Neuronal ceroid lipofuscinosis

Neuronal ceroid lipofuscinosis (NCL) refers to a group of conditions that affect the nervous system. Signs and symptoms vary widely between the forms but generally include a combination of dementia, vision loss, and epilepsy. Although the NCLs were historically classified according to their age of onset and clinical symptoms, the most recent classification system is primarily based on their underlying genetic cause. Most forms are inherited in an autosomal recessive manner; however, autosomal dominant inheritance has been reported in one adult-onset form (neuronal ceroid lipofuscinosis 4B).

Infantile and late-infantile neuronal ceroid lipofuscinoses (NCLs) are invariably fatal lysosomal storage diseases associated with defects in lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT-1) or tripeptidyl peptidase 1 (TPP1) activity.

Diagnosis

Kufs disease is the major adult form of neuronal ceroid lipofuscinosis, but is rare and difficult to diagnose. Diagnosis was traditionally dependent on the demonstration of characteristic storage material, but distinction from normal age-related accumulation of lipofuscin can be challenging. Mutation of CLN6 has emerged as the most important cause of recessive Kufs disease but, remarkably, is also responsible for variant late infantile ceroid lipofuscinosis. Here we provide a detailed description of Kufs disease due to CLN6 pathogenic variants. We studied 20 cases of Kufs disease with CLN6 pathogenic variants from 13 unrelated families. Mean age of onset was 28 years (range 12-51) with bimodal peaks in teenage and early adult life. The typical presentation was of progressive myoclonus epilepsy with debilitating myoclonic seizures and relatively infrequent tonic-clonic seizures. Patients became wheelchair-bound with a mean 12 years post-onset. Ataxia was the most prominent motor feature. Dementia appeared to be an invariable accompaniment, although it could take a number of years to manifest and occasionally cognitive impairment preceded myoclonic seizures. Patients were usually highly photosensitive on EEG. MRI showed progressive cerebral and cerebellar atrophy. The median survival time was 26 years from disease onset. Ultrastructural examination of the pathology revealed fingerprint profiles as the characteristic inclusions, but they were not reliably seen in tissues other than brain. Curvilinear profiles, which are seen in the late infantile form, were not a feature. Of the 13 unrelated families we observed homozygous CLN6 pathogenic variants in four and compound heterozygous variants in nine. Compared to the variant late infantile form, there was a lower proportion of variants that predicted protein truncation. Certain heterozygous missense variants in the same amino acid position were found in both variant late infantile and Kufs disease. There was a predominance of cases from Italy and surrounding regions; this was partially explained by the discovery of three founder pathogenic variants. Clinical distinction of type A (progressive myoclonus epilepsy) and type B (dementia with motor disturbance) Kufs disease was supported by molecular diagnoses. Type A is usually caused by recessive pathogenic variants in CLN6 or dominant variants in DNAJC5. Type B Kufs is usually associated with recessive CTSF pathogenic variants. The diagnosis of Kufs remains challenging but, with the availability of genetic diagnosis, this will largely supersede the use of diagnostic biopsies, particularly as biopsies of peripheral tissues has unsatisfactory sensitivity and specificity [1)].

Treatment

Treatment options are limited to therapies that can help relieve some of the symptoms.

Current therapies are supportive in nature. NCLs involving lysosomal enzymes are amenable to therapies that provide an exogenous source of protein, as has been used for other LSDs. Those that involve transmembrane proteins, however, require new approaches. Areas covered: This review will discuss potential gene and cell therapy approaches that have been, are, or may be in development for these disorders and those that have entered clinical trials. Expert opinion: In animal models, gene therapy approaches have produced remarkable improvements in neurological function and lifespan. However, a complete cure has not been reached for any NCL, and a better understanding of the limits of the current crop of vectors is needed to more fully address these diseases. The prospects for gene therapy, particularly those that can be delivered systemically and treat both the brain and peripheral tissue, are high. The future is beginning to look bright for NCL patients and their families [2)].

Previous preclinical studies have demonstrated that human CNS stem cells (HuCNS-SCs) produce both PPT-1 and TPP1 and result in donor cell engraftment and reduced accumulation of storage material in the brain when tested in an NCL mouse model.

HuCNS-SC transplantation was tested in an open-label dose-escalation Phase I clinical trial as a potential treatment for infantile and late-infantile NCL. Study design included direct neurosurgical transplantation of allogeneic HuCNS-SCs into the cerebral hemispheres and lateral ventricles accompanied by 12 months of immunosuppression.

Six children with either the infantile or late-infantile forms of NCL underwent low- (3 patients) and high- (3 patients) dose transplantation of HuCNS-SCs followed by immunosuppression. The surgery, immunosuppression, and cell transplantation were well tolerated. Adverse events following transplantation were consistent with the underlying disease, and none were directly attributed to the donor cells. Observations regarding efficacy of the intervention were limited by the enrollment criteria requiring that patients be in advanced stages of disease.

This study represents the first-in-human clinical trial involving transplantation of a purified population of human neural stem cells for a neurodegenerative disorder. The feasibility of this approach and absence of transplantation-related serious adverse events support further exploration of HuCNS-SC transplantation as a potential treatment for select subtypes of NCL, and possibly for other neurodegenerative disorders [3)].

Ten patients with late infantile neuronal ceroid lipofuscinosis disease each underwent infusion of AAV2(CU)hCLN2 (3 x 10(12) particle units) into 12 distinct cerebral locations (2 depths/bur hole, 75 minutes/infusion, and 2 microl/minute). Innovative surgical techniques were developed to overcome several obstacles for which little or no established techniques were available. Successful infusion relied on preoperative stereotactic planning to optimize a parenchymal target and diffuse administration. Six entry sites, each having 2 depths of injections, were used to reduce operative time and enhance distribution. A low-profile rigid fixation system with 6 integrated holding arms was utilized to perform simultaneous infusions within a practical time frame. Dural sealant with generous irrigation was used to avoid CSF egress with possible subdural hemorrhage or altered stereotactic

registration.

Radiographically demonstrated changes were seen in 39 (65%) of 60 injection sites, confirming localization and infusion. There were no radiographically or clinically defined complications.

The neurosurgical considerations and results of this study are presented to offer guidance and a basis for the design of future gene therapy or other clinical trials in children that utilize direct therapeutic delivery [4].

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 [5].

In patients with an acceptable pathological diagnosis of Kufs disease, two major forms have been identified: Type A presenting as progressive myoclonus epilepsy around the age of 30, and Type B presenting in the same age range with dementia as well as cerebellar and/or extra-pyramidal signs. In adolescence, two subgroups of Neuronal ceroid lipofuscinosis (NCL) emerge. The first group consists of patients resembling either type A or B Kufs disease, but with earlier onset (20% of all cases). These must be distinguished from the second group of rare patients with protracted juvenile NCL presenting with early and prominent visual failure. Although Kufs disease is rare, diagnosis during life should now be possible.

The advantages, techniques, and pitfalls of biopsy diagnosis are presented by Carpenter et al. [1988].

Berkovic et al., believe that delineation of these two clinical syndromes should aid in the identification of other possible cases of Kufs disease, leading to appropriate pathological examinations to confirm the diagnosis. Knowledge of whether this clinical distinction is biologically meaningful must await the discovery of the more fundamental biochemical defects [6].

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