SWISS SOCIETY OF NEONATOLOGY

Congenital hypomyelination neuropathy

February 2005

Hauri-Hohl A, Capone Mori A, Pasquier S, Zeilinger G, Pahnke J, Children's Hospital of Aarau (HHA, CMA, PS, ZG), Aarau, Department of Pathology (PJ), University Hospital Zurich, Switzerland

A 23-year-old G1/P1 delivered a premature baby at 36 6/7 weeks by Cesarean section due to breech presentation with a birth weight of 2420 g (P3-10), a length of 45 cm (< P3) and a head circumference of 35.2 cm (P75). Two years earlier, the mother had undergone hemihepatectomy, cholecystectomy, and diaphragmic resection followed by repair with a plastic prosthesis due to an echinococcal cyst with hepatic and intraperitoneal involvement. Polyhydramnion (2 liters of amniotic fluid) of unclear etiology was detected at 36 weeks of gestation. The mother did not report a history of decreased fetal movements. The Apgar scores were 0 and 3 at 1 and 5 minutes, respectively, and the arterial cord blood pH was 7.25 with a base excess of -0.4 mmol/l. The newborn was intubated due to lack of spontaneous breathing.

After birth, fractures of the right femur, the right ulna and the right radius were detected by clinical and radiological exam. They were most likely due to difficult extraction during the Cesarian section. Club deformities of both hands and feet were noted as well (Fig. 1, 2). The umbilical cord consisted of three vessels and contained a pseudocyst (Fig. 3). The newborn infant developed cephalohematomas in biparietal and temporo-frontal locations (Fig. 4). The palate was high-arched and thin. Both testicles were undescended. The initial neurological exam was limited due to sedation required for intubation and mechanical ventilation.

The infant demonstrated persistent minimal spontaneous muscle movement limited to the distal muscles of the arm and the facial musculature, suggesting a neuromuscular disorder. The parents had no signs or symptoms of neuromuscular disease.

After the first week of life, the boy developed progressive edema and increasing ventilatory requirements. The chest X-ray demonstrated new bilateral pleural effusions (Fig. 5) which were drained by thoracentesis. The effusions were chylous in nature. Although his nutrition was changed from normal milk to Basic-F® 19% (i.e., a fat free formula) and Liquigen® (medium chain triglycerides) (table 1), the infant developed recurrent chylous pleural effusions every few weeks that presented with vomiting, grey skin color and increasing ventilatory requirements. Pleural drainage of 150-200 ml of straw-colored fluid (Fig. 6, 7) resulted in clinical improvement.

The patient was initially fed through an NG tube and later through a gastrostomy. The boy never recovered spontaneous respirations and underwent tracheostomy at 4 months of age. Echocardiography and abdominal ultrasound examination were normal. Ophthalmologic examination was unremarkable. Chromosomal analysis revealed a normal karyotype (46, XY). MRI of the head at the age of two and a half months showed signs of dolichocephaly, chronic galeal hematomas,

cortical atrophy with enlargement of the ventricular system.

He did not suffer from a progressive neurological disease since he started to learn to move his eyebrows and his right hand. Various tests (summarized in table 2) were preformed due to the broad differential diagnosis of metabolic disease, myopathies, muscular dystrophy, mitochondrial diseases, inflammatory diseases and neuropathies.

The boy died at the age of 8 months following sudden cardiac arrest. The mother got pregnant a second time. On prenatal ultrasound, there was again polyhydramnion and the fetus had club hands and club feet. This pregnancy was terminated.

Shortly after birth; note fractured right femur and club foot deformities.

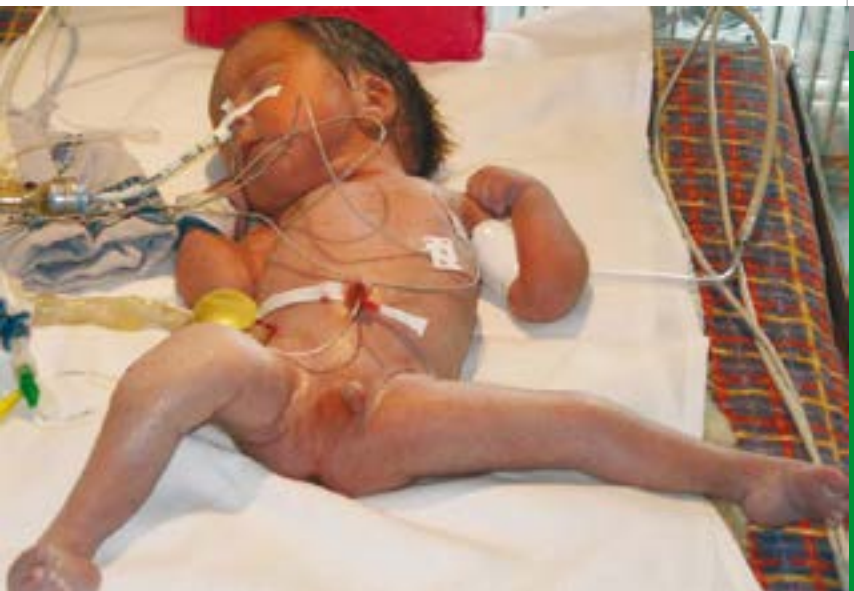

Fig. 1

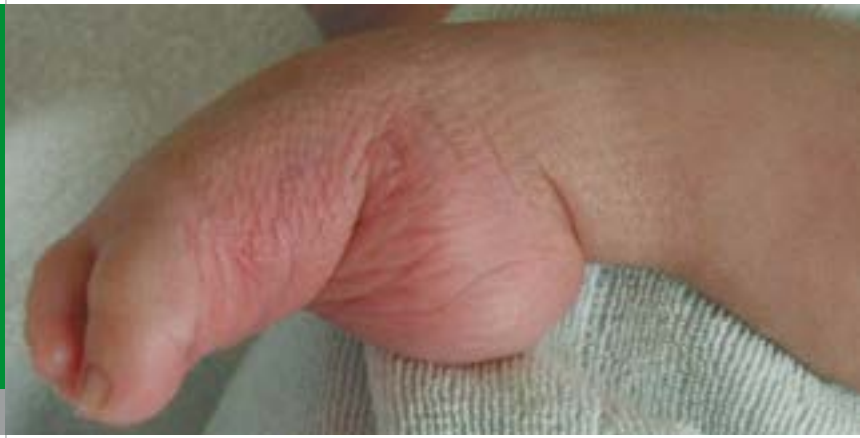

Fig. 2

Right-sided club foot.

Pseudocyst of the umbilical cord.

Fig. 3

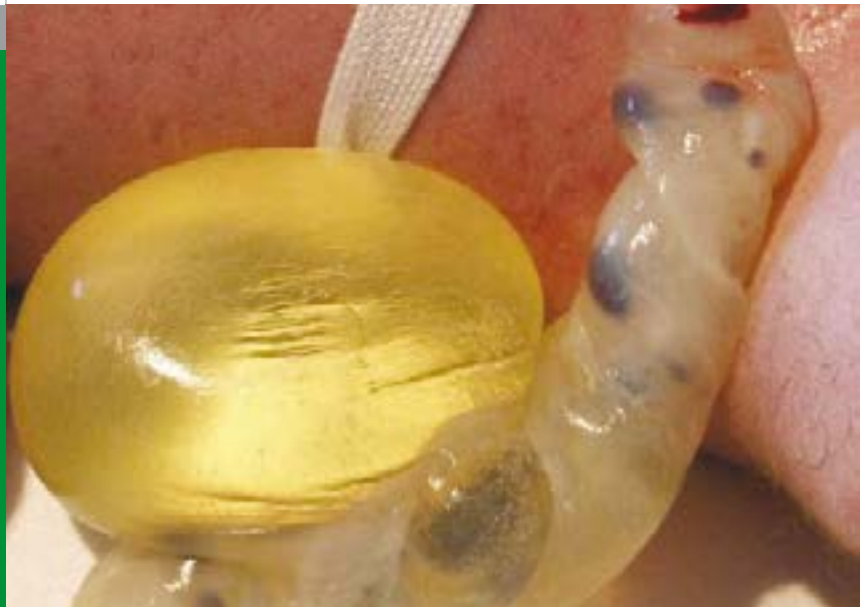

Fig. 4

Dolichocephaly and cephalo-hematomas.

Chest X-ray with bilateral effusions (second week of life).

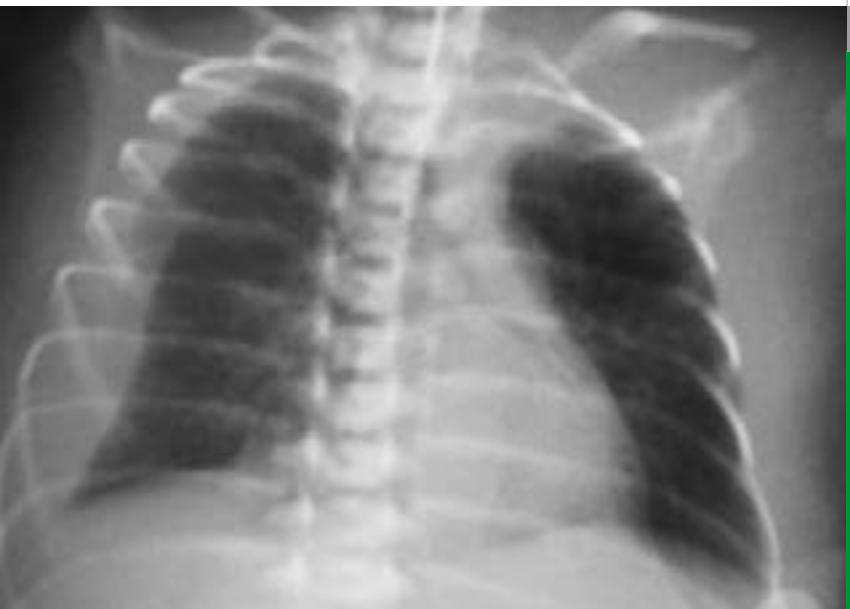

Fig. 5

Fig. 6

Straw-colored pleural fluid (specimen obtained while receiving enteral nutrition with Basic-F® and Liquigen®).

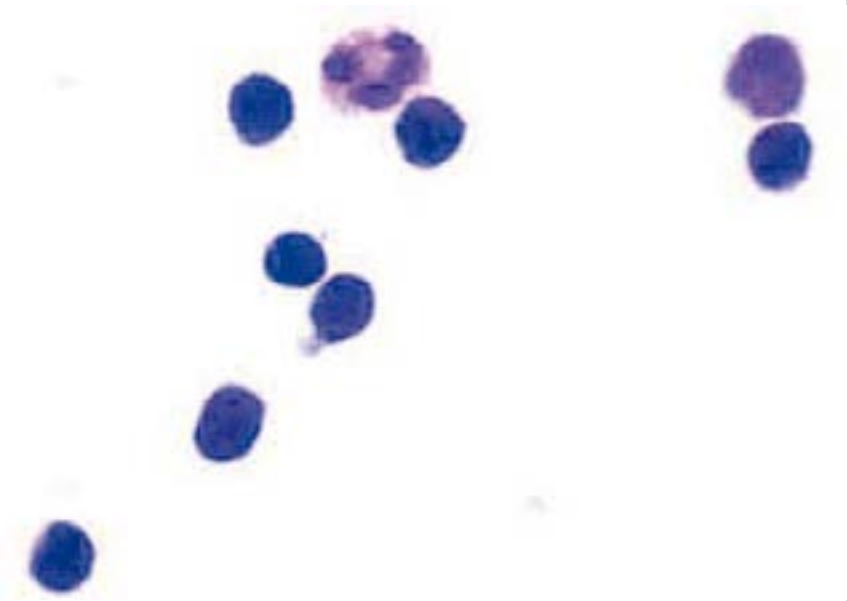

Fig. 7

Predominance of lymphocytes in aspirated pleural fluid.

Table 1

Nutrition	Breast milk or formula	Basic-F 19% with Liquigen
Color	white	strawcolored
Cell count	3400/ul	9100/ul
Lymphocytes	95-98%	95-98 %
Cholesterol	37.0 mmol/l	< 1.3 mmol/l
Triglycerides	13.2 mmol/l	0.7 mmol/l

Changing composition of chylous fluid depending on the infant's nutrition.

Disease	Test	Comment
Metabolic disorders	Urine for organic acids Plasma for amino acids and acyl-carnitine	Normal except for elevated plasma glutaminic acid
Myopathy	Creatine kinase Muscle biopsy (Fig. 8)	Decreased: 7 IU/l (normal 35-235 IU/l), no evidence for structural myopathy (e.g. myotubular myopathy), muscular dystrophy (e.g. myotonic muscular disease, M. Curschmann Steinert) or spinal muscular atrophy
Spinal muscular atrophy	DNA anaylsis of the SMN1 gene	Normal
Prader-Willi syndrome	Molecular genetic analysis of the methylation pattern	Normal
Myotubular myopathy	Molecular genetic analysis of the MTM1 mutation (X-linked)	Normal
Neuropathy	Nerve conduction velocity	Not measurable
Neuropathy	Biopsy of N. suralis (Fig. 9, 10)	Loss of small and large myelinated fibers; myelinated fibers all large with thin myelin sheaths; no onion-bulb structures (signs of remyelination); some areas with loss of myelinated fibers in a fascicular distribution **Findings consistent with congenital hypomyelination neuropathy**

Table 2

Investigations and results.

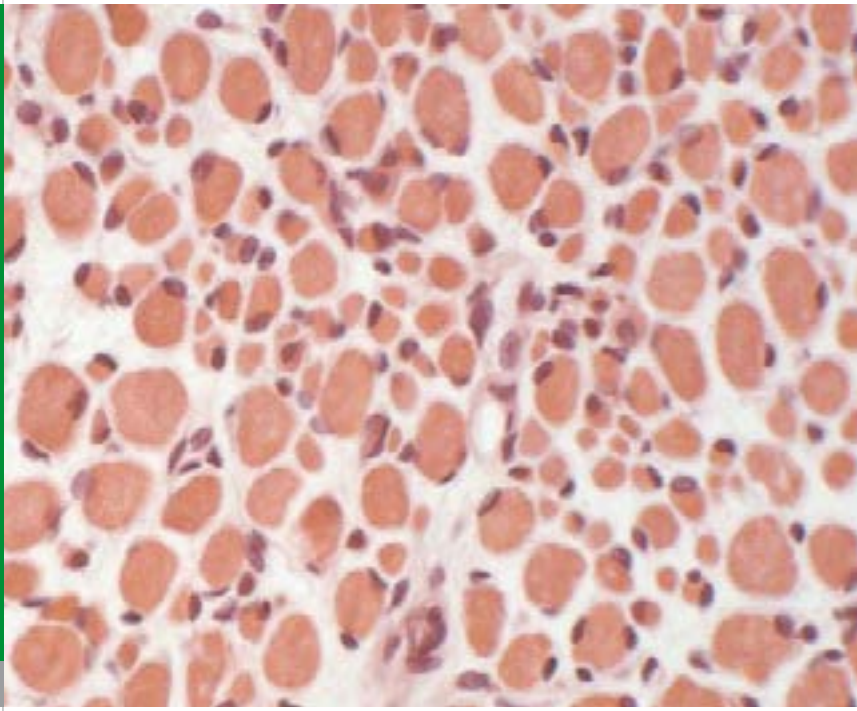

Fig. 8

Muscle biopsy.

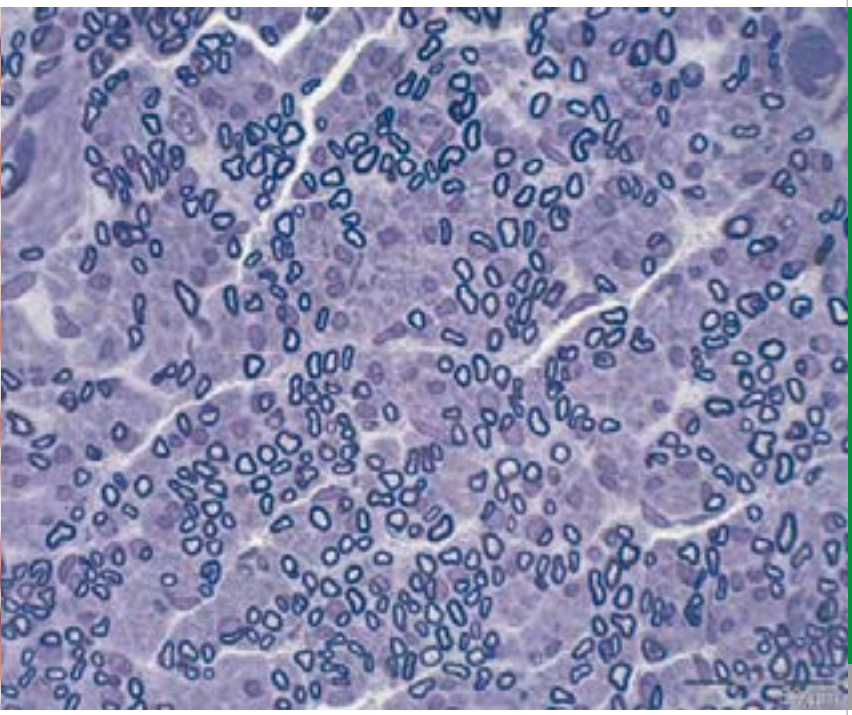

Fig. 9

N. suralis (Luxol stain): Thick myelinated fibers with less strength and thickness of myelin in congenital hypomyelination neuropathy.

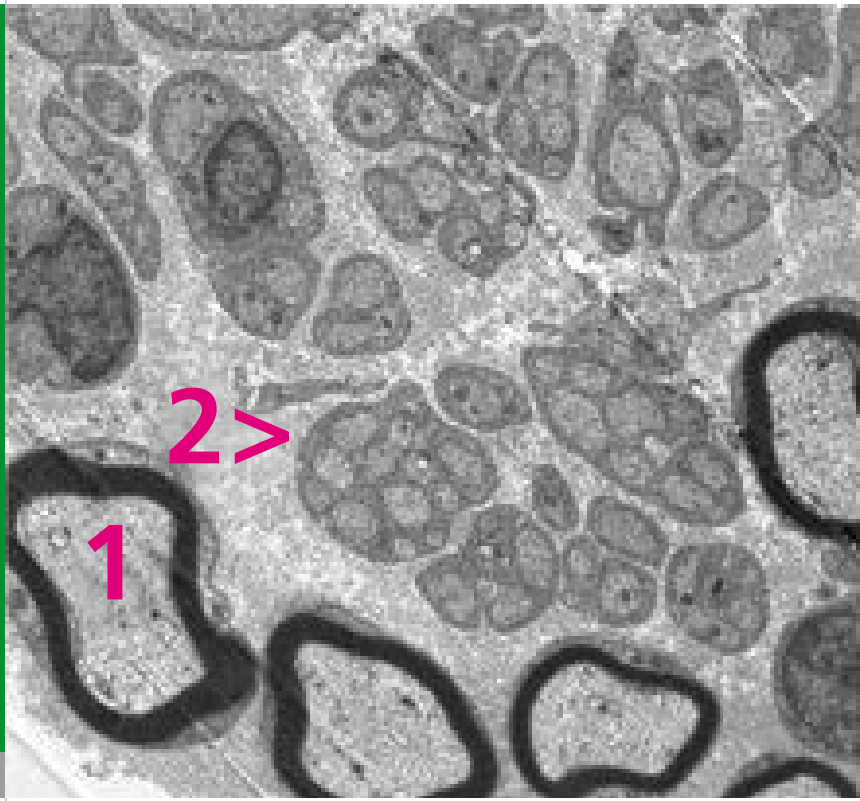

Fig. 10

TEM image of N. suralis (5600x): 1) myelinated fiber with reduced myelin sheath thickness; 2) group of unmyelinated fibres.

The first clear case description of congenital hypomyelination neuropathy dates from 1969 (1). The name of the disease was introduced by Kennedy and colleges to describe a severe neuropathy with congenital absence of myelin or a nerve sheath consisting mainly of basal membranes (2). The mode of transition of the relevant gene defect remains unclear. Most cases occur sporadically, although there are case reports that suggest an autosomal inheritance pattern. Consanguinity among some parents has been observed.

Clinical characteristics in the neonatal period include hypotonia with respiratory or feeding problems. Other infants do not demonstrate symptoms until a few months of age. These infants have poor head control and fail to reach normal motor milestones. Many patients are unable to walk without support and become wheelchair-dependent at an early age. Ambulation is often hindered by sensory ataxia. Sensory deficit, pes cavus, areflexia and the development of scoliosis are often present in affected children. Motor and sensory nerve conduction velocities are very low or not detectable. The CSF protein is usually elevated (3).

Congenital hypomyelination neuropathy has been found to be caused by different mutations of the myelin protein zero (MPZ/PO) which encodes a major structural component in the myelin sheath of peripheral nerves (4, 5), of the peripheral myelin protein 22

(PMP22) which is a membrane protein localized in the compact myelin of the peripheral nerves (6) and of the early growth response 2 (EGR2) gene that encodes a transcription factor crucial for Schwann cell differentiation (7). In our case, molecular genetic analysis did not detect a mutation in the peripheral-myelin-protein 22 (Pmp22), the myelin-protein-zero (MPZ) and the Connexin 32 (Cx32) gene.

REFERENCES

1. Lyon G: Ultrastructural study of a nerve biopsy from a case of early infantile chronic neuropathy. Acta Neuropathol 1969;13:131-142

2. Kennedy WR, Sung JH, Berry JF. A case of congenital hypomyelination neuropathy. Clinical, morphology, and chemical studies. Arch Neurol 1977;34:337-345 *(Abstract)*

3. Jones HR, De Vivo DC, Darras BT. Neuromuscular disorders of infancy, childhood and adolescence: a clinician's approach. Butterworth Heinemann Elsevier Science 2003

4. Szigeti K, Saifi GM, Armstrong D, Belmont JW, Miller G, Lupski JR. Disturbance of muscle fiber differentiation in congenital hypomelinating neuropathy caused by a novel myelin protein zero mutation. Ann Neurol 2003;54:398-402 *(Abstract)*

5. Kochanski A, Kabzinska D, Ryniewicz B, Rowinska-Marcinska K, Nowakowski A, Hausmanowa-Petrusewicz I. A novel MPZ gene mutation in congenital neuropathy with hypomyelination. Neurology 2004;62:2122-23 *(Abstract)*

6. Fabrizi GM, Simonati A, Taioli F, Cavallaro T, Ferrarini M, Rigatelli F, Pini A, Mostacciuolo ML, Rizzuto N. PMP22 related congenital hypomyelination neuropathy. J Neurol Neurosurg Psychiatry 2001;70:123-126 *(Abstract)*

7. Warner LE, Svaren J, Milbrandt J, Lupski JR. Functional consequences of mutations in the early growth response gene (EGR2) correlate with severity of human myelinapathies. Hum Mol Genet 1999;8:1245-1251 *(Abstract)*

8. Hahn JS, Henry M, Hudgins L, Madan A. Congenital hypomyelination neuropathy in a newborn infant: unusual cause of diaphragmatic and vocal cord paralysis. Pediatrics 2001;108:95-98 *(Abstract)*

concept & design by mesch.ch

SUPPORTED BY

NYCOMED

CONTACT

Swiss Society of Neonatology
www.neonet.ch
webmaster@neonet.ch