Acta Neuropathol (1993) 86: 399–404

Acta Neuropathologica

Inherited syndrome of infantile olivopontocerebellar atrophy, micronodular cirrhosis, and renal tubular microcysts: review of the literature and a report of an additional case

Yuan Chang[1], Jeffery L. Twiss[2], Dikran S. Horoupian[2], Sherrie A. Caldwell[3], Kathreen M. Johnston[4]

[1] Department of Pathology, Division of Neuropathology, Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York, NY 10032, USA
[2] Department of Pathology, Division of Neuropathology, Stanford University School of Medicine, Stanford, CA 94305, USA
[3] Department of Pathology, The Children's Hospital, Denver, CO 80215, USA
[4] Department of Pediatrics, Division of Genetics, Stanford University School of Medicine, Stanford, CA 94305, USA

Received: 8 March 1993/Revised: 24 May 1993/Accepted: 2 June 1993

Abstract. An 8-month-old male infant who presented in the neonatal period with failure to thrive, bilateral pleural and pericardial effusions, and hepatic insufficiency characterized by elevated liver functions tests and hypoalbuminemia was found at autopsy to have an unusual combination of olivopontocerebellar atrophy (OPCA), micronodular cirrhosis, and renal tubular microcysts. Metabolic evaluation was significant only for elevated urine dicarboxylic acids. In the brain, sections from the cerebellum showed marked atrophy of folia most severe in the vermal and paravermal regions. In addition, mild neuronal loss was present in the basis pontis and inferior olivary nuclei accompanied by gliosis. Residual Purkinje cells in the cerebellar hemispheres exhibited greatly expanded and swollen arbors, which ultrastructurally were found to contain densely packed membranous cytoplasmic body-like inclusions that had the appearance of unwinding, lamellar coils. Review of the literature shows that this constellation of findings has been associated with carbohydrate-deficient transferrin. This biochemical marker along with the distinctive clinical presentation and pathological features clearly delineates a unique subset of OPCA.

Key words: Olivopontocerebellar atrophy – Renal tubular microcysts – Micronodular cirrhosis – Membranous cytoplasmic bodies – Carbohydrate-deficient glycoprotein syndrome

Olivopontocerebellar atrophy (OPCA) is a syndrome that includes a heterogeneous group of disorders of largely unknown etiology. Designated pathological hallmarks encompass degenerative changes in the cerebellum, pontine nuclei, transverse pontine fibers, middle cerebellar peduncles, and inferior olivary nuclei. Variable degrees of atrophy may involve the following: substantia nigra, basal ganglia, thalamus, lower brain stem nuclei, and the spinal cord. The clinical picture also may vary considerably; however, the majority of patients demonstrate progressive cerebellar dysfunction associated with other neurological features. Case-to-case differences in pathology and clinical presentation have resulted in considerable nosological difficulties. Konigsmark and Weiner [16] advanced a classification system that relied on genetic, clinical and pathological features to separate the OPCA into subgroups I through V. All are characterized by an autosomal dominant mode of inheritance except for type II, which is reported to be an autosomal recessive disorder. They additionally recognized sporadic cases that did not fit into any of these subgroups. More recently, insight into the pathogenesis of some cases of OPCA was accomplished with the documentation of glutamate dehydrogenase deficiency in a subset of patients [2, 7, 22]. The finding of argyrophilic oligodendroglial and neuronal inclusions in other cases of OPCA, frequently associated with striatonigral degeneration, has also generated interest in the delineation of another subset of OPCA on the basis of pathological findings [12, 15, 19, 20].

The vast majority of patients with OPCA present in adulthood; its occurrence in infants and children is infrequent [3, 5, 8]. We report a case of infantile OPCA with remarkable systemic manifestations involving liver and kidney superficially resembling Zellweger's cerebro-hepato-renal syndrome (ZS). The central nervous system (CNS), however, unlike that seen in ZS, shows an intact cerebrum while the cerebellum exhibits marked atrophy and peculiar dendritic inclusions in the Purkinje cell dendrites.

Case report

The patient was an 8-month-old white male who was delivered by cesarean section for fetal distress at 32 weeks gestational age to a 30-year-old G3PSab1 who previously had one pregnancy which ended as a result of spontaneous abortion at 8 weeks gestation and another normal term pregnancy. The patient's birth weight was 2210 g; apgar scores were 8/9. The neonatal course was complicated

Correspondence to: Y. Chang

by hyperbilirubinemia, poor feeding and failure to thrive. At 6 1/2 months of age, the patient was hospitalized after an apneic episode. He was a thin, pale infant with profound developmental delay but without dysmorphic features. Tachypnea, bilateral rales, and a grade 2/6 systolic murmur at the upper sternal border were present. Liver edge was about 3–4 cm below the right costal margin. The patient was admitted to the Intensive Care Unit after chest x-ray revealed marked cardiomegaly and echocardiogram showed a very large pericardial effusion with near tamponade. The patient also had pleural effusions, elevated liver function tests, anemia, and hypoalbuminemia. Despite aggressive treatment with a continuous albumin infusion, recurrent pericardial effusion was a persistent problem necessitating repeated placement of multiple draining percutaneous chest tubes. Empirical trial of steroids was without benefit.

Laboratory examinations for cytomegalovirus, HIV, rubella, Epstein-Barr virus, hepatitis A and B, and toxoplasma were negative. Liver biopsy revealed mild periportal fibrosis and marked steatosis, but no active inflammation, viral inclusions or congestion. Metabolic evaluation showed moderately increased urine glycine and leucine with normal plasma quantitative amino acids. Urine quantitative organic acids revealed mildly elevated dicarboxylic acids on two occasions. Urine reducing substances were negative. Very-long-chain fatty acids and plasmalogen synthesis were normal in fibroblasts. Alpha-1-antitrypsin was normal. Assay for β-galactosidase activity of leukocytes was normal. Plasma carnitine was mildly abnormal and an empiric trial of oral carnitine was initiated without any benefit.

The patient had two febrile courses with positive pleural cultures for group B Streptococcus and Xanthomonas maltophilia. These were treated with appropriate antibiotics. He also had chronic diarrhea which did not improve despite elemental formulas. Malabsorption studies were unremarkable. Eventually, the patient was placed on bowel rest with total parenteral nutritional support. An esophagogastroduodenoscopy revealed edema and intestinal biopsy demonstrated lymphangiectasia.

Neurological evaluation included an abnormal electroencephalogram with infrequent burst intervals. Brain stem auditory evoked response test revealed a normal brain stem function with bilateral peripheral hearing loss. Computerized tomography (CT) scan of the head showed a small vermis, enlargement of quadrigeminal cistern and cisterna magna, and mild cortical atrophy. There was no evidence of TORCH infections. Subsequently, magnetic resonance imaging of the head was notable for a mega cisterna magna with cerebellar atrophy (Fig. 1).

Failure to control the pleural and pericardial effusions and inability to find any specific metabolic process that could explain the patient's multisystem problems led to the decision to provide the patient with comfort care. He died secondary to cardiopulmonary arrest.

Family history was noncontributory. Parental consanguinity was denied. The patient had one older female sibling who is alive and well.

Pathological findings

General autopsy findings included bilateral pleural effusions, fibrinous pleuritis, pericardial adhesions, ventricular hypertrophy, ascites and soft tissue edema. Sections of liver showed micronodular cirrhosis formed by very regular delicate bridging fibrosis with bile ductal/ductular proliferation, minimal portal lymphocytic infiltration, and frequent preservation of central veins (Fig. 2). Moderate microvesicular fatty change was also present. There was no evidence of cholestasis, pseudoacinar change or excess iron stores. Kidney sections showed microcystic change diffusely involving the cortex with sparing of medullary pyramids (Fig. 3). The cysts were lined by tubular epithelium which appeared to be of both proximal and distal types, and no glomerular cysts were seen. The spectrum of cystic change ranged from mild tubular ectasia to cysts measuring up to 0.5 mm in size.

External examination of the brain which weighed 630 g was unremarkable except for a small cerebellum (Fig. 4). Combined weight of the cerebellum and brain stem was 52 g. Horizontal sections of the cerebellum displayes severe atrophy of the folia and firm white matter (Fig. 5).

Microscopic examination of the cerebral cortex and basal ganglia were unremarkable. The white matter was well myelinated. Periodic acid-Schiff (PAS) stain showed no abnormal inclusions. Ubiquitin immunoperoxidase studies for oligodendroglial inclusions were negative.

Sections of the cerebellum showed marked atrophy of the folia, most severe in the vermal and paravermal regions. This was accompanied by Bergman gliosis, attenuation of the molecular layer, and depletion of Purkinje and internal granule cells. Residual Purkinje cells showed greatly expanded dendritic processes which formed asteroid-like profiles in the molecular cell layer and stained intensely with the Bielschowsky and Luxol fast blue preparations (Fig. 6). Electron microscopic studies of these processes showed that they were densely packed with inclusions formed of concentric lamellar coils. No limiting membrane was discernible surrounding individual or groups of inclusions. They were predominantly round to oval and ranged from 570 to 1070 nm in diameter (mean 900 nm), but a few were irregularly elongated and had curved or parallel lamellae. The concentric forms showed no regular periodicity to the coils and the width of individual membranes of lamellae ranged from 35 to 50 nm (Fig. 7). The cortex and basal ganglia failed to show similar neuronal intracytoplasmic inclusions.

There was mild neuronal loss in the basis pontis and inferior olivary nuclei accompanied by gliosis. The middle cerebellar peduncles demonstrated mild atrophy and gliosis. The neurons in the substantia nigra, locus ceruleus, and cranial nerve nuclei were unremarkable. The pyramids had a normal configuration without evidence of tract degeneration. Spinal cord was unremarkable.

Discussion

This 8-month-old male infant with a history of failure to thrive, effusions, and hepatic dysfunction was found at autopsy to have a peculiar combination of OPCA, micronodular cirrhosis, and renal cortical microcysts. OPCA in the neonatal period is uncommon. Chou et al. [3] reported three young patients and reviewed over a dozen other cases of infants with OPCA. Their main clinical presentation was that of severe hypotonia, areflexia, failure to thrive and respiratory insufficiency. Pathologically, they had evidence of spinal muscular

Fig. 1. Magnetic resonance imaging scan at 7 months of age demonstrates an enlarged cisterna magna in association with hypoplastic cerebellar hemispheres

Fig. 2. Regular bridging portal fibrosis with prominent bile duct proliferation in liver. Hematoxylin and eosin, × 40

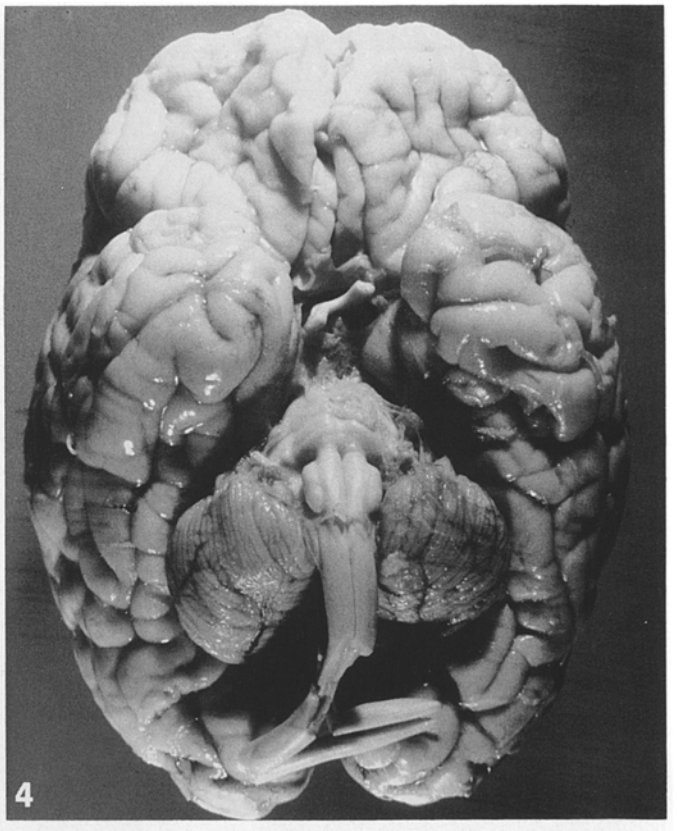
Fig. 3. Diffuse involvement of renal cortex by microcystic change affecting exclusively tubules and sparing glomerular spaces. Hematoxylin and eosin, × 100

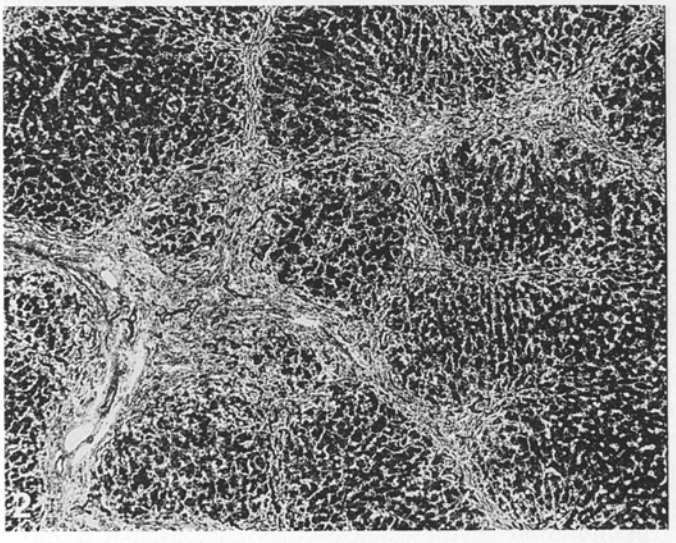
Fig. 4. Base of brain showing marked atropy of cerebellar hemispheres

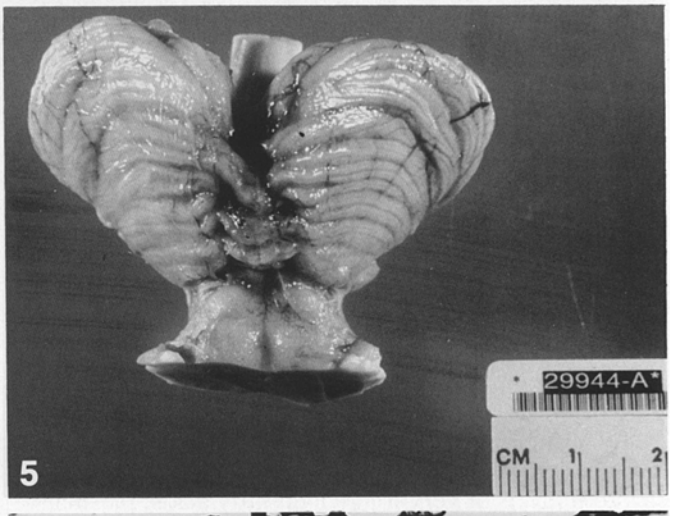
Fig. 5. Cerebellar atrophy most severe in vermal and paravermal regions

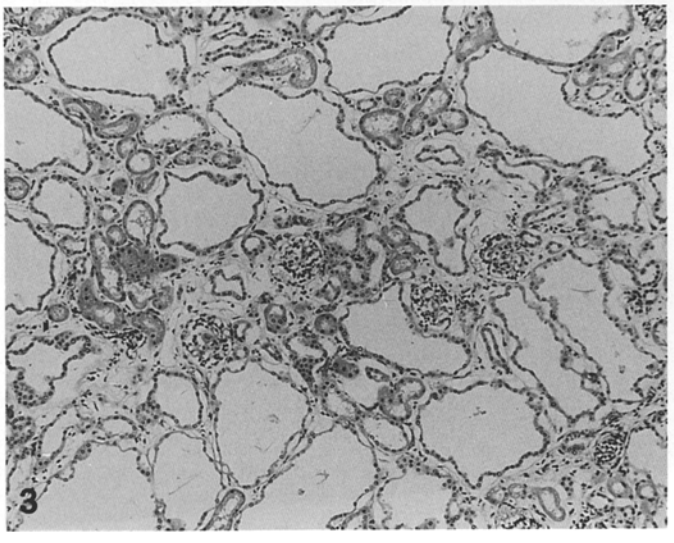
Fig. 6. Swollen dendritic processes of Purkinje cells forming asteroid-like profiles in molecular layer of atrophic folia. Bielschowsky, × 200

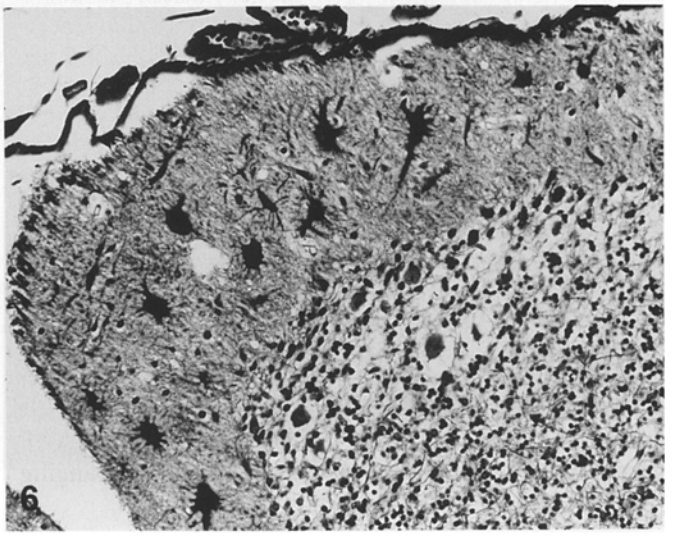

1
I95


4


2


29944-A*
CM
1
2
5


3


6

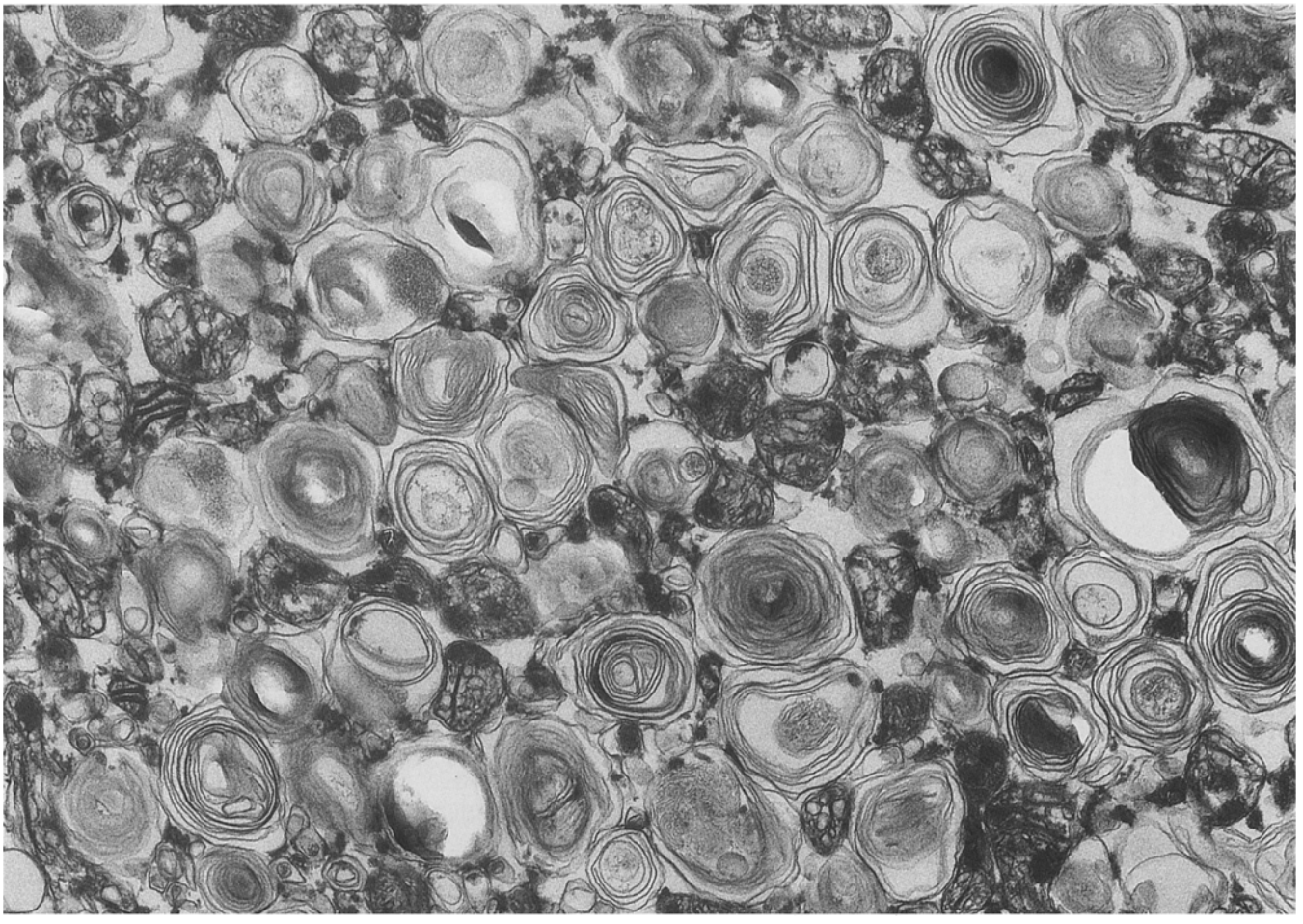


Fig. 7. Purkinje dendrites packed with membranous cytoplasmic body-type inclusions with concentrically arranged lamellae. × 33,700

atrophy which was not a feature in our patient. Furthermore, these patients had no liver and kidney involvement. We briefly entertained the possibility of ZS, which is an autosomal recessive disorder characterized by dysmorphic features, hepatorenal pathology, neurologic dysfunction, and biochemical abnormalities resulting from peroxisomal deficiency. Patients with ZS show elevated levels of very-long-chain fatty acids, plasmalogen deficiency, and dihydroxyacetone phosphate acyltransferase deficiency [24]. Neuropathological findings include aberrant gyral patterns, decreased myelination, abnormal neuronal migration and sudanophilic globoid cells [6]. These features were not found in the present case. In addition, the pathology of the liver and kidneys in our case differed from that described in ZS. The micronodular cirrhosis in ZS is characterized by hepatic lobular disarray with irregularly distributed fibrosis around lobules and individual cells. In contrast, the cirrhosis in this case was produced by regularly bridging portal fibrosis with frequent preservation of central veins. Bile duct proliferation is generally not a feature of ZS and was a prominent component of the portal fibrosis in this case. The renal cysts in ZS are highly variable in number and involve both tubules and glomeruli, ranging from microscopic to macroscopic in size. In the present case, the renal cortex was diffusely involved by microcystic change affecting exclusively tubules and ranged in size from mild ectasia to 0.5 mm in diameter [9].

Ultrastructural examination of the Purkinje cell inclusions found in this case resemble the neuronal inclusions described in the gangliosidosis referred to as membranous cytoplasmic bodies (MCB). MCB have been described as round to oval structures ranging in size from 0.5 to 2.0 μm, averaging 1.0 μm. They are composed of multicentric, electron-dense lamellae and have central amorphous or granular cores [23]. Some are also described as having stacked, parallel lamellae with an arrangement resembling the zebra bodies seen in the mucopolysaccharidosis. While MCB in gangliosidosis occur within the distended neurons and neurites throughout the CNS, these inclusions were limited to Purkinje cells in our patient. In addition, this case does not have other features of the gangliosidosis such as PAS-positive histiocytes in GI biopsies, nor were there large foamy histiocytes in the bone marrow.

Electron microscopic studies on the cerebellum in OPCA have reported striped bodies and Lafora body-like inclusions [21] and vermiform tubules in association

with crystalline inclusions within Purkinje cells and dendrites [18]. However, these inclusions may have represented artifacts.

Recently, ubiquitinated oligodendroglial cytoplasmic inclusions and argyrophilic neuronal inclusions in pontine nuclei were described in certain forms of OPCA [12, 15, 19, 20]. By electron microscopy, the oligodendroglial inclusions were made up of approximately 25-nm-wide fibrils coated with granules, while those in the neurons were formed of intermediate filaments [11]. These findings help distinguish this subtype of OPCA and multiple system atrophy from other forms of neurodegenerative diseases, especially those affecting the brain stem and cerebellum. These inclusions could not be identified in this infantile case of OPCA. Interestingly, Costa et al. [4] found that, while all nine cases of multiple system atrophy they studied showed oligodendroglial inclusions, a single case of autosomal dominant olivopontocerebellar atrophy lacked these oligodendroglial inclusions. This suggested to them that the autosomal dominant form is an entity distinct and separate from multiple system atrophy.

The present case has a strong resemblance to the two siblings who had OPCA described by Agamanolis et al. [1]. The failure to thrive, ascites and anasarca and the pathological changes of the liver, kidney and CNS were very similar to our observations. In particular, the distinctive swollen Purkinje dendrites which contained MCB-type inclusions were analogous. Agamanolis et al. [1] also reported these inclusions in the thalamus; however, despite extensive search, we were unable to find them outside the cerebellum. The pontine atrophy was also more severe in their cases possibly reflecting a more advanced stage of the disease.

In 1988, Harding et al. [10] also reported two siblings who presented in the neonatal period with failure to thrive, hypotonia, pericardial effusions, limitation of joint movement, retinal dystrophy and blindness. Clinical and pathological descriptions were strikingly similar to our case and the two siblings reported by Agamanolis et al. [1]. Although ultrastructural examination was not performed on the expanded Purkinje dendrites, the reported light microscopic description is convincingly similar.

Recently, Horslen et al. [13] pointed out that the four cases of neonatal OPCA, referred to above, demonstrated clinical and pathological similarities to patients with the disialotransferrin developmental deficiency syndrome or carbohydrate-deficient glycoprotein syndrome. This syndrome may be an inborn error of glycoprotein metabolism. A biological marker consisting of an abnormal sialic acid transferrin pattern on isoelectric focusing of serum or cerebrospinal fluid has been found to be helpful in the identification of affected individuals [14, 17]. In serum from normal individuals, the predominant form of transferrin has four sialic acid residues. In this syndrome, transferrin isoelectric focusing shows pronounced increases of transferrin with 0 or 2 sialic acid residues. Most patients diagnosed with this syndrome have been reported to survive into early adulthood; however, they all have a history indicating neonatal onset of OPCA, liver disease, and pericardial effusions. This suggests that the patients reported to have the carbohydrate-deficient glycoprotein syndrome may manifest a less severe form of the same genetic disorder found in the patients who succumbed in the neonatal period. Indeed, Horslen et al. [13] were able to demonstrate aberrant isoelectric focusing patterns for transferrin, similar to that found in older patients with the disialotransferrin developmental deficiency syndrome, in two cases of OPCA with neonatal deaths.

Taken together, these cases delineate a profile of a subset of OPCA which is characterized clinically by an autosomal recessive inheritance pattern and a neonatal presentation with failure to thrive, pericardial and pleural effusions, hypoalbuminemia, and hepatic dysfunction. The pathological criteria consist of (1) hepatic micronodular cirrhosis, (2) renal microcysts, and (3) cerebellar atrophy with Purkinje dendrite expansions containing membranous cytoplasmic body-like inclusions. Presently a biological marker has been identified; however, the mechanism that causes the changes in these three organs and anasarca remain elusive.

Acknowledgements. The authors wish to thank Pauline Chu for technical assistance, Darlene Whitney and Linda J. Anderson for electron microscopy, and Phil Verzola for photography. We would also like to recognize Matthew Eisenberg M.D. and Susan Schelley M.P.H. for excellent medical care of this family.

References

1. Agamanolis DP, Potter JL, Naito HK, Robinson HBJ, Kulasedaran T (1986) Lipoprotein disorder, cirrhosis, and olivopontocerebellar degeneration in two siblings. Neurology 36:674–681
2. Chokroverty S, Khedekar R, Derby B, Sachdeo R, Yook C, Lepore F, Nicklas W, Duvoisin R (1984) Pathology of olivopontocerebellar atrophy with glutamate dehydrogenase deficiency. Neurology 34:1451–1455
3. Chou SM, Gilbert EF, Chun RWM, Laxova R, Tuffli GA, Sufit RL, Krassikot N (1990) Infantile olivopontocerebellar atrophy with spinal muscular atrophy (infantile OPCA + SMA). Clin Neuropathol 9:21–32
4. Colan RV, Snead C, Ceballos R (1981) Olivopontocerebellar atrophy in children: a report of seven cases in two families. Ann Neurolog 10:355–363
5. Costa C, Duyckaerts C, Cervera P, Hauw J-J (1992) Les inclusions oligodendrogliales, un marguerur des atrophies multisystematisees. Rev Neurol (Paris) 148:274–280
6. de Leon GA, Grover WD, Huff DS, Morinigo-Mestre G, Punnett HH, Kistenmacher ML (1977) Globoid cells, glial nodules, and peculiar fibrillary changes in the cerebro-hepato-renal syndrome of Zellweger. Ann Neurol 2:473–484
7. Duvoisin RC, Chokroverty S, Lepore F, Nicklas W (1983) Glutamate dehydrogenase deficiency in patients with olivopontocerebellar atrophy. Neurology 33:1322–1326
8. Furman JM, Baloh RW, Chugnai H, Waluch V, Bradley WG (1985) Infantile cerebellar atrophy. Ann Neurol 17:399–402
9. Gilchrist KW, Gilbert EF, Goldfarb S, Goll U, Spranger JW, Opitz JM (1976) Studies of malformation syndromes of man XIB: the cerebro-hepato-renal syndrome of Zellweger: comparative pathology. Eur J Pediatr 121:99–118

10. Harding BN, Dunger DB, Grant DB, Erdohazi M (1988) Familial olivopontocerebellar atrohy with neonatal onset: a recessively inherited syndrome with systemic and biochemical abnormalities. J Neurol Neurosurg Psychiatry 51:385–390
11. Horoupian DS (1992) Oligodendroglial and neuronal cytoplasmic inclusions in multisystem atrophy. Prog Brain Res 94:423–428
12. Horoupian DS, Dickson DW (1991) Striatonigral degeneration, olivopontocerebellar atrophy and "atypical" Pick disease. Acta Neuropathol 81:287–295
13. Horslen SP, Clayton PT, Harding BN, Hall NA, Keir G, Winchester B (1991) Olivopontocerebellar atrophy of neonatal onset and disialotransferrin developmental deficiency syndrome. Arch Dis Child 66:1027–1032
14. Jaeken J, van Eijk HG, van der Heul D, Corbeel L, Eeckels R, Eggermont E (1984) Sialic acid-deficient serum and cerebrospinal fluid transferrin in a newly recognized genetic syndrome. Clin Chim Acta 144:245–247
15. Kato S, Nakamura H, Hirano A, Ito H, Llena JF, Yen S (1991) Argyrophilic ubiquitinated cytoplasmic inclusions of Leu-7-positive glial cells in olivopontocerebellar atrophy (multiple system atrophy). Acta Neuropathol 82:488–493
16. Konigsmark BW, Weiner LP (1970) The olivopontocerebellar atrophies: a review. Medicine 49:227–241
17. Kristiansson B, Andersson M, Tonnby B, Hagberg B (1989) Disialotransferrin developmental deficiency syndrome. Arch Dis Child 64:71–76
18. Landis DMD, Rosenberg RN, Landis SC, Schut L, Nyhan WL (1974) Olivopontocerebellar degeneration. Clinical and ultrastructural abnormalities. Arch Neurol 31:295–307
19. Nakazato Y, Yamazaki H, Hirato J, Ishida Y, Yamaguchi H (1990) Oligodendroglial microtubular tangles in olivopontocerebellar atrophy. J Neuropathol Exp Neurol 49:521–530
20. Papp MI, Kahn JE, Lantos PL (1989) Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). J Neurol Sci 94:79–100
21. Petito CK, Hart MN, Porro RS, Earle KM (1973) Ultrastructural studies of olivopontocerebellar atrophy. J Neuropathol Exp Neurol 32:503–522
22. Plaitakis A, Nicklas WJ, Desnick RJ (1980) Glutamate dehydrogenase deficiency in three patients with spinocerebellar syndrome. Ann Neurol 7:297–303
23. Terry RD, Weiss M (1963) Studies in Tay-Sachs disease. II. Ultrastructure of the cerebrum. J Neuropathol Exp Neurol 22:18–25
24. Wilson GN, Holmes RG, Custer J, Lipokowitz JL, Stover J, Datta N, Hajra A (1986) Zellweger syndrome: diagnostic assays, syndrome delineation, and potential therapy. Am J Med Genet 24:69–82