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Cerebral Metabolic Alterations in McLeod Syndrome

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Key Words
McLeod syndrome · Neuroacanthocytosis · Chorea

Abstract
The X-linked McLeod neuroacanthocytosis syndrome is a multisystem disorder with central nervous system manifestations resembling Huntington's disease. We examined 5 McLeod patients and 5 asymptomatic heterozygous females with fast multiple spin-echo spectroscopic imaging. Three patients with pronounced psychiatric or cognitive manifestations had pathological N-acetyl aspartate/(creatine + choline) ratios in frontal, temporal, and insular areas, with an individual pattern. Two patients with a severe choreatic movement disorder had unilateral thalamic alterations. One patient with moderate movement disorder and personality disorder had bilateral occipital alterations. One female heterozygote had unilateral insular metabolic alterations, possibly indicating subclinical cerebral involvement. Although the prominent psychiatric and cognitive manifestations in McLeod patients suggest significant and widespread cortical abnormalities, previous neuroradiological and histopathological data had not revealed definite extrastriatal pathology. Our findings demonstrating metabolic abnormalities in different brain regions of McLeod patients might either reflect neuronal dysfunction due to impaired basal ganglia-thalamo-cortical circuits or subtle structural alterations in the particular cerebral areas.

Introduction

The McLeod neuroacanthocytosis syndrome (MIM 314850) is an X-linked multisystem disorder caused by mutations in the *XK* gene [1–4]. Neuromuscular manifestations may be subclinical or mild, and include myopathy, cardiomyopathy and sensorimotor axonal neuropathy [4–6]. Central nervous system manifestations resemble Huntington's disease and comprise a choreatic movement disorder, psychiatric symptoms, subcortical cognitive decline, and generalized epileptic seizures [1, 3, 4].

The prominent neuropsychiatric manifestations and the presence of generalized seizures in McLeod patients indicate a significant and widespread cortical, rather than purely subcortical dysfunction [1, 3, 4]. Previous neuroradiological and neuropathological examinations, however, have not demonstrated extrastriatal brain pathology. Computed tomography and magnetic resonance imaging revealed variable atrophy of the caudate nucleus and the putamen, particularly in advanced disease stages [1, 3, 4]. ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography demonstrated impaired FDG uptake restricted to the striatum in McLeod patients, as well as in presymptomatic males and heterozygote females [3, 7]. These neuroradiological data were consistent with the limited neuropathological observations in 2 patients with McLeod syndrome, which demonstrated neuronal loss and astrocytic gliosis in the striatum [1, 8, 9].

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Table 1. Clinical characteristics and MRSI findings

Participant	Age years	Chorea[1]	Psychiatric symptoms	Cognitive impairment[2]	CK, U/l	MRSI alterations
Affected males						
IV-4	51	1	bipolar disorder	+	2,341	In r/l
IV-5	50	2	schizoaffective disorder	++	1,476	Fr r/l; Te r/l; In, r/l
IV-6	42	4	none	none	1,568	Th l
IV-7	37	2	schizotypal personality disorder	none	633	Oc l
IV-13	51	4	schizotypal personality disorder	+++	3,131	Te l; Th l
Heterozygote females						
IV-2	45	0	none	none	96	none
IV-10	53	0	none	none	n.d.	none
IV-11	53	0	none	none	70	In l
IV-12	35	0	none	none	106	none
V-4	29	0	none	none	n.d.	none

Fr = Frontal lobe; Te = temporal lobe; In = insula; Oc = occipital lobe; Th = thalamus; r = right; l = left; n.d. = not determined.

[1] 0 = Absent; 1 = slight/intermittent; 2 = common or moderate/intermittent; 3 = moderate/common; 4 = marked/prolonged.

[2] + = Mild; ++ = moderate; +++ = severe.

The prominent psychiatric and cognitive manifestations in McLeod patients were therefore explained by neuronal dysfunction due to impaired basal ganglia-thalamo-cortical circuits [10].

The aim of the present study was to investigate subtle cerebral metabolic alterations in McLeod patients and asymptomatic heterozygous females in different brain regions, and to correlate the findings with clinical symptoms.

Methods

Participants

We examined 5 male McLeod patients (mean age 46.2 ± 6.4 years) and 5 heterozygous women (mean age 45.0 ± 9.8 years) from one Swiss McLeod family, and 12 age- and gender-matched healthy controls (6 men, mean age 43.7 ± 9.7 years, and 6 women, mean age 40.3 ± 10.5 years). The clinical characteristics of patients and heterozygous women have previously been described [3, 10]. The local ethical committee approved the procedures, and all participants gave their written informed consent prior to the examinations.

All male McLeod patients had red blood cell (RBC) acanthocytosis, elevated serum creatine kinase (CK) levels, absent Kx RBC antigen and weak Kell RBC antigens [3]. Neurological examinations revealed consistently absent tendon reflexes reflecting subclinical sensorimotor axonopathy. Only 1 patient (IV-13) had a manifest myopathy, and none had cardiac manifestations (table 1) [6]. Three male McLeod patients (IV-4, IV-5, IV-13) had predominant psychiatric or cognitive manifestations. Psychiatric symptoms were classified according to the DSM-IV criteria [11], and included bipolar disorder, schizoaffective disorder, or personality disorder (table 1). Current medications comprised clozapine (IV-5, IV-13), quetiapine (IV-5), and valproate (IV-13). Cognitive testing was performed using a battery of standard tests, and detailed cognitive findings had been reported previously [3]. All patients had a choreatic movement disorder of variable degree. Chorea was rated according to the Unified Huntington's Disease Rating Scale as absent (0), slight/intermittent (1), common or moderate/intermittent (2), moderate/common (3), or marked/prolonged (4) (table 1).

The 5 female heterozygotes had no neuromuscular or neuropsychiatric signs or symptoms. Laboratory workup revealed no abnormalities (in particular no acanthocytosis) and normal serum CK levels (table 1). Immunohematological testing revealed a normal XK/Kell blood group serotype [3]. RBC flow cytometry using several anti-Kell antibodies was performed as previously described [12]. Between 10 and 60% of RBCs in females carried the McLeod blood group phenotype, indicating a blood group mosaicism in all female heterozygotes (data not shown).

Magnetic Resonance Spectroscopy Measurements

Magnetic resonance spectroscopic imaging (MRSI) was performed on a 3-tesla MRI system (Philips Medical Systems, Best, The Netherlands). Data were acquired with fast multiple spin-echo spectroscopic imaging, also called turbo spectroscopic imaging (TSI), from a slice oriented along the anterior commissure-posterior commissure line on the level of the caudate nucleus (MRSI matrix of 32 × 32 voxels, slice thickness = 15 mm, field of

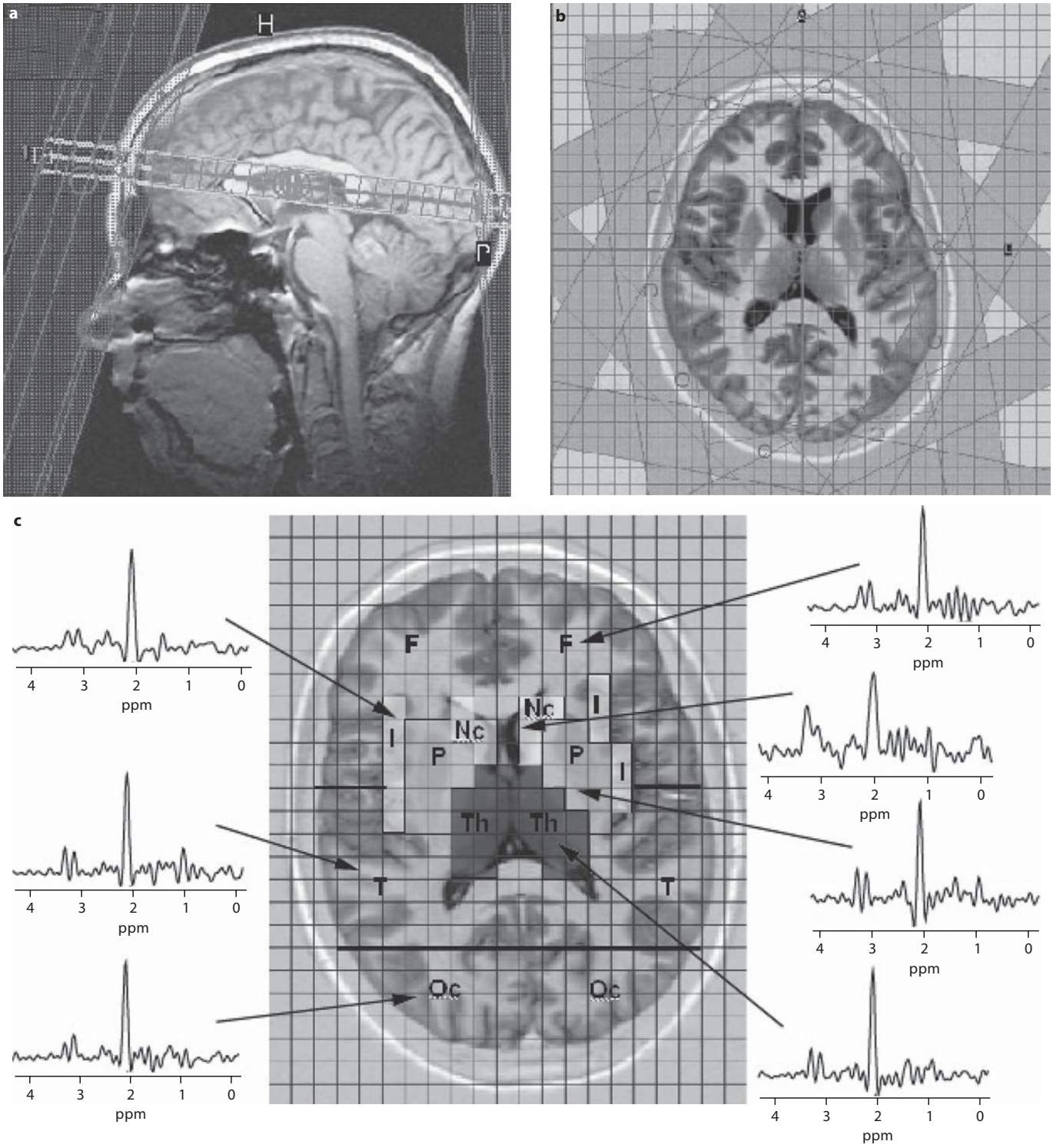

Fig. 1. a Representative example of the MRSI setup in a selected healthy control person. The MRSI slice is placed along the anterior commissure-posterior commissure line and outer-volume suppression slabs are used to suppress signal from subcutaneous fat. **b** Axial inversion recovery image of the MRSI slice in the same subject, as was used for tissue segmentation purpose. **c** ROIs and representative MRSI spectra of the same subject. F = Frontal lobe; I = insula; Nc = caudate nucleus; P = putamen; Th = thalamus; T = parietotemporal lobe; Oc = occipital lobe.

Table 2. Regional mean NAA/(Cr + Cho)

Participants	Side	Frontal		Temporal		Insula		Occipital		Caudate		Putamen		Thalamus	
		patient	controls[1]	patient	controls[1]	patient	controls[1]	patient	controls[1]	patient	controls[1]	patient	controls[1]	patient	controls[1]
IV-4	left	1.77	1.7 (0.2)	2.2	2.3 (0.2)	*1.41*	1.9 (0.1)	2.26	2.5 (0.3)	n.a.	n.a.	1.91	2.4 (1.0)	1.87	1.74 (0.1)
	right	1.65	1.8 (0.3)	2.04	2.3 (0.2)	*1.51*	1.9 (0.1)	n.a.		n.a.	n.a.	1.71	2.4 (1.0)	1.41	1.27 (0.1)
IV-5	left	*1.21*	2.0 (0.3)	*1.83*	2.3 (0.2)	*1.23*	1.8 (0.1)	n.a.		1.36	2.2 (0.4)	1.62	2.2 (0.5)	2.49	1.69 (0.1)
	right	*0.89*	2.0 (0.3)	*1.24*	2.3 (0.2)	*1.31*	1.8 (0.1)	n.a.		1.71	2.5 (0.3)	1.23	2.2 (0.5)	1.88	1.85 (0.1)
IV-6	left	2.41	2.1 (0.3)	2.75	2.3 (0.2)	1.86	1.8 (0.2)	n.a.	n.a.	n.a.	n.a.	2.55	2.3 (1.0)	*1.22*	1.67 (0.2)
	right	1.8	1.9 (0.2)	2.47	2.3 (0.2)	n.a.	1.8 (0.1)	n.a.	n.a.	n.a.	n.a.	2.36	2.3 (1.0)	1.36	1.30 (0.1)
IV-7	left	2.02	1.8 (0.2)	3.05	2.3 (0.2)	1.87	1.8 (0.1)	*1.7*	2.6 (0.3)	n.a.	n.a.	2.03	2.3 (0.4)	2.25	1.79 (0.1)
	right	1.9	1.8 (0.2)	2.68	2.3 (0.2)	2.26	1.7 (0.1)	3.74	2.6 (0.3)	n.a.	n.a.	2.1	2.4 (0.3)	1.58	1.30 (0.1)
IV-13	left	1.37	1.8 (0.3)	*1.83*	2.3 (0.2)	n.a.		3.42	2.4 (0.2)	n.a.	n.a.	n.a.	n.a.	*1.10*	1.79 (0.1)
	right	1.64	1.8 (0.3)	2.07	2.2 (0.1)	2.04	1.7 (0.1)	2	2.6 (0.3)	n.a.	n.a.	2.54	2.4 (1.0)	2.84	1.79 (0.1)
IV-02	left	n.a.	n.a.	2.4	2.6 (0.3)	n.a.	n.a.	2.66	2.4 (0.2)	n.a.	n.a.	n.a.	n.a.	2.07	1.72 (0.0)
	right	n.a.	n.a.	2.78	2.6 (0.3)	n.a.	n.a.	2.35	2.4 (0.2)	n.a.	n.a.	n.a.	n.a.	1.49	1.74 (0.1)
IV-10	left	n.a.	n.a.	2.29	2.6 (0.3)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	2.19	1.77 (0.1)
	right	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	2.56	2.2 (0.5)	2.10	1.77 (0.1)
IV-11	left	3.59	2.1 (0.3)	2.16	2.4 (0.2)	*1.52*	1.8 (0.1)	2.18	2.3 (0.2)	2.48	n.a.	n.a.	n.a.	2.46	1.75 (0.1)
	right	1.74	n.a.	3.15	2.4 (0.2)	2.2	1.7 (0.1)	n.a.		n.a.	n.a.	2.53	2.4 (0.3)	2.58	1.76 (0.1)
IV-12	left	n.a.	n.a.	2.8	2.3 (0.2)	2.15	1.8 (0.2)	2.92	2.4 (0.3)	n.a.	n.a.	1.97	2.3 (0.4)	1.70	1.79 (0.1)
	right	2.19	1.9 (0.2)	2.07	2.3 (0.2)	1.87	1.8 (0.1)	n.a.	n.a.	n.a.	n.a.	1.76	2.3 (0.5)	1.41	1.67 (0.1)
V-4	left	2.65	2.0 (0.3)	3.64	2.3 (0.2)	1.79	1.8 (0.1)	2.68	2.5 (0.3)	2.35	2.5 (0.3)	2.99	2.3 (0.5)	1.92	1.85 (0.1)
	right	2.01	2.0 (0.3)	2.43	2.3 (0.2)	3.39	1.9 (0.1)	2.55	2.5 (0.3)	1.53	2.2 (0.4)	4.03	2.3 (0.4)	1.68	1.67 (0.1)

Figures in italics indicate significant difference from controls (≥2 SD of mean controls). n.a. = Not available.
[1] Mean with SD in parentheses of NAA/(Cr + Cho) in controls matched to mean %WM in each individual participant.

view = 240 mm) (fig. 1a) [13]. Further acquisition parameters comprised TR/TE = 1,700/288 ms, echo spacing = 144 ms, echo train length = 4, bandwidth = 2,250 Hz, n = 256 samples. Total acquisition time per measurement was 7 min. This fast MRSI with relatively lower spectral quality had to be used due to the movement disorder. T_1-weighted inversion recovery images with high tissue contrast were acquired for tissue segmentation purposes.

Data Processing

Raw data were filtered with a cosine function in the spatial k-space dimensions before Fourier transformation. Data processing included exponential spectral filtering, a digital shift algorithm for improved water suppression, B0 correction, and linear phase correction. Voxels showing spectra of good quality (i.e. no baseline distortions, all peaks resolved) were selected from various regions of interest (ROIs) including left and right frontal lobe, insula, temporoparietal lobe, occipital lobe, putamen/globus pallidus, caudate nucleus, and thalamus (fig. 1c). Spectra were analyzed with jMRUI2.1 [14]. After removal of residual water and baseline correction, peak areas of N-acetyl aspartate (NAA)-, creatine (Cr)- and choline (Cho)-containing compounds were fitted using AMARES [15]. Tissue composition for each voxel was computed by segmenting inversion recovery images, aligning the MRI data with the MRSI slice, and convolving each tissue map with the spatial response function of the MRSI acquisition. For all voxels, the ratio of NAA/(Cr + Cho) was calculated to correct for intraslice variations of metabolite intensities due to B0 inhomogeneities.

Data Analysis

Due to the small number of available probands and variable numbers of voxels in the regions to be compared, a group analysis was not feasible. Therefore, a single subject threshold analysis was performed. In patients and heterozygotes, the mean NAA/(Cr + Cho) ratio and the mean percentage of white matter (%WM) of all voxels in each ROI were calculated. In order to identify ROIs with abnormally low NAA/(Cr + Cho) ratio in patients and heterozygotes, an individual threshold value for each ROI was defined. For this purpose, voxels in the corresponding ROI of controls were selected to match the mean %WM found in the ROI of each individual patient or heterozygote. After calculation of mean and standard deviation (SD) of NAA/(Cr + Cho) in the selected ROIs of controls, the threshold for pathological low NAA/(Cr + Cho) in the individual patient or heterozygote ROI was defined as:

mean [NAA/(Cr + Cho)] of controls – 2 SD [NAA/(Cr + Cho)]

of controls. ROIs with NAA/(Cr + Cho) at or below this threshold value were defined as abnormal.

Results

All male McLeod patients had significantly lower NAA/(Cr + Cho) ratios in some brain areas with variable extent and localization (tables 1, 2). One patient with schizoaffective disorder and moderate chorea (IV-5) had

the most extended alterations localized in frontal, temporal, and insular areas. One patient with severe cognitive impairment and severe chorea (IV-13) had left-sided alterations in temporal and thalamic areas. One patient with bipolar disorder and mild chorea (IV-4) had bilateral alterations in insular areas. One patient with severe chorea (IV-6) had left-sided alterations in thalamic areas, and another patient with moderate chorea and personality disorder (IV-7) had unilateral alterations in occipital areas. One female heterozygote had metabolic alterations in left insular areas (IV-11), whereas the other females had no significant alterations irrespective of the degree of RBCs carrying the McLeod blood group phenotype (data not shown). There were a high number of low-quality spectra in ROIs covering the striatal areas, in particular the caudate nucleus. Therefore, no definite conclusion about these regions was possible. Available ROIs covering the putamen were not significantly different between individual patients and the mean of the control group (table 2).

Discussion

Using fast TSI, we were able to demonstrate metabolic alterations in extrastriatal cerebral areas of McLeod patients with prominent psychiatric or cognitive manifestations. Due to the small number of patients and the variability of symptoms within the family, however, the specific interpretation of these MRSI findings is complex. In the patient with schizoaffective disorder, the metabolic alterations were located in frontal and temporal brain areas. These findings correlate with the data obtained from patients with idiopathic schizophrenia [16]. The patient with the pronounced cognitive impairment had metabolic alterations in left temporal brain areas, and there was a strong tendency for decreased NAA/(Cr + Cho) ratios in frontal brain areas. Definite metabolic alterations in comparable frontotemporal brain regions were observed in patients with frontotemporal dementia [17].

The patient with the bipolar disorder had bilateral metabolic alterations in insular brain areas. MRSI studies of patients with idiopathic bipolar disorders demonstrated metabolic alterations in frontal and, in particular, dorsolateral prefrontal brain areas, as well as in the basal ganglia [18]. Since the insula is not implicated in the pathogenesis of bipolar disorders, our findings might be explained by a spatial overlap of the insular ROIs with the neighboring putamen. However, the ROIs covering the putamen in this patient exhibited only a nonsignificant tendency towards decreased NAA/(Cr + Cho). One patient with moderate choreatic movement disorder and personality disorder had metabolic alterations in left occipital brain regions. In Huntington's disease, elevated lactate levels have previously been found in occipital areas [19, 20]. However, these studies used large single voxels without segmentation, and no ^{1}H-MRSI data were reported [19, 21–23]. In addition, the occipital cortex is not primarily implicated in the pathogenesis of movement disorders or neuropsychiatric syndromes. Therefore, the significance of the occipital metabolic alterations remains uncertain.

The 2 McLeod patients with isolated or predominant choreatic movement disorder demonstrated significant metabolic alterations in the left thalamus. Neuroradiological and pathological examinations of McLeod patients in the literature did not reveal significant atrophy or other pathological changes of the thalamus [1, 3, 8, 9]. On the other hand, disinhibition of the thalamus plays an important role in the generation of chorea, and might therefore contribute to the decreased thalamic NAA/(Cr + Cho) ratios in our patients. However, the chorea in our patients was generalized without important lateralization, and the observed asymmetry warrants an alternative explanation such as sample inhomogeneity or skewed threshold effect. The thalamus was not included as an ROI in several single-voxel MRSI studies in Huntington's disease [19, 21–23]. In Huntington patients, however, decreased neuron and glial cell numbers and the presence of fibrous astroglia have been demonstrated in the mediodorsal thalamic nucleus, probably reflecting altered neuronal circuits [24].

One female heterozygote had left insular metabolic alterations. Since only 1 out of 5 female heterozygotes had pathological changes, the MRSI does not constitute a reliable method for the detection of subclinical cerebral involvement. Using flow cytometry, in contrast, all female heterozygotes demonstrated important blood group mosaicism. A previous FDG positron emission tomography showed reduced striatal FDG uptake in 1 female heterozygote of the same family, who unfortunately did not agree to participate in the present study [3]. All the recruited female heterozygotes were clinically asymptomatic. However, there have been reports in the literature of rare symptomatic manifestations in female heterozygotes [1, 25]. These findings can probably be interpreted as a consequence of an unfavorable inactivation of the X chromosome carrying the normal *XK* gene [26].

With our methodology, we were not able to obtain conclusive spectroscopic results from the striatum. The movement disorder of the McLeod patients necessitated

the use of a fast MRSI technique resulting in a lower spectral quality. For extrastriatal regions, we obtained good-quality, high-resolution TSI data suitable for quantitative assessment. In ROIs covering the caudate nucleus, however, there were large numbers of low-quality spectra not suitable for further analysis. This was probably due to susceptibility artifacts arising from the neighboring sinuses. These artifacts were pronounced at the high field strength used. ROIs covering the putamen demonstrated no significant differences between individual patients and the mean of the control group, indicating that the putamen might not be the primary location of striatal pathology in McLeod syndrome. In fact, the few neuropathological examinations demonstrate nonspecific neuronal loss and reactive astrocytic gliosis predominantly in the head of the caudate nucleus, and markedly less pronounced in the putamen [1, 8, 9].

Based on the clinical, neuroradiological, and neuropathological data, McLeod syndrome shares many similarities with Huntington's disease. MRSI studies in Huntington patients have demonstrated significant striatal metabolic alterations that correlated with the disease severity and the CAG repeat number [21, 22]. These studies, however, used a single-voxel technique covering variable proportions of the basal ganglia, and only one study used a tissue segmentation technique to correct for the different contributions from cerebrospinal fluid and white matter [22]. To the best of our knowledge, no multivoxel MRSI studies have been reported from human Huntington's disease. A single-voxel MRSI study demonstrated a decreased NAA/Cho ratio in the frontal lobe of Huntington patients [27]. The lack of multivoxel MRSI studies, the extended voxel size, the missing correction for contributions from nonbasal ganglia tissue, and the possible influence of susceptibility artifacts arising from the skull base hamper a direct comparison with our striatal MRSI findings.

In conclusion, our study demonstrates that MRSI techniques are a useful tool for the examination of extrastriatal cerebral metabolic alterations in basal ganglia disorders. We were able to demonstrate subtle metabolic abnormalities in different extrastriatal brain regions of McLeod patients. Although interpretation is limited due to the sparse neuropathological data available, our findings might either reflect a neuronal dysfunction due to impaired basal ganglia-cortical circuits or subtle structural alterations in the particular brain areas.

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