Congenital Hypomyelination Neuropathy in a Newborn Infant: Unusual Cause of Diaphragmatic and Vocal Cord Paralyses

Jin S. Hahn, MD*; Marion Henry; Louanne Hudgins, MD‡; and Ashima Madan, MD‡

ABSTRACT. We report a case of congenital hypomyelination neuropathy presenting at birth. The infant had generalized hypotonia and weakness. There was decreased respiratory effort along with a right phrenic nerve and left vocal cord paralyses. Tongue fasciculations were present. Deep tendon reflexes were absent in the upper extremities and hypoactive (1+) in the lower extremities. Magnetic resonance imaging of the head revealed no intracranial abnormalities, including normal cerebral myelination. Nerve conduction study showed absence of motor and sensory action potentials in the hands when the nerves in the upper limbs were stimulated. A motor response could be elicited only in the proximal leg muscles. Needle electromyography study was normal in the proximal limb muscles, but showed active denervation in the distal muscles of the arm and leg. These findings were thought to be consistent with a length-dependent sensorimotor peripheral polyneuropathy of axonal type with greater denervation of the distal muscles. A biopsy of the quadriceps muscle showed mild variability in fiber diameter, but no group typing or group atrophy. The muscle fibers showed no intrinsic abnormalities. Biopsy of the sural nerve showed scattered axons with very thin myelin sheaths. There was also a nearly complete loss of large diameter myelinated fibers. No onion bulb formations were noted. These findings were thought to be consistent with congenital hypomyelination neuropathy with a component of axonopathy. DNA analysis for identification of previously characterized mutations in the genes MPZ, PMP22, and EGR2 was negative.

Several attempts at extubation failed and the infant became increasingly ventilator-dependent with increasing episodes of desaturation and hypercapnea. He also developed increasing weakness and decreased movement of all extremities. He underwent surgery at 2 months of age for placement of a gastrostomy tube and a tracheostomy. He was discharged from the hospital on a ventilator at 6 months of age. The infant was 13 months old at the time of submission of this report. Although he appears cognitively normal, he remains profoundly hypotonic and is on a home ventilator. There was no evidence of progressive weakness.

Congenital hypomyelination neuropathy is a rare form of neonatal neuropathy that should be considered in the differential diagnosis of a newborn with profound hypotonia and weakness. It appears to be a heterogeneous disorder with some of the cases being caused by specific genetic mutations. Pediatrics 2001;108(5). URL: http://www.pediatrics.org/cgi/content/full/108/5/e95; congenital peripheral neuropathy, myelin, hypomyelination.

ABBREVIATIONS. CHN, congenital hypomyelination neuropathy; EMG, electromyogram; HMSN, hereditary motor and sensory neuropathy; DSS, Dejerine-Sotome syndrome; EGR2, early growth response 2 gene; PMP22, peripheral myelin protein 22 gene; MPZ or MP0, myelin protein zero gene; Cx32/GJB1, connexin32 gene.

When faced with a newborn with severe hypotonia and weakness in the absence of an encephalopathy, pediatricians often consider neuromuscular disorders. Among these neuromuscular disorders, spinal muscular atrophy and congenital muscular dystrophies come to mind because they are the most common cause of neuromuscular disorders in newborns. Congenital neuropathies in general are rare. We report a case of congenital hypomyelination neuropathy (CHN) to bring attention to this rare form of congenital neuropathy that can cause severe hypotonia and weakness in the newborn period. CHN is a rare condition characterized by distal weakness, hypotonia, areflexia, slow nerve conduction, and absence of large myelinated nerve fibers. Patients may present either in the neonatal period with weakness and hypotonia or during infancy with hypotonia and developmental delay. Little is known about the long-term outcome of neonates presenting with CHN, but the neonatal form appears to be more severe, often leading to early mortality.1 The infantile form appears to be more benign, and thus can result in longer survival. The neonatal form of CHN is indeed rare. To date only 15 cases have been reported.1 In some of these cases DNA mutations have been identified in the MPZ gene, PMP22 gene, or EGR2 gene.1–6 We report a case of CHN presenting at birth with generalized hypotonia and decreased respiratory effort. This form of congenital neuropathy should be considered in severely hypotonic and weak neonates.

CASE REPORT

This infant was a 2800-g male product of a 40-week gestation. He was born to a 39-year-old gravida 4 para 2312 female of Hispanic origin who had received good prenatal care. The pregnancy was reported to be normal with no history of decreased fetal movements. There was no known exposure to teratogens or medications. The infant has 2 elder brothers, who are reportedly healthy and developmentally normal. Family history was negative for birth defects, genetic diseases, multiple miscarriages, and neurologic or neuromuscular disease. There was no consanguinity. He was delivered by normal spontaneous vaginal delivery and had Apgar scores of 8 at 1 minute and 9 at 5 minutes.

From the Departments of *Neurology and Neurological Sciences and ‡Pediatrics, Stanford University School of Medicine, Lucile Packard Children’s Hospital at Stanford, Stanford, California. Received for publication Apr 10, 2001; accepted Jun 20, 2001.
Reprint requests to (J.S.H.) Department of Neurology, A343, 300 Pasteur Dr, Stanford, CA 94305-5235. E-mail: jhahn@stanford.edu
PEDIATRICS (ISSN 0031-4005). Copyright © 2001 by the American Academy of Pediatrics.
At approximately 2 hours of age he developed grunting, nasal flaring, and retractions. He later developed an inspiratory stridor and mild oxygen desaturation, necessitating administration of supplemental oxygen by an oxyhood. A sepsis work-up was initiated. A chest radiograph performed at the referring hospital showed an elevation of the right hemidiaphragm. The infant was intubated, placed on the ventilator on low settings, and transferred to Lucile Packard Children’s Hospital at Stanford.

The physical examination revealed a nondysmorphic infant with decreased respiratory effort and generalized hypotonia who was intubated and on a ventilator. He was alert and awake. His head was normocephalic. The face appeared normal, but micrognathia and high-arched palate were present. The extremities were normal in length and proportion. His hands were in a "raking" position with flexion of the middle and distal interphalangeal joints. He had proximally placed thumbs and a transverse left palmar crease.

Cranial nerve examination showed normal ocular movements and pupillary responses to light. Tongue fasciculations were present. He was profoundly hypotonic, although he was able to move all extremities spontaneously against gravity. He was noted to have decreased wrist movement, finger extension, and flexion. Sensation appeared intact to tactile stimulation, and normal vibratory sense was elicited to light percussion. Deep tendon reflexes were absent in the upper extremities and hypoactive (1+) in the lower extremities. Babinski signs were absent.

Creatine phosphokinase level was 244 IU/L. Serum electrolytes were within normal limits. Serum lactate was mildly elevated at 3.1 mmol/L. Leukocyte lysosomal enzyme screen study, urine organic acids, and serum amino acids were normal. The infant had normal ophthalmologic and audiologic examinations. High-resolution chromosome analysis was normal (46, XY).

He was extubated on the second day and weaned to room air. However, he was noted to have occasional desaturation episodes attributable to poor respiratory effort. A fluoroscopy examination confirmed the presence of right diaphragm paralysis. He underwent a direct laryngoscopy examination that revealed a left-sided vocal cord paralysis and right-sided decreased vocal cord mobility. Magnetic resonance imaging of the head revealed no intracranial abnormalities, including normal cerebral myelination. An electromyogram (EMG)/nerve conduction study showed absence of motor and sensory action potentials in the hands to electrical stimulation of the upper limb. A motor response could be elicited only in the proximal leg muscles. Needle EMG findings showed normal patterns in the proximal limb muscles, but there was evidence of active denervation in the distal muscles of the arm and leg. These findings were thought to be consistent with a length-dependent sensorimotor peripheral polyneuropathy of axonal type with greater denervation of the distal muscles.

He had some feeding problems initially attributable to poor sucking but was breastfeeding well by 3 weeks of age. He was discharged from the hospital at 3 weeks of age.

He was readmitted to Lucile Packard Children’s Hospital at Stanford at 1 month of age because of cyanosis and an apneic episode. The chest radiograph was consistent with atelectasis or pneumonia. A severe apneic episode necessitated intubation, and he was placed on the ventilator.

The infant underwent a left quadriceps and left sural nerve biopsy during this admission. The muscle biopsy showed mild variability in fiber diameter but no group typing or group atrophy. The muscle fibers showed no intrinsic abnormalities. Biopsy of the sural nerve showed scattered axons with very thin myelin sheaths (Fig 1A). There was also a nearly complete loss of large diameter myelinated fibers. No onion bulb formations were noted. In addition, there were rare axons undergoing Wallerian degeneration (Fig 1B). These findings were thought to be consistent with congenital hypomyelination neuropathy with a component of axonal neuropathy.

DNA analysis for identification of previously characterized mutations in the genes MPZ, PMP22, and EGR2 was negative.

During this hospitalization, several attempts at extubation failed and the infant became increasingly ventilator-dependent with increasing episodes of desaturation and hypercapnea. He also developed increasing weakness and decreased movement of all extremities. He underwent surgery at 2 months of age for placement of a gastrostomy tube and a tracheostomy. He was discharged from the hospital on a ventilator at 6 months of age. The infant is currently 13 months old, and his motor function appears to be stable. He remains ventilator-dependent for respirations.

Fig 1. Electron microscopic examination of the sural nerve demonstrates marked reduction in the number of large myelinated fibers and scattered large axons with thin myelin sheaths (A). There are occasional large axons undergoing Wallerian denervation (arrow, B). No onion bulb formations were seen. Bars represent 1 μm.
DISCUSSION

Only a few cases of neonatal CHN have been described in medical literature. Hypotonia was a common feature in all of the previously reported cases of neonatal CHN. The neonatal course is characterized by severe weakness often leading to ventilator support, delayed motor development, and death from 5 weeks to 7 years of age. Nerve biopsy usually shows severe hypomyelination of the nerve fibers. Onion bulbs, which represent reinnervation, may or may not be present in CHN.

The neurologic findings in the present case were significant for profound weakness in the distal muscles encompassing multiple peripheral nerves. This is a somewhat unusual distribution of neuromuscular weakness in newborns, who usually have more proximal weakness.

The differential diagnosis of isolated peripheral neuropathy in newborns and infants includes CHN, Charcot-Marie-Tooth disease, spinal muscular atrophy, hereditary motor and sensory neuropathies (HMSNs), Dejerine-Sottas syndrome (DSS), infantile neuronal degeneration, and acquired demyelinating polyneuropathy.

CHN shares many characteristics HMSN III (or DSS). DSS is also a congenital neuropathy that presents in childhood with hypotonia and weakness and slow nerve conduction.

In patients with various forms of HMSN, more than 250 distinct mutations have been identified in

http://www.pediatrics.org/cgi/content/full/108/5/e95 3 of 4
Downloaded from http://pediatrics.aappublications.org/ by guest on October 3, 2017
CONGENITAL HYPOMYELINATION NEUROPATHY

REFERENCES

Congenital Hypomyelination Neuropathy in a Newborn Infant: Unusual Cause of Diaphragmatic and Vocal Cord Paralyses
Jin S. Hahn, Marion Henry, Louanne Hudgins and Ashima Madan

Pediatrics 2001;108;e95
DOI: 10.1542/peds.108.5.e95

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/108/5/e95

References
This article cites 7 articles, 2 of which you can access for free at:
http://pediatrics.aappublications.org/content/108/5/e95.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Neurology
http://classic.pediatrics.aappublications.org/cgi/collection/neurology_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2001 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005.
Congenital Hypomyelination Neuropathy in a Newborn Infant: Unusual Cause of Diaphragmatic and Vocal Cord Paralyses
Jin S. Hahn, Marion Henry, Louanne Hudgins and Ashima Madan
*Pediatrics* 2001;108;e95
DOI: 10.1542/peds.108.5.e95

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/108/5/e95