Correspondence

Novel Xp21.1 deletion associated with unusual features in a large McLeod syndrome kindred

ARTICLE INFO

Keywords:
McLeod syndrome
Neuromyopathy
XK gene

1. Introduction

McLeod syndrome (MLS) is a rare adult-onset, progressive and in-
curable X-linked multisystem disorder characterized by chronic, pro-
finitive decline, seizures, polyneuropathy, myopathy and dilated car-
diomyopathy with subsequent heart failure and increased risk for
arrhythmia [1]. Variable psychiatric symptoms are common; the pre-
sence of achacrhocytes on blood smears, elevated CK levels and striatal
atrophy are other features. MLS is caused by mutation in the XK gene
which encodes a membrane transport protein containing the Kh ery-
throcyte antigen [1]. So far, less than 200 MLS cases have been re-
ported. In general, women harboring XK mutations rarely manifest
symptoms. In addition, myoclonus has not been described in associ-
ation with MLS and functional imaging studies are scarce.

2. Methods

All the examined patients consented to participate in this char-
acterization which was approved by the local ethics committees in
Vasa, Finland and in Stockholm, Sweden.

2.1. Patients

The family is from the Ostrobothnia region in Western Finland
(Pedigree in Fig. 1A).

2.2. Clinical investigations

Comprehensive clinical characterization, analysis of blood smears,
Ks and Kell antigens as well as genotyping. Brain MRI was performed in
2 symptomatic males, the index case underwent brain FDG PET.
Neuropathology was performed in his affected cousin. In addition, 4
women were examined by neurologists (B.U., O.S. and M.P.), pheno-
type assignment in some was based on history provided by relatives.

2.3. Genetics

Targeted analysis of the XK gene was performed using the stepwise
partitioning method [2].

3. Results

3.1. Clinical features and neurophysiological tests

The clinical features are summarized in Table e–1. Briefly, in-
trafamilial heterogeneity is in line with previous descriptions [1,3]. The
index case (IV:2) is a 72-years-old man who presented with insidious
onset of involuntary movements with vocalizations, eating difficulties
and personality change at age 45. Reduced short term memory, lack of
insight, perseveration and severe insomnia were also reported; his CK
was mildly elevated and ENMG displayed a mild demyelinating sen-
sorimotor polyneuropathy and proximal myopathy. ECG revealed first-
degree AV block at age 69 and echocardiography demonstrated dilated
cardiomyopathy with reduced ejection fraction (30–35%). An ACE in-
hibitor was started and a pace maker was inserted later. Range for age
at onset in males was 35–45 years, disease duration was slow (16–27
years) and age at death ranged between 56 and 72 years. Two men in
this family succumbed to sudden death (II:1 and IV:7). Myoclonus was
the first symptom in IV:7. Neuropathology demonstrated sensorimotor
polyneuropathy in IV:7 and in the index case (IV:2); in the latter signs of
proximal myopathy abnormalities were also evident. Patient IV:7
suffered from severe behavioral and psychiatric symptoms. Patients
II:1, III:6 and III:8 never sought medical care. Neither did 2 females
(II:5 and III:7) affected by involuntary movements suggesting chorea.
Botulinum toxin injections in both geniohyoid muscles (7.5 U) at-
temiated feeding dystonia in the index case (Video file).

Supplementary video related to this article can be found at https://
doi.org/10.1016/j.parkreldis.2018.09.014.

3.2. Biochemistry

Achacrhocytes, compensated hemolysis, elevated CK were present in
VI:2 and IV:7 (Table e–2). Immunohematological analyses in both
patients demonstrated absence of Ks antigen and weak reactions to the
Kell antigens k, Kpb and Jsb.

3.3. Genetics

A 1.94 mbp deletion in Xp21.1 starting 23.306 bp 5’ of the A of ATG
of the MAEBH6 gene and contiguous into intron 2 + 22.197 bp of the
XK gene was detected in the 2 affected males (IV:2 and IV:7) and in 4
asymptomatic females (Fig. 1B). The resulting sequence is differing from all other 17 cases with contiguous gene deletions, reported so far. The diagnostically relevant breakpoint sequence will be submitted to the European Nucleotide Archive (ENA).

3.4. Neuroimaging and neuropathology

In the index case, progressive striatal atrophy (MRI exams done at age 61 and 70) and bilateral atrophy of the hippocampus was found. Marked hypometabolism in the striatum, temporal, parietal, occipital lobes, and prefrontal regions was evident. In addition, metabolism was enhanced in the primary motor cortex, supplementary motor area and vermis (Fig. e-1 and e-2). Patient IV:7 had severe striatal atrophy and hyperintensities in the caudate nuclei (Fig. e-1). Severe neuronal loss was found in the striatum, in which the striatal hyperintensities were corresponded by neuronal loss and severe gliosis (Fig. e-3). Muscle biopsy in IV:7 indicated myopathy (Fig. e-4).

4. Discussion

This large Finnish kindred, the first report of MLS in Scandinavia, had a 1.94 mbp novel deletion at Xp21.1. New findings for MLS are the neuroimaging abnormalities and the presence of myoclonic jerks at onset in one male. Progressive striatal atrophy and widespread white matter abnormalities have been reported before in MLS [3,5] but hyperintensities in the caudate nuclei are new, corresponding to severe gliosis on neuropathology. Only 5 publications have provided data on functional imaging in MLS (Appendix). Donak et al. found reduced D2 receptor density and striatal hypometabolism in 1 MLS patient [4]. A similar pattern of hypometabolism, which correlated with disease duration, was reported in 5 patients from the largest MLS family so far reported [5]. Similar findings were documented in 2 additional patients, one of them, pre-symptomatic, another MLS patient with predominant hypokinnesia had reduced DAT binding but limited response to levodopa (References 10 and 11 in Appendix). Hypometabolism in the occipital lobes was also found in a previous study (Appendix), however the degree of widespread hypometabolism in our index case is a new finding and likely reflects longstanding disease with dementia.
Elevated metabolism in motor cortices has not been reported before for MLS, but it has been described in hyperglycemia-induced chorea [6]. This phenomenon may represent a compensatory activity in chorea.

The core neuroacanthocytosis syndromes MLS and chorea-acentochytosis (ChAc) overlap with each other, but the presence of dilated cardiomyopathy and loss of the public red blood cell antigen Kx differentiate MLS from ChAc. Two patients in the Finnish MLS family died suddenly likely due to cardiac arrhythmia illustrating the importance of cardiac management for survival in this disease. Unmatched blood transfusions constitute another potential hazard for MLS patients [1]. Feeding dystonia is sometimes a disabling feature of neuroacanthocytosis syndromes, in particular in ChAc. The condition is usually refractory to pharmacological treatment; however, treatment with botulinum toxin injections can be beneficial as demonstrated in this work.

Some missense KX mutations are associated with a milder phenotype [1]. Large deletions of variable size at Xp21.1 affecting CYBB, RPRGR, DMD and OTA may cause chronic granulomatous disease (XCGD), retinitis pigmentosa, Duchenne muscular dystrophy and urea cycle defects in addition to neuroacanthocytosis [1]. Larger Xp21 deletions affecting XK and other genes but sparing CYBB, RPRGR, DMD and OTA are not necessarily associated with a more severe MLS phenotype as demonstrated previously and supported by our work. Females harboring a heterozygous XK mutation may develop symptoms likely correlated to the degree of skewed X-chromosome inactivation [1]. So far, 39 small nucleotide variants and 17 cases with a partial, or complete deletion of XK plus contiguous gene deletions (6 of 17 with full characterization on the molecular level) are recognized by the International Society for Blood Transfusion (ISBT), representing the most complete repository of XK variants associated with an X-linked phenotype. Five XK point mutations have been reported to be found in more than one study, all others were reported from single patients or family groups only.

In conclusion, the main novel findings we describe for MLS-hyperintensities in the striatum and widespread brain hypometabolism-appear to be unique for the 1.94 mb deletion in Xp21.1. However, this possibility has to be nuanced by the lack of longitudinal functional imaging, scarce longitudinal structural imaging studies on a few MLS patients [3,5] and because the impact of gene modifiers for this disease remains largely unexplored.

Author contributions

M. Paucar, B. Udd, O. Sveinsson, C. Engström and B. Frey: study concept, data collection and writing of the manuscript; M. Paucar wrote the first draft. C. Gassner carried out the genetic analysis; C. Engström and B. Frey performed the immunohematological analyses; I. Savichcheva contributed with imaging data; G. Solders performed the neurophysiology in the index case; S. Hertegård treated the patient for feeding dystonia. H. Jung and M. Tolnay performed the neuropathological assessment. O. Sveinsson, P. Svenningson, C. Gassner, C. Engström, J. Laffita-Mesa, G. Solders, S. Hertegård, I. Savichcheva, H. Jung, M. Tolnay and B. Frey: editing of the manuscript.

Study funding

Stockholm County Council.

Disclosures

The authors report no disclosures relevant to the manuscript.

Acknowledgments

We are truly grateful to the patients and their families for their kind participation in this characterization. Thanks to Dr Alberto Espay for his opinion on the manuscript and to psychologist Birgitta Ausen for her cognitive evaluation on the index case.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.09.014.

References


Olof Sveinsson
Department of Neurology, Karolinska University Hospital, Stockholm, Sweden
Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
Bjarne Udd
Neuromuscular Research Center, Tampere University Hospital and University of Tampere, Tampere, Finland
Department of Neurology, Vaasa Central Hospital, Vaasa, Finland
Per Svenningsson
Department of Neurology, Karolinska University Hospital, Stockholm, Sweden
Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
Christoph Gassner, Charlotte Engström
Blood Transfusion Service Zürich, Swiss Red Cross (SRC), Zürich, Switzerland
José Miguel Laffita-Mesa
Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
Göran Solders
Department of Neurology, Karolinska University Hospital, Stockholm, Sweden
Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
Department of Neurophysiology, Karolinska University Hospital, Stockholm, Sweden
Stellan Hertegård
Department of Otorhinolaryngology, Karolinska University Hospital, Stockholm, Sweden
Irina Savichcheva
Department of Nuclear Medicine, Karolinska University Hospital, Stockholm, Sweden
Correspondence

Hans H. Jung
Department of Neurology, University Hospital Zurich, Switzerland

Markus Tolnay
Department of Neuropathology, Institute of Pathology, University Hospital in Basel, Switzerland

Beat M. Frey
Blood Transfusion Service Zurich, Swiss Red Cross (SRC), Zurich-Schlieren, Switzerland

Martin Paucar
Department of Neurology, Karolinska University Hospital, Stockholm, Sweden
Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

E-mail address: martin.paucar.arce@ki.se (M. Paucar)

* Corresponding author. Department of Neurology, Karolinska University Hospital Huddinge, 141 86, Stockholm, Sweden.
1 Equal contribution.