Hexosaminidase Activities in a Case of Systemic G_{M2} Gangliosidosis of Late Infantile Type (34613)

LARRY SCHNECK, JOAN FRIEDLAND, MOHAMAD POURFAR, ABRAHAM SAIFER, AND BRUNO W. VOLK

Isaac Albert Research Institute and the Department of Pediatrics, Kingsbrook Jewish Medical Center, Brooklyn, New York 11203

Tay-Sachs disease (TSD), a G_{M2} gangliosidosis of infantile type, is considered the prototype of the various ganglioside-storage diseases. It has a highly predictable clinical course and characteristic pathological and biochemical features (1). Recently, an "exceptional" case of TSD was reported with unusually high concentrations of the asialoganglioside residue and of kidney globoside. Equally significant were the very low levels of activity of *N*-acetyl-hexosaminidase activity in brain and viscera (2).

The case to be described herein is a G_{M2} gangliosidosis of the late infantile type which is clinically, pathologically, and enzymatically different from the "exceptional" as well as the classical type of TSD. Since the clinical and pathological features and the ganglioside analysis of this case were described in detail in a previous publication (3), the findings will be summarized only briefly. The patient, a non-Jewish boy, was hospitalized at 2 years of age with a history of slowly progressive psychomotor deterioration. At age 2 years, he had appendicular ataxia and impoverished speech, but was still ambulatory. Ophthalmoscopic examination was negative. Hepatosplenomegaly was absent, head circumference was within normal limits, and skeletal X-rays were unremarkable. The child died at age 6 years in a spastic vegetative state. An older sister died of a disease with a similar clinical course. The significant pathological findings were limited to the central nervous system. Histologically, by light microscopy, the ballooned-out neurons, with a slightly eosinophilic vacuolated cytoplasm, were similar to those seen in TSD. However, by electron microscopy, these neurons were seen to be filled with pleomorphic lipid bodies which contained flat and occasional concentrically arranged circular membranes. The latter were similar to the membranous cytoplasmic bodies of TSD. The astrocytes were filled with similar cytosomes and also they contained lipofuscin-like granules. Liver cells were normal by light microscopy. By electron microscopy, many hepatocytes were seen to be filled with these membrane-bound pleomorphic lipid bodies, and also dense lipid bodies were found in the vicinity of bile canaliculi. Biochemically, there was an abnormally high concentration of G_{M2} ganglioside in brain and viscera.

Methods. Hexosidase activities in this case were compared with three verified cases of TSD and three control brains and livers from patients of similar age. The enzymatic fluorimetric assay using 5% tissue homogenate (4,5) was performed on methylumbelliferyl glycosides obtained from Koch-Light (England). The following sub-

TABLE I. Mean Hexosidase Activity in Brain of G_{M2} Variant as Compared with that of Three Classical Tay-Sachs Cases and Three Non-neurological Controls.

	Control (3 cases)	Tay-Sachs (3 cases)	G_{M2} variant
β-Galactosidase (μmoles × 10^{-6}/g/hr)	3.4 (3.2 –3.6)	6.7 (6.5 –6.8)	5.6
β-Glucosidase (μmoles × 10^{-6}/g/hr)	1.3 (1.1 –1.3)	2.6 (2.3 –2.7)	2.1
N-Acetyl-galactosaminidase (μmoles × 10^{-6}/g/hr)	5.72 (5.0 –6.5)	13.0 (12.0–13.0)	5.0
β-Glucuronidase (μmoles × 10^{-6}/g/hr)	0.50 (0.40–0.55)	3.40 (3.30–3.50)	1.23

TABLE II. Mean Hexosidase Activity in Liver of G_{M2} Variant as Compared with that of Three Classical Tay-Sachs Cases and Three Non-neurological Controls.

	Control (3 cases)	Tay-Sachs (3 cases)	G_{M2} variant
β-Galactosidase (μmoles × 10^{-6}/g/min)	0.68 (0.65–0.70)	0.58 (0.56–0.59)	1.70
β-Glucosidase (μmoles × 10^{-6}/g/min)	0.04 (0.03–0.05)	0.05 (0.04–0.06)	0.29
N-Acetyl-galactosaminidase (μmoles × 10^{-6}/g/min)	0.45 (0.43–0.48)	0.33 (0.30–0.35)	0.37
β-Glucuronidase (μmoles × 10^{-6}/g/min)	0.55 (0.55–0.56)	0.56 (0.52–0.58)	2.2

strates were used at the optimum pH as indicated. (1) 4-Methylumbelliferyl-2-acetamido-2-deoxy-β-D-galactopyranoside (for *N*-acetyl-β-galactosaminidase) pH 4.0; (2) 4-methylumbelliferyl-β-D-galactopyranoside (for β-galactosidase) pH 3.6; (3) 4-methylumbelliferyl-β D-glucopyranoside (for β-glucosidase) pH 5.0; (4) methylumbelliferyl-β-D-glucuronide (for β-glucuronidase) pH 5.0.

Results. The comparative results of the enzyme assay on brain and liver are summarized in Tables I and II, respectively. It can be noted that there is no deficiency of the mean hexosaminidase activity in the brain and liver homogenate of this case and in TSD. The other brain hexosidase activities in both types of G_{M2} gangliosidoses are higher than normal. In the liver, whereas the TSD and control levels are equivalent, the variant has increased levels of activity for all the hexosidase enzymes.

Discussion. The case described differs clinically from TSD in that the psychomotor deterioration was at a slower rate and there was no evidence of a cherry-red macula or of macrocephaly. Pathologically, the relative paucity of the membranous cytoplasmic bodies and the marked increase of plemorphic lipid bodies as well as lipofuscin distinguish this case from the characteristic pathological findings in TSD. The variant described by Sandhoff and co-workers had much lower levels of hexosaminidase activity. Finally, there appears to be suggestive evidence in the enzyme assay that the hexosaminidase activity in the present case also differs from TSD and from the controls.

We have, therefore, presented a case which is phenotypically different from the classical type of G_{M2} gangliosidosis and the "exceptional" case of TSD described by Sandhoff *et al.* (2). It is suggested that the abnormal gene of the classical form of TSD and the variant types of G_{M2} gangliosidoses may be allelomorphs. If modifying genes were responsible for the clinical and biochemical variations seen in these G_{M2} gangliosidoses, one would expect to find occasional families in which both the classical and variant types of G_{M2} gangliosidoses appeared. To the best of our knowledge this does not occur.

Summary. An unusual systemic G_{M2} gangliosidosis of late infantile type was shown to have high levels of hexosaminidase activity in brain and liver. It, therefore, differs from another G_{M2} variant of late infantile type reported by Sandhoff *et al.* (2), in which hexosaminidase activity was absent.

Addenum. Okada and O'Brien reported that the isoenzyme hexosaminidase A was absent in TSD tissue (6). The percentage of hexosaminidase A and B in brain extracts from the present case and from a TSD and control case were analyzed by acrylamide gel electrophoresis and quantitative fluorometric scanning using 4-methylumbelliferyl-2-acetamide-2-deoxy-β-D-glucopyranoside as substrate. In the present case the A fraction comprised 40% of the total hexosaminidase activity in contrast to 60% in a control and 0% in TSD brain.

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