Adult neuronal ceroid lipofuscinosis with clinical findings consistent with a butterfly glioma

Case report

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The authors report a case of neuronal ceroid lipofuscinosis (Kufs’ disease) confirmed by stereotactically obtained brain biopsy findings and initially diagnosed as a butterfly glioma. The presenting symptoms in the 64-year-old patient were mental alterations with progressive dementia, followed by muscular atrophy and myoclonia with distal preponderance. The mild initial disturbances of coordination increased, and the patient developed a markedly ataxic gait. Computerized tomography (CT) scanning and magnetic resonance imaging revealed generalized cerebral atrophy and a bifrontal space-occupying lesion involving the callosum. The original “clearcut” diagnosis of glioblastoma multiforme, based on CT scans, was unexpectedly disproved by examination of stereotactically obtained brain biopsy specimens, which revealed a neuronal ceroid lipofuscinosis (Kufs’ disease). To the authors’ knowledge, this is the first report of a case presenting with both diffuse brain atrophy and localized accumulation of neuronal lipofuscin, mimicking a mass lesion on radiological studies.

KEY WORDS • glioma • Kufs’ disease • ceroid lipofuscinosis • thesaurismosis


Euronal ceroid lipofuscinosis is a generic term for all forms of storage disease in which deposits of ceroid lipofuscin pigment are found. The adult type of this disease was first described by Kufs in 1925. Early symptoms are nonspecific psychological changes that progress to organic psychosis and dementia. The most important criterion for distinguishing the adult type of sphingolipidosis from juvenile forms is the absence of visual disorders. Only a few of the cases reported in the literature as Kufs’ disease fulfill the criteria currently accepted for this disorder. The nonspecific clinical symptoms, the absence of detectable genetic or enzymatic defects, and the fact that brain atrophy is the only radiological correlate of the disease, pose diagnostic problems. In addition, a histological diagnosis can be made in vivo only by means of studies of biopsy specimens of skin, muscle, brain tissue, rectal mucosa, and cornea, and only electron microscopy can reveal the typical ultrastructural features of the accumulated pigment.

We report the case of a woman who presented with a bifrontal cerebral mass tentatively diagnosed as a butterfly glioma, and in whom a brain biopsy specimen was stereotactically obtained prior to radiotherapy. Unexpectedly, analysis of the biopsy material led to the diagnosis of adult neuronal ceroid lipofuscinosis (Kufs’ disease).

Case Report

History. This 64-year-old woman had suffered from progressive lethargy and disorientation for 2 years and had become unable to care for her household. She was not oriented to time and space.

Examination. On admission, the patient appeared prematurely aged. Her general condition and state of nutrition were satisfactory, although she exhibited trunk obesity. The results of laboratory tests were within normal limits. The neurological examination revealed a frontal lobe syndrome with initial signs of neglect, hypodynamia, changes in mood, and occasional aggressive outbursts. Symptoms of incipient dementia and urinary incontinence were also present. Cranial nerve function was normal; in particular, there was no visual disturbance. Tests of her extremities showed muscular atrophy with distal preponderance. Sensation and tendon reflexes were normal, and no pyramidal tract signs were noted. The patient exhibited a moderate gait ataxia, and the finger–nose test showed a mild disturbance of coordination. Ophthalmological examination demonstrated no abnormalities. An electroencephalographic study showed moderate-to-severe bifrontal disturbances.

Neuroradiological Findings. Computerized tomography
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(CT) (Fig. 1 left) and magnetic resonance (MR) (Fig. 1 center and right) imaging demonstrated a bifrontal mass involving the callosum, as well as generalized brain atrophy. Carotid injection angiography performed to confirm the diagnosis of glioblastoma showed no tumor vascularization. There was only a slight displacement of the left anterior cerebral artery to the opposite side.

**Histological Findings.** Stereotactically obtained brain biopsy specimens confirmed the CT diagnosis prior to initiation of radiation treatment. Nine 1-mm tissue specimens were obtained 2 mm apart from each other. Three of the samples were immediately frozen in liquid nitrogen, cut on a cryostat, and stained with hematoxylin and eosin and Diff-Quick. The remaining specimens were fixed in Somogyi–Takugi solution and embedded in paraffin. The frozen sections contained a finely granulated material diffusely distributed within the cytoplasm of the nerve cells. The nuclei of the affected neurons appeared to be displaced to the periphery. Another notable finding was the presence of swollen astrocytes with reactive alterations. On the basis of these observations, a storage disease (thesaurosis) was suspected (Fig. 2). This was confirmed in the specimens embedded in paraffin and stained with hematoxylin and eosin, Nissl’s, periodic acid–Schiff, and Heidenhain–Woelke. In none of the tissue samples were there findings indicative of a tumor.

Because light microscopic studies alone did not allow determination of the type of material stored (lipofuscin or lipopigment), selected specimens were reembedded for electron microscopic examination. This method demonstrated neuronal inclusions in the form of rounded, lipofuscin-like bodies. Fingerprint patterns and curvilinear cytosomes were also seen (Fig. 3).

After the diagnosis of a thesaurism was histologically confirmed, we performed an electromyelographic study (upper and lower limbs), which revealed diffuse axonal damage resembling that seen in polyneuropathy. No decrease in nerve conduction velocity (upper and lower limbs) was seen. Enzyme concentrations in serum (aryl-sulfatase, α-galactosidase, and α-hexosaminidase A and B) were within normal ranges.

**Treatment and Outcome.** The patient was transferred to a neuropsychiatric unit. When we conducted a follow-up review 8 months later, she had developed complete dementia and she was no longer able to walk unaided. The coordination disturbances and distal muscular atrophies were more pronounced and were accompanied by continuous spontaneous myoclonus. She had not suffered an epileptic seizure. Nuclear MR imaging performed at this time showed that the bifrontal mass remained unchanged, whereas cerebellar atrophy had progressed (Fig. 4). Altogether, the patient’s condition had deteriorated to such an extent that she was unable to care for herself, and 16 months after diagnosis of Kufs’ disease, the patient died in the final stage of dementia. Permission for an autopsy was denied by her relatives. On the basis of the clinical symptoms, the negative enzymatic studies, and the morphological findings, this case must be classified as one of adult neuronal ceroid lipofuscinosis.

**Discussion**

The nosology of the adult form of neuronal ceroid lipofuscinosis remains unclear. Only some of the published cases withstand scrutiny by modern diagnostic procedures: reevaluation of all 118 cases reported before 1988 showed a reliable diagnosis in only 50 (42.4%). Currently, visualization of intracellular lipopigments, fingerprints, and curvilinear cytosomes by using electron microscopy is regarded as obligatory for the diagnosis of adult neuronal ceroid lipofuscinosis. So far the characteristic electron microscopic findings have only been demonstrated in 29 cases. Other modern diagnostic procedures yield little additional information, because enzymatic and genetic defects have not been demonstrated, and because the cause and pathogenesis of ceroid lipofuscinosis remain unknown.

Neuroimaging studies (CT and MR imaging) may demonstrate general brain atrophy with dilated ventricles, but there are no reliable diagnostic radiological criteria for a storage disease. Individual variations in symptomatology make clinical diagnosis of this disease difficult. There have been cases in which patients were misdiag-
nosed and confined to psychiatric wards for years for treatment of schizophrenia or dementia.

The age at onset and the progressive course are likewise unspecific. A reliable in vivo diagnosis can be established only by means of studies of biopsy samples of skin, muscle, rectal mucosa, liver, or brain tissue.

However, even a diagnosis established by means of biopsy specimen studies may be unreliable, because neuronal ceroid lipofuscinosis is not the only disease associated with an accumulation of lipopigments. The different ultrastructural properties of stored lipopigment and lipofuscin permit a reliable distinction within the central nervous system. This distinction is more difficult in systemic cases and may require repeated examination of biopsy specimens from more than one organ. Additional diagnostic information may be obtained from neurophysiological studies, such as evoked potentials, although no characteristic findings were obtained in Kufs' disease as opposed to infantile forms of sphingolipidosis.

Obtaining a brain biopsy specimen is certainly an invasive diagnostic procedure. However, if a brain tumor is suspected a biopsy becomes mandatory prior to radiation therapy. In our case it offered the advantage of diagnostic reliability, in particular regarding the architectonic distrib-

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**Fig. 2.** Upper: Photomicrograph of a stereotactically obtained biopsy specimen showing reactive astrocytes with granulated material. Lower: Photomicrograph of a stereotactically obtained biopsy specimen showing finely granulated material (lipofuscin) stored within the cytoplasm. H & E, original magnification × 300.
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Fig. 3. Electron micrographs of a biopsy specimen illustrating the typical ultrastructural features, with fingerprint patterns (left), and curvilinear cytosomes and neuronal inclusions of rounded, lipofuscin-like bodies (right). Original magnification × 96,000.

ution of pigments and the selective involvement of individual cortical layers. Of particular importance is Layer III, where a pronounced accumulation of lipopigments may be expected in the perikaryon of nerve cells. Other specific features of neuronal ceroid lipofuscinosis include the loss of nerve cells in Layers II and Va, and the involvement of frontal rather than occipital areas.

A false diagnosis may result from studies of biopsy specimens that contain only nerve cells with stored lipofuscin, whereas other nerve cells may be present that show a typical fingerprint pattern on electron microscopic examination. The distribution of involved areas may also vary from case to case, although the areas of predilection can be regarded as constant.

Conclusions

Our patient was initially diagnosed as having a brain tumor because the neuroradiological findings were indicative of a bifrontal mass, and its appearance was typical of a glioma of the corpus callosum. Histological examination of the frozen sections indicated a storage disease and diag-

Fig. 4. Left: Contrast-enhanced CT scans obtained 8 months after initial diagnosis of ceroid lipofuscinosis. Right: Contrast-enhanced MR images obtained at the same time. Both studies show no change in the bifrontal mass, but progression of cerebellar atrophy.
nosis was confirmed by using electron microscopy. Other diseases (for example, GM2 gangliosidosis and metachromatic leukodystrophy) were excluded by enzymatic studies. In the later course of her illness, the patient developed myoclonia and cerebellar disorders, two features that are also indicative of Kufs’ disease. The fact that this lesion does not constitute a genuine expanding process was also confirmed by the follow-up review 8 months after the initial diagnosis. Sixteen months after the diagnosis, the patient died in the final stage of dementia. A survey of the literature found no other report of a case of Kufs’ disease in which neuronal lipopigment was stored in the form of a cerebral mass lesion.

References

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