

SHORT REPORT

Neuroleptic malignant syndrome in Kufs' disease

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A patient with adult neuronal ceroid lipofuscinosis (ANCL; Kufs' disease) is described in whom neuroleptic malignant syndrome occurred, initially presenting as catatonic syndrome. Comprehensive neuroimaging studies were conducted including FDG-PET, IBZM-SPECT, and β -CIT-SPECT, electrophysiological examinations and an ex vivo contracture test exposing muscle biopsy specimens to neuroleptics. Collectively the results argued for an involvement of the muscle in neuroleptic malignant syndrome at least in ANCL.

Adult neuronal ceroid lipofuscinosis (ANCL; Kufs' disease) represents a subgroup of the neuronal ceroid lipofuscinoses.¹ Berkovic distinguished two phenotypes of ANCL: a more common type A, featuring progressive myoclonus epilepsy, and type B consisting of initial behavioural abnormalities, dementia, motor disturbances, and facial dyskinesia.² Kufs' disease is rare with an incidence of about 1:1 000 000 and thought to be caused by a mutation in a yet unidentified *CLN₄* gene, which may code for a lysosomal glycoprotein.

Neuroleptic malignant syndrome (NMS) is a life threatening side effect of neuroleptic agents with unknown pathophysiology. Symptoms include hyperthermia, autonomic symptoms, rigidity, extrapyramidal symptoms, and an increase in creatine kinase. NMS is rare and occurs in about 0.3% of all patients receiving neuroleptics.³ There is no report on the combination of both disorders.

CASE REPORT

A 30 year old woman was referred to our department for further therapy of treatment resistant NMS. On admission, she was in a catatonic stupor displaying marked rigidity, tremor and autonomic symptoms.

There was no family history of neuropsychiatric diseases. The developmental milestones were delayed; however, she became able to look after herself and to fulfil simple jobs. At the age of 29, she had to be admitted to a psychiatric hospital for behavioural disturbances and psychotic symptoms; akinetic states were followed by excitation. After mirtazapine and olanzapine treatment, she partly recovered although constant cognitive decline was noted thereafter. Several months later, readmission was unavoidable because of hyperorality, inappropriate behaviour, mutism and immobility alternating with states of excitement. Slight motor symptoms (facial dyskinesias, tremor, spastic muscle tone) were observed. The diagnosis of catatonic psychosis was applied and oral fluphenazine was prescribed. In the following days she developed autonomic symptoms, an increase in creatine kinase, fever, stupor and rigor, which were interpreted as NMS. Neuroleptic agents were withdrawn but the symptoms only partly recovered upon diazepam, biperiden, and dantrolene administration. The patient thus was referred to our department for electroconvulsive treatment (ECT).

After 10 ECTs, vegetative symptoms, rigor, and inner tension gradually improved. The patient was still mutistic, inactive, and displayed spastic muscle tone. Three weeks after ECT was stopped the first voluntary movements could be noted; however unspecific catatonic signs such as waxy flexibility and rigidity were prominent. As she persistently lacked drive, we started amantadine treatment. After the first dose, she began to speak single words and seemed even tempered. She recovered rapidly now: voluntary movements started, she spoke short sentences and the emotional state improved. Soon she was able to walk and eat alone. Occasionally excitational states occurred, in which the patient was frightened and fearful. We thus combined amantadine with quetiapine, which was well tolerated and effective, so that we could refer her for rehabilitation. An interview with the caregiver eight months later revealed that the patient's health state was stable, yet cognitive impairments in the form of presenile dementia persisted.

Laboratory findings

We conducted comprehensive laboratory investigations including serological tests for neurotrophic viruses, anti-amphiphysine, anti-GAD-II-antibodies, long chain fatty acids, carnitine, phenylalanine, phytanic acid, glutamine, alanine, citrulline, and ammoniac, which were normal as were the lysosomal enzymes β -hexosaminidases, hexosaminidase A, β -galaktosidase, acidic phosphatase, arylsulphatase A, and galaktocerebrosidase. All investigated CSF parameters including protein 14–3–3 and S100 were normal. The patient had a normal female karyotype, an E3/E3 ApoE4 allele, and a regular number of huntingtin CAG-repeats. An analysis of the FTDP-17 τ -gene revealed none of the known mutations.

Electrophysiological investigations

Four EEGs were conducted and consistently displayed pharmacologically altered β frequency. The P300 component of event related potentials had decreased amplitude, and AEP suggested delayed brain stem conduction. The first electromyographic examination (two weeks after admission) revealed positive sharp waves and fibrillation potentials of the left M quadriceps and M triceps humeri, which was confirmed in a second examination one week later. No repetitive discharges were found; the pattern at voluntary effort was normal. EMG was repeated when the patient was anaesthetised; spontaneous muscular activity and muscular stiffness ceased shortly after thiopental administration. A fourth EMG three months later revealed no abnormalities.

Neuroimaging

Cranial computed tomography was entirely normal as were three MRI scans. Briefly after the last ECT treatment, we conducted β -CIT-SPECT and IBZM-SPECT (before amantadine or

Abbreviations: ANCL, adult neuronal ceroid lipofuscinosis; NMS, neuroleptic malignant syndrome

Table 1 Experimental in vitro muscle contracture test upon exposition to neuroleptic agents

Compound	Minimum concentration ($\mu\text{g/ml}$)	Maximum concentration (mg/ml)	Concentration level causing relevant contracture (>2 mN)
Clozapine	12.5	2.0	No contracture
Sulpiride	12.5	5.0	11
Olanzapine	2.5	5.0	9
Risperidone	1.0	1.0	8
Fluphenazine	1.25	0.6	7
Haloperidol	2.5	1.0	6
Perazine	2.5	2.5	6
Flupenthixol	12.5	2.0	1

Muscle bundles from a fresh biopsy (about 2.5 cm long, 200 mg each) were exposed to neuroleptics in geometrically increasing concentrations. All other conditions were analogous to the European Malignant Hyperthermia Group IVCT protocol.⁵ Atypical neuroleptics were less prone to cause pathological muscle contractures. In muscle biopsy specimens of MH patients, no contractures could be observed in the same experimental setting (not shown).

quetiapine treatment), revealing no abnormalities. At the same time, FDG-PET scanning showed generally reduced glucose uptake in both hemispheres, which was prominent in frontal, temporal, and parieto-occipital brain areas. To rule out changes attributable to ECT, PET scans were performed 9 and 14 weeks later, producing similar results.

Muscle biopsy and contracture tests

Two months after admission the left M vastus lateralis was biopsied. Histopathological examination revealed increased fibre size variability with many single type II fibre atrophies and type I fibres predominance. The number of central nuclei was normal. Small vacuolar changes were found in several fibres on trichrome staining. Oil red staining revealed inhomogeneously distributed fatty deposits in 50% of the fibres. Electron microscopy revealed myelin figures and dense deposits configured as fingerprints indicating the presence of ANCL.

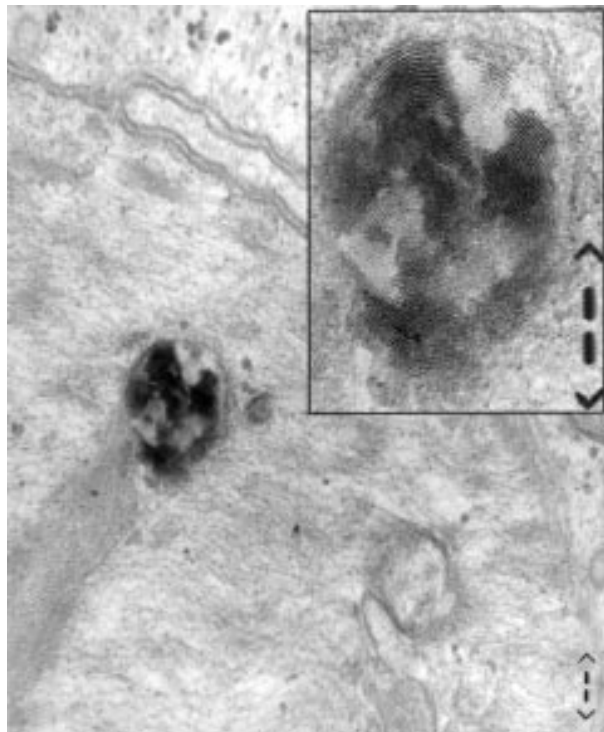


Figure 1 Electron microscopy of a skin biopsy specimen. Ultrastructural examination shows dense deposits, which are configured as fingerprint profiles typical for ANCL (electron microscopy; original magnification: 1:30 000; inset, 1:69 000; the internal scale marker represents 0.25 μm).

We performed an in vitro contracture test established for the diagnosis of malignant hyperthermia (MH).^{4,5} No significant contracture of biopsied muscle bundles was found upon either halothane or caffeine incubation, so that a disposition towards MH could be ruled out. In an analogous setting, the muscular contracture upon exposition towards neuroleptic agents was measured to examine the disposition of the isolated muscle to react pathologically towards neuroleptics. Atypical neuroleptics were less prone to cause pathological muscle contractures (table 1). When muscles biopsy specimens of MH patients were exposed to neuroleptics in the same manner, no pathological contractures could be observed (A Hoyer, unpublished data). Interestingly, we noted that the muscular compliance was reduced by the factor of 4.5. These findings point towards a yet unrecognised abnormality of denervated muscle fibres in NMS and/or ANCL.

Skin biopsy

Electron microscopy of ultra-thin skin sections revealed large amounts of lipopigments in sweat glands and several fingerprint profiles in smooth muscle cells (fig 1), confirming the diagnosis of ANCL.

DISCUSSION

We could positively diagnose ANCL from biopsies of skin and muscle,^{6,7} revealing myelin figures and fingerprint patterns in two organs. Other lysosomal diseases causing lipopigment accumulation could be ruled out by laboratory examinations. Clinically, our case fulfilled all diagnostic criteria of type B ANCL: behavioural changes as an initial symptom, followed by dementia, motor abnormalities, and facial dyskinesia.²

In contrast with previous MRI studies in ANCL,⁸⁻¹⁰ MRI in our patient was strikingly normal probably because of the comparatively early examination in the course of the disease. SPECT and PET findings in ANCL as well as NMS are sparse; only one study dealt with FDG-PET scanning in ANCL.⁹ Similar to our findings, temporoparietal and prefrontal hypoperfusion was observed. NMS as well as ECT might be confounding factors in our case; however, both NMS and ECT tend to increase perfusion rather than to decrease it.¹¹ Considering this, the observed abnormalities were thus most probably attributable to ANCL. PET thus might be more sensitive than MRI in the early diagnosis of ANCL.

Additionally, we used two different SPECT tracers: ¹²³I-IBZM, which binds to D2 dopamine receptors, and β -CIT, binding to the dopamine transporter DAT. None of these methods have yet been applied in ANCL; in NMS, only one study used ¹²³I-IBZM SPECT.¹² Surprisingly, no pathological findings could be observed with both tracers, indicating that neither D2 nor DAT are involved in the symptomatology of ANCL, nor does ECT or NMS change D2 and DAT density.

Interestingly, we noted remarkable changes in the muscle itself by the means of histopathological examination and electron microscopy in line with several other studies reporting on pathological muscle changes in NMS.¹³ In addition to structural changes, we found altered mechanical properties in the in vitro muscle contracture test: when exposed to neuroleptics, significant muscle contractures occurred. "Typical" compounds, including fluphenazine that caused NMS in this case, resulted in instant pathological contractures even at very low concentrations probably related to disturbances in the calcium metabolism of muscle cells in the course of ANCL. In contrast, atypical compounds caused contractures either in higher concentrations or not at all, in line with clinical evidence suggesting that atypicals are less likely to provoke NMS.³

In ANCL, lipopigments were also found in extracerebral tissues including muscle and comprise of subunit c of mitochondrial ATP synthase and sphingolipid activators.¹⁴ It is not exactly known whether and how lipopigments can change cellular function. Mutations of membrane spanning proteins, which are expressed in the cerebrum and in extracerebral tissues, are now known to play a key part in the pathogenesis of several NCL subgroups.¹⁵ Similarly, deficiency of a distinct membrane spanning protein might be responsible for muscle pathology in our case. We thus hypothesise that muscle cell metabolism or muscle membrane function were disturbed upon application of "typical" neuroleptics. Having in mind the electromyography results as well, we speculate that besides the brain also the muscle might react pathologically in NMS at least in ANCL, probably because of similar target structures for neuroleptic agents as in the CNS.

The identification of NMS pathophysiology is of utter importance and might enable the pharmacogenomic detection of subjects prone to this fatal side effect. In our case, with ANCL as an underlying disease, neuroimaging, electrophysiology as well as in vitro contracture testing together argue for an muscular abnormality in NMS.

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