests were within normal limits. Serum ceruloplasmin levels were normal. MRI brain study performed on a 1.5 T MR scanner revealed atrophic changes involving the caudate and lentiform nuclei causing the dilation of both frontal horns of the lateral ventricles. The normally convex inner aspects of the caudate nuclei had become flat to concave. On FLAIR images, hypointensity was noted in the globus pallidus and putamen suggestive of prematurely increased iron deposition in basal ganglionic regions. The cer-

Figure 2 MR FLAIR coronal images (A,B) show striatal atrophy and hypointensity in the lentiform nuclei (small arrows) suggesting iron deposition. Also note minimal generalized cerebral atrophy and minimal cerebral peduncle thinning (thick arrow).

bral peduncles showed minimal atrophy with minimal apparent reduction in the size of the pars compacta. Minimal prominence of ventricles, sulci and cisterns was also noted for his age, suggestive of minimal cerebral atrophy. The possibilities of Huntington's disease and neuroacanthocytosis were raised in view of the typical neostriatal atrophy. Subsequently, a further work-up was done. Peripheral blood smear examination done twice revealed increased acanthocyte counts of 12 and 16% respectively. Serum creatine phosphokinase (CPK) level was 1422 IU/L (increased). Serum lipid profile was within normal limits. Immunohaematology and erythrocyte membrane protein western blotting analysis confirmed the McLeod blood group phenotype by demonstrating negative Kell antigen. Electromyography and nerve conduction studies were suggestive of motor axonal degeneration in both lower limbs. Abdominal sonography revealed mild splenomegaly. The patient is being treated symptomatically.

Discussion

Neuroacanthocytosis is an umbrella term used to describe a group of disorders. The important disorders and their main distinguishing features are listed in Table 1⁴⁻¹⁵. Chorea-acanthocytosis is linked to a 6-cM region of chromosome 9q21. It is common in Japan with onset usually in the third to fifth decades⁹⁻¹¹. Orofaciolingual dyskinesia, chorea and dementia are the most predominant features. Many features are also shared by McLeod syndrome, a distinct form of neuroacanthocytosis with more prominent myopathy and peripheral neuropathy.

Dilated cardiomyopathy, peripheral myopathy (leading to severe rhabdomyolysis and wasting of the lower limb muscles), and autonomic disturbances are also commonly described with this syndrome/phenotype^{10,12,13}. The movement disorder commonly develops in the fifth decade and is progressive, affecting the limbs, trunk and face.

Figure 3 Other described imaging features in neuroacanthocytosis in other cases. A) FLAIR axial brain image in a patient with pentothenate kinase-associated neurodegeneration, showing the typical “eye of a tiger” appearance with peripheral hypointensity due to iron deposition and central hyperintensity due to gliosis. T2-weighted axial brain images showing increased iron deposition in the globus pallidus (B) and neostriatal (putamen and caudate nucleus) hyperintensities (C). D) Sagittal T2-weighted image of the cervical spine showing dorsal tract hyperintensities in a case of abetalipoproteinaemia (see Table 1).

Table 1 Important distinguishing features of various neuroacanthocytosis diseases.

Neuroacanthocytosis (elevated serum acanthocyte levels)					
Normal serum lipoprotein levels		Abnormal serum lipoprotein levels		Others	
Normal K cell antigen activity	Reduced K cell antigen activity	Abetalipoproteinaemia **	HARP syndrome	Late infantile neuro-axonal dystrophy	Also showing acanthocytes
Chorea-acanthocytosis*	McLeod phenotype	<ul style="list-style-type: none"> – Fat intolerance – Malabsorption – Fat soluble vitamin E deficiency – Spinocerebellar ataxia – Peripheral neuropathy – Retinitis pigmentosa – MRI: dorsal cord hyperintensity, spinocerebellar tract hyperintensities, cerebellar atrophy 	<ul style="list-style-type: none"> – Hypoprebetalipoproteinaemia – Acanthocytosis – Retinitis pigmentosa – Pallidal degeneration – Globus pallidus iron accumulation / “eye of a tiger” sign on MRI 	Hallervorden Spatz disease, Pentothenate kinase-associated neurodegeneration “Eye of a tiger” appearance in globus pallidus	<ul style="list-style-type: none"> Liver disease Haemolytic anaemia Anorexia nervosa Cystic fibrosis Hypothyroidism Post-splenectomy Myelodysplasia DIC Haemangiosarcoma
<ul style="list-style-type: none"> – Autosomal recessive – Orofaciolingual dyskinesia, chorea & dementia most predominant – Posterior thigh muscles more symmetric involvement 	<ul style="list-style-type: none"> – X linked, only males – Myelopathy, neuropathy & autonomic disturbances most predominant – Posterior thigh muscles more asymmetric involvement 				

* Other names: Levine-Critchley syndrome, familial amyotrophic choreo-acanthocytosis.

** Bassen-Kornzweig syndrome

Positron emission tomography with 18F-deoxyglucose (FDG) shows a reduction of the striatal FDG uptake¹⁵. Computed tomography (CT) scans of lower leg muscles reveal a selective pattern of fat infiltration in the posterior compartment with spared gracilis, semitendinosus, and the lateral head of the gastrocnemius in both McLeod syndrome and chorea-acanthocytosis. However, asymmetrical muscle

involvement may be seen during the process of degeneration only in McLeod syndrome and may be helpful in distinguishing this disease from chorea-acanthocytosis¹⁶.

MR may show signal changes and atrophy in the neostriatum (caudate nucleus and putamen), non-specific minimal white matter changes and minimal cerebral and cerebellar atrophy¹¹.

On imaging, neostriatal atrophy involving the caudate and putamen leads to dilatation of the frontal horns of the lateral ventricles. Bicaudate diameter, bicaudate index and frontal horn/bicaudate ratio are altered¹⁷. Increased diffuse cerebral atrophy and secondary iron deposition in the basal ganglia (causing signal loss in these regions) may be noted. Some of them account for dementia and other abnormalities of the higher functions noted later in the disease.

Abnormal accentuated iron deposition in the basal ganglia may also be seen secondarily in various pathologies of the basal ganglia viz. demyelination, dysmyelination, ischaemia, infarction, chronic disorders, haemochromatosis, etc.¹⁸.

Somewhat symmetrical minimal hyperintensity may be seen on T2-weighted images in the neostriatum and is also reported in Wilson's disease, mitochondrial disorders, striatal necrosis, hepatic disorders, progressive supranuclear palsy, Huntington's disease, CJ disease, viral encephalitis, leucodystrophies, multisystem atrophy, hypoglycaemia, hypertension, haemolytic uremic syndromes, methanol intoxication, purpura, etc.^{11,18}. Dorsal spinal cord hyperintensities may be seen with abetalipoproteinaemia (one neuroacanthocytosis).

These are also seen in Friedrich ataxia, ataxia with vitamin E deficiency, subacute combined degeneration (vitamin B12 deficiency), posterior column ataxia with retinitis pigmentosa, etc.¹⁹.

Chorea, tics, personality changes and neostriatal atrophy on MRI are also known in Huntington's disease. However, attention to other features viz., absence of ocular motility disturbances, prominent orofacial dyskinesia, exclusively male patients, amyotrophy, areflexia, EMG evidence of axonopathy, raised serum CPK levels and the typical erythrocytic acanthocytosis can help to establish the correct diagnosis. Huntington's disease is inherited in an autosomal dominant pattern and its marker is linked to the short arm of chromosome 4. In view of the implications for genetic counselling, careful clinical and laboratory evaluation is always warranted to exclude neuroacanthocytosis in all suspected cases of Huntington's disease^{18,20}.

In conclusion, whenever marked atrophy of the neostriatum is observed on imaging, it is worthwhile considering the possibility of neuroacanthocytosis as well and do acanthocyte counts in all patients with suspected Huntington's disease.

References

- Estes JW, Marley TJ, Levine IM. A new hereditary acanthocytosis syndrome. *Am J Med.* 1967; 42: 868-881.
- Allan FH, Krabbe SMR, Corcoran PA. A new phenotype (McLeod) in the Kell group system. *Vox Sanguinis.* 1961; 6: 555-560.
- Rampoldi L, Danek A, Monaco AP. Clinical features and molecular bases of neuroacanthocytosis. *J Mol Med.* 2002; 80 (8): 475-491.
- Orrell RW, Amrolia PJ, Heald A, et al. Acanthocytosis, retinitis pigmentosa, and pallidal degeneration: a report of three patients, including the second reported case with hypoprebetalipoproteinemia (HARP syndrome). *Neurology.* 1995; 45 (3): 487-492.
- Higgins JJ, Patterson MC, Papadopoulos NM, et al. Hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration (HARP syndrome). *Neurology.* 1992; 42 (1): 194-198.
- Kohler B. Hallervorden-Spatz syndrome with acanthocytosis. *Monatsschr Kinderheilkd.* 1989; 137 (9): 616-619.
- Bohlega S, Riley W, Powe J. Neuroacanthocytosis and aprebetalipoproteinemia. *Neurology.* 1998; 50 (6): 1912-1914.
- Hardie RJ, Pullon HW, Harding AE, et al. Neuroacanthocytosis. A clinical, haematological and pathological study of 19 cases. *Brain.* 1991; 114 (Pt 1A): 13-49.
- Bohlega S, Al-Jishi A, Dobson-Stone C, et al. Chorea-acanthocytosis: clinical and genetic findings in three families from the Arabian peninsula. *Mov Disord.* 2003; 18 (4): 403-407.
- Kageyama Y, Kodama Y, Tadano M, et al. A case of chorea-acanthocytosis with dilated cardiomyopathy and myopathy. *Rinsho Shinkeigaku.* 2000; 40 (8): 816-820.
- Danek A, Rubio JP, Rampoldi L, et al. McLeod neuroacanthocytosis – genotype and phenotype. *Ann neurol.* 2001; 50: 755-764.
- Jung HH, Brandner S. Malignant McLeod myopathy. *Muscle Nerve.* 2002; 26 (3): 424-427.
- Malandrini A, Fabrizi GM, Truschi F, et al. Atypical McLeod syndrome manifested as X-linked chorea-acanthocytosis, neuromyopathy and dilated cardiomyopathy: report of a family. *J Neurol Sci.* 1994; 124 (1): 89-94.
- Danek A, Tison F, Rubio J, et al. The chorea of McLeod syndrome. *Mov Disord.* 2001; 16 (5): 882-889.
- Oechsner M, Buchert R, Beyer W, et al. Reduction of striatal glucose metabolism in McLeod choreoacanthocytosis. *J Neurol Neurosurg Psychiatry.* 2001; 70 (4): 517-520.
- Ishikawa S, Tachibana N, Tabata KI, et al. Muscle CT scan findings in McLeod syndrome and chorea-acanthocytosis. *Muscle Nerve.* 2000; 23 (7): 1113-1116.
- Serra S, Xerra A, Scribano E, et al. Computerized tomography in amyotrophic choreo-acanthocytosis. *Neuroradiology.* 1987; 29 (5): 480-482.
- Jack CR, Lexa FJ, Trojanowski JQ, et al. Ch. 22: Normal ageing, dementia and neurodegenerative diseases. In: Atlas AW (ed). *Magnetic resonance imaging of brain and spine.* 3rd ed. Philadelphia: Lippincott Williams and Wilkins; 2002. p. 1177-1240.
- Vedolin L, Gonzalez G, Souza CF, et al. Inherited cerebellar ataxia in childhood: A pattern-recognition approach, using brain MRI. *Am J Neuroradiol.* 2013 (in print).
- Meenakshi-Sundaram S, Arun Kumar MJ, Sridhar R, et al. Neuroacanthocytosis misdiagnosed as Huntington's disease: a case report. *J Neurol Sci.* 2004; 219 (1-2): 163-166.
- Feinberg TE, Cianci CD, Morrow JS, et al. Diagnostic tests for choreo-acanthocytosis. *Neurology.* 1991; 41: 1000-1006.
- Palek J. Acanthocytosis, stomatocytosis, and related disorders. In: Beutler E, Lichtman M, Coller B, Kipps T (eds.). *William's Hematology.* 5th ed. New York: McGraw-Hill Inc.; 1995. p. 557-560.
- Rampoldi L, Danek A, Monaco AP. Clinical features and molecular bases of neuroacanthocytosis. *J Mol Med.* 2002; 80: 475-491.
- Kay J, Stricker R. Hematologic and immunologic abnormalities in anorexia nervosa. *South Med J.* 1983; 76: 1008-1010.
- Doll DC, List AF, Dayhoff DA, et al. Acanthocytosis associated with myelodysplasia. *J Clin Oncol.* 1989; 7 (10): 1569-1572.
- Mehndiratta MM, Malik S, Kumar S, et al. McLeod syndrome (a variant of neuro-acanthocytosis). *J Assoc Physicians India.* 2000 Mar; 48 (3): 356-357.

Jeshil R. Shah, MD
 Department of CT MRI
 Gokuldas Tejpal Hospital Spectrum Imaging Centre
 Mumbai, 400001, India
 Tel.: 91-22-2262 6226/91-22-43538100
 Mobile: 91-9224455612, 91-9920087667
 Fax: 91-22-43538102
 E-mail: shahjeshil@yahoo.com