case report

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Congenital CLN disease in two siblings

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Summary
Background Neuronal ceroid lipofuscinoses (NCL) is characterized by a combination of retinopathy, dementia, and epilepsy. As a group, they encompass ten distinct biological and clinical entities and are the most common type of childhood neurodegenerative disease.

Patients and methods Case reports.

Results We demonstrate the clinical course of two neonates (brother and sister) with infantile neuronal ceroid lipofuscinoses (NCL) (CLN 10 disease) presenting with intractable seizures and respiratory insufficiency immediately after birth. Characteristic clinical, radiological and pathological findings of this form of NCL are presented.

Conclusions We conclude that the diagnosis of CLN10 should be kept in mind as a differential diagnosis in newborns presenting with respiratory insufficiency and severe epilepsy that is largely refractory to anti-epileptic drugs (AED) treatment. Because of the severity of CLN10 disease and futility of treatment, important ethical issues arise when caring for children with this clinical entity.

Keywords Neuronal ceroid lipofuscinoses · CLN 10 disease · Epilepsy · Palliative care

Kongenitale CLN10 Erkrankung bei zwei Geschwistern

Zusammenfassung
Hintergrund Die neuronalen Zeroidlipofuszinosen (NCL) sind klinisch charakterisiert durch die Trias: Retinopathie, dementieller Abbau und Epilepsie. Die NCLs umfassen 10 verschiedene Krankheitsentitäten/Subtypen und stellen insgesamt die größte Gruppe der neurodegenerativen Erkrankungen im Kindesalter dar.

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Patienten und Methodik Fallberichte.

Ergebnisse Es wird der klinische Verlauf von zwei Neonaten (Bruder und Schwester) mit infantiler NCL (CLN 10) dargestellt. Klinisch im Vordergrund standen unmittelbar postnatal einsetzende, schwerste, therapierefraktäre zerebrale Anfälle mit begleitender respiratorischer Insuffizienz. Die charakteristischen klinischen, radiologischen und pathologischen Befunde der CLN 10-Erkrankung werden dargestellt.

Zusammenfassung Wir schlussfolgern, dass Erkrankungen aus dem Formenkreis der NCL (CLN 10) als Differenzialdiagnose bei Neugeborenen mit therapierefraktärem Anfallsleiden und respiratorischer Insuffizient in Betracht gezogen werden sollten. Aufgrund der Schwere der Erkrankung und der fehlenden therapeutischen Optionen sind bei Neonaten mit CLN10-Erkrankung schwerwiegende ethische Entscheidungen zu treffen (Therapieabbruch).

Schlüsselwörter Neuronale Zeroidlipofuszinosen · CLN 10-Erkrankung · Epilepsie · Palliativversorgung

Introduction

The clinical hallmark of neuronal ceroid lipofuscinoses (NCL) is almost invariably a combination of retinopathy, dementia, and epilepsy. As a group, they are the most common type of childhood neurodegenerative disease encompassing ten distinct biological and clinical entities that vary in age of onset, specific neurologic phenotype, and rate of progression [4, 5]. Histopathology of NCLs is characterized by intracellular accumulation of an autofluorescent lipopigment.

Substantial progress has been made toward identifying the genetics and understanding the pathobiology of NCLs. However, in practical terms, clinical recognition and diagnosis of this devastating clinical entity at the bedside remain challenging [6].

Here, we report two neonates (brother and sister) with infantile NCL (CLN 10 disease) presenting with intractable seizures and respiratory insufficiency immediately after birth. Characteristic clinical, radiological and pathological findings of this form of NCL are presented.

Case report

A 24-year-old (gravida I) was first referred at 21 + 4 weeks of gestation for prenatal ultrasound screening, which showed no sign for fetal malformation. At 35 weeks she returned for follow-up and this time the ultrasound examination showed mild ventriculomegaly (posterior horns of lateral ventricles 12 mm left, 13 mm on the right side) with dilated third ventricle, corpus callosum agenesis, arachnoidal cyst (beside the 3rd ventricle) and a choroid plexus cyst (Fig. 1a–b). The parents were consanguineous. At 36^4/40 weeks of gestation cesarean section was performed because of premature rupture of the membranes and breech position. A male neonate was born (patient 1). Postnatal adaptation was poor with APGAR scores of 1, 7, and 7, pH 7.20. Birth weight was 2495 g (10th percentile), body length: 45 cm (5th percentile), and head circumference: 33 cm (10th–25th percentile). Immediately after birth, the neonate suffered from severe, intractable myoclonic seizure activity that did not respond well to anti-epileptic drugs (AED) treatment (Video 1; supplemental file).

Because of severe respiratory compromise, the infant was initially started on noninvasive continuous positive airway pressure (CPAP) support, but later required intubation and mechanical ventilation. Otherwise, the physical examination was unremarkable. Laboratory diagnostic work-up including serum chemistry showed elevated creatinine kinase (CK) levels on the first days of life (peak level: 2327 U/l; reference range: 0–652 U/l) and lactate dehydrogenase (LDH) levels (peak level: 1130 U/l; reference range: 0–944 U/l). Neuron specific enolase (NSE) concentration on the second day of life was 66.2 µg/l (reference range: < 16). Infectious work-up for bacterial and viral infections was unrevealing. Electroencephalography recordings in the first week of life showed a burst-suppression pattern. Initial routine work-up for inborn errors of metabolism was normal as were the results from cytogenetic studies (normal male karyotype; 46 XY).

Cerebral imaging studies (ultrasonography and MRI) demonstrated severe global cerebral and cerebellar hypoplasia with profound enlargement of all four ventricles, and pachygyria (Fig. 2a, b and c). During the clinical

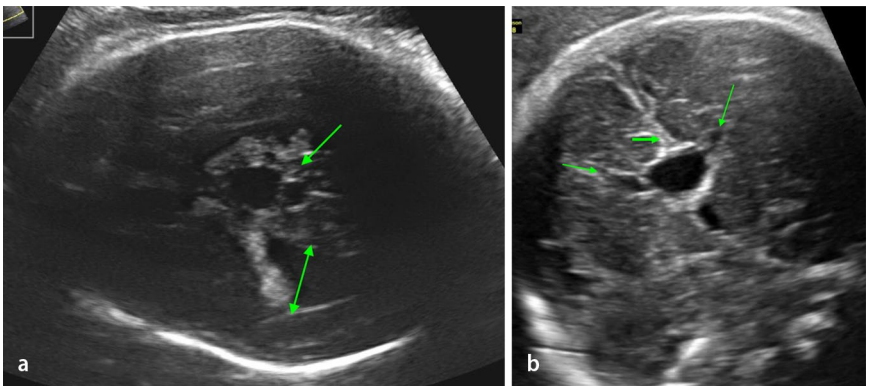

Fig. 1 **a** 35 weeks of pregnancy: mild ventriculomegaly (posterior horns of lateral ventricles 12 mm *left*, 13 mm on the *right* side) with dilated third ventricle and an arachnoidal cyst (*beside* the third ventricle) is shown. **b** Corpus callosum agenesia is shown with typical lateralization of the frontal horns of the lateral ventricles and lack of the corpus callosum

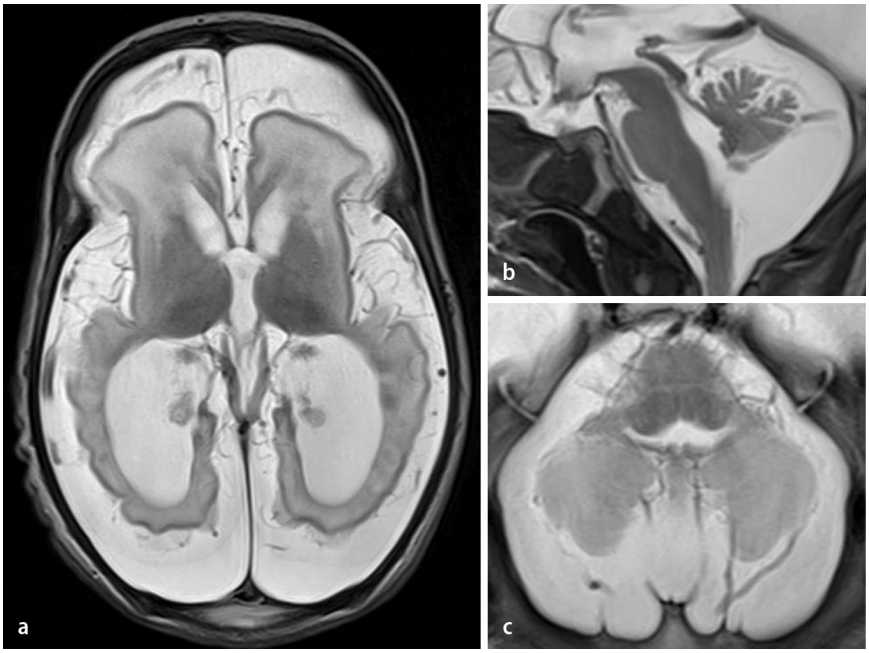

Fig. 2 Cerebral MRI of the male neonate at the age of 10 days. Axial T2-weighted image **a** demonstrates severe cerebral atrophy and pachygyria. Midline sagittal (**b**) and axial (**c**) T2-weighted images of the posterior fossa show cerebellar atrophy

course, progressive brain atrophy with further enlargement of ventricles was noted on ultrasonography. Pontocerebellar hypoplasia was initially suspected, but widely excluded by genetic analyses. After 4 weeks of birth, palliative care was initiated and the infant died shortly thereafter.

Postmortem autopsy demonstrated severe microcephaly with marked cerebellar atrophy, massive reduction of brain weight (88.5 g after formalin fixation), ventricular distension, and pachygyria. The brain tissue was markedly firm. Histopathological examination revealed characteristic widespread storage of granular, poorly to strong periodic acid–Schiff (PAS)-positive (Fig. 3b) and autofluorescent (Fig. 3c) material in both neurons and astrocytes. The deposition of lipopigments was accompanied by extensive loss of neurons, foremost in the cerebral and cerebellar cortices, virtually lack of myelin in the white matter, and massive reactive gliosis (Fig. 3a).

Approximately, 1 year after the death of the above mentioned infant, the patient (sibling of patient 1) was referred for prenatal ultrasound at 32 + 0 SSW. This time, there was no ventriculomegaly, but a dilated third ventricle was found and corpus callosum agenesis and a lack of normally developing gyri in the brain were suspected (Fig. 4a, b and c). A hypotrophic sister was born to the same family at $36^{6}/40$ gestational age (birth weight: 2480 g; length 45 cm; head circumference: 30.5 cm). The clinical course was also characterized by early onset severe myoclonic seizure activity that was partially responsive to phenobarbitone and levetiracetam treatment. Cerebral imaging studies demonstrated cerebral and cerebellar hypoplasia with enlargement of ventricles. The infant died as well shortly after birth because of respiratory failure.

Genetic and biochemical studies (absent cathepsin-D activity in fibroblasts) confirmed the diagnosis of cathepsin D deficiency CLN 10 disease (homozygous insertion c.268_269insC in exon 3 of the cathepsin D gene) in both infants. In both parents, the same insertion c.268_269insC in exon 3 of the cathepsin-D gene was found in heterozygous form, confirming an autosomal-recessive trait.

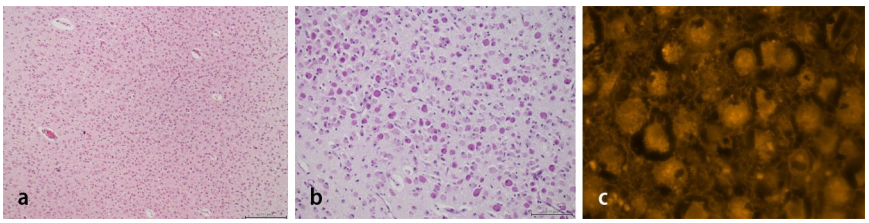

Fig. 3 Neuropathological examination of male neonate. The deposition of lipopigments is virtually ubiquitous and is accompanied by a loss of neurons and massive gliosis; hematoxylin and eosin (H&E), objective ×10 (**a**). The cerebral cortex shows a widespread deposition of granular periodic acid–Schiff (PAS)-positive lipopigments in neurons and astrocytes; PAS, objective ×20 (**b**). Fluorescence microscopy reveals strong autofluorescence of lipopigments; filter for spectrum orange tetramethylrhodamine (TRITC), objective ×60 (**c**)

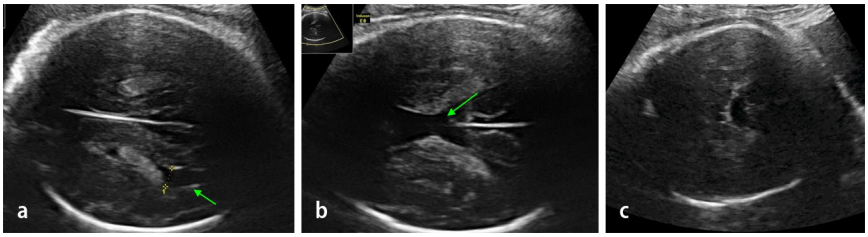

Fig. 4 **a** 32 weeks of pregnancy: there is no ventriculomegaly. **b** Cystic dilated midline structure with dilated third ventricle is shown. **c** Corpus callosum agenesis can be seen with typical lateralization of the frontal horns of the lateral ventricles and lack of the corpus callosum

Discussion

Here, we report the clinical course of two siblings with severe, refractory myoclonic epilepsy and respiratory failure secondary to CLN10 disease.

The NCLs are a heterogeneous group of devastating inherited neurodegenerative lysosomal storage disorders characterized by progressive deterioration of cognitive function, loss of vision as well as occurrence of epilepsy [3, 8]. Based on affected NCL genes, NCLs can be subdivided into ten clinical entities, with CLN 1 constituting the classical infantile NCL form. While distinct genetic entities of NCL have long been recognized, ongoing advances in genetics are substantially widening the NCL genotypic and phenotypic spectrum [2]. While clinical signs and symptoms of CLN 1 commonly become apparent within the first year of life, CLN 10—as seen in our two affected siblings—may manifest itself at birth with respiratory insufficiency and status epilepticus [3]. Moreover, CLN 10 disease is typically characterized by microcephaly with extremely small brains and premature death within hours to weeks as seen in our patients [1, 7]. However, and of note, head circumference was normal in one of the two siblings.

In CLN 10 disease, subtotal loss of neurons in the cerebral cortex as well as generalized activation of astrocytes and microglia is seen. Moreover, severe cerebellar atrophy—as noted in our two patients—is a typical hallmark of this disease. Another characteristic finding is that the white matter apparently lacks myelin [1]. Most cells of the CNS are loaded with autofluorescent storage bodies, showing a granular ultrastructure, the so-called granular osmiophilic deposits (GROD) [1]—as depicted in Fig. 2a–c.

In summary, we conclude that the diagnosis of CLN10 disease should be kept in mind as a differential diagnosis in newborns presenting with respiratory insufficiency and severe epilepsy that is largely refractory to AED treatment. Because of the severity of this disease and futility of treatment, important ethical issues (withdrawal of intensive care treatment) arise when caring for children with CLN10 disease. Moreover, after establishing the diagnosis of CLN 10 disease, genetic counselling can be provided to affected families.

Electronic supplement

Video recording (first day of life) demonstrating intractable myoclonic seizures in male infant.

Conflict of Interest

S. Meyer, U. Yilmaz, Y.-J. Kim, R. Steinfeld, G. Meyberg-Solomayer, B. Oehl-Jaschkowitz, A. Tzschach, L. Gortner, J. Igel,and O. Schofer declare that there are no actual or potential conflicts of interest in relation to this article.

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