Galactocerebrosidase Deficiency in Globoid Cell Leucodystrophy of Late Onset

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Young, E., Wilson, J., Patrick, A. D., and Crome, L. (1972). *Archives of Disease in Childhood*, **47**, 449. **Galactocerebrosidase deficiency in globoid cell leucodystrophy of late onset.** Three children with progressive neurological disease are described in whom there was deficient galactocerebrosidase activity in white cells. Necropsy in one patient showed the neuropathological features of globoid cell leucodystrophy, and it is suggested that these patients suffered from a clinically and genetically distinct late form of Krabbe's disease.

The usual age of onset of symptoms of globoid cell leucodystrophy (GLD) is in early infancy (Krabbe's disease), but there are reports (Guillain, Bertrand, and Gruner, 1941; Christensen, Melchior, and Andersen, 1960; Liu, 1970) of late-onset forms suggesting clinical and genetic heterogeneity comparable to that seen in other hereditary degenerative diseases of children, e.g. G_{M1} - and G_{M2} -gangliosidoses. In the latter groups of conditions biochemical differentiation is also apparent with respect to relative deficiencies of the different forms of multicomponent lysosomal hydrolases. A deficiency of galactocerebroside β -galactosidase (galactocerebrosidase) was recently shown for tissues, leucocytes, and serum of patients with Krabbe's disease (Suzuki and Suzuki, 1970, 1971). We confirm this finding and also report a similar deficiency in 3 patients apparently suffering from a late-onset form of GLD.

Because a full clinicopathological account will appear elsewhere, only brief details of the patients are presented here.

Patients

The 3 patients belonged to two unrelated families, without consanguinity.

Case 5 was a previously normal girl who had defective vision from 5½ years, while her brother (Case 3) had been considered to be globally retarded to a moderate degree before he developed a rapidly progressive cere-

bellar syndrome at 2½ years. Despite the confusingly dissimilar presentation as the disease progressed, in both children the clinical picture came to be dominated by dementia, cortical blindness, optic atrophy, and pyramidal signs. The boy died of hypostatic pneumonia at 5 years, while his sister is still alive, now nearly 11 years old. The boy's necropsy showed the typical histological features of GLD.

The third patient (Case 6) is a boy who has always been moderately retarded, and at the age of 6½ years went into status epilepticus for no apparent reason. Failing vision due to 'cortical' blindness developed when he was just over 8 years old, and by 9 years there was evidence of early dementia, with asymmetrical pyramidal signs in the limbs, and early optic atrophy. He has two sibs, one of whom is mentally defective, and the other a poorly controlled epileptic also mentally handicapped.

There is neither clinical nor electrophysiological evidence of peripheral neuropathy in our patients.

Enzyme Studies

Galactocerebroside labelled with tritium at carbon 6 of the galactose moiety was prepared from bovine brain cerebroside (Koch-Light Laboratories Ltd.) by the method described for ^3H -lactosylceramide (Radin *et al.*, 1969). Measurement of galactocerebrosidase activities of whole homogenates of leucocytes and brain in water was based on the methods of Suzuki and Suzuki (1970, 1971). For purposes of comparison, other lysosomal glycosidases, including total N-acetyl- β -glucosaminidase of brain and leucocytes, and β -galactosidase, α -galactosidase, and α -glucosidase of leucocytes, were assayed using the respective 4-methylumbelliferyl derivatives as substrates.

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Necropsy specimens of grey and white matter from two cases of infantile GLD were almost totally deficient in galactocerebrosidase activity, and activity was also reduced to similarly low levels in necropsy and biopsy specimens of brain from a case (Case 3) of late-onset GLD (Table I). In addition, correspondingly low

to a presumptive heterozygote level, compared with age-matched controls, while the value for his elder sister was within the normal range. It is interesting to note that the galactocerebrosidase activity of normal leucocytes appears to develop slowly throughout infancy and childhood.

The activities of all the other lysosomal glycosidases tested were within the normal ranges.

TABLE I
*Galactocerebrosidase Activity of Brain**

Specimen	Grey Matter	White Matter
<i>Necropsy</i>		
Controls (11)		
Range (and mean)	24-136 (69)	41-122 (78)
GLD, infantile		
Case 1	0.8	1.7
Case 2	0.6	1.0
GLD, late-onset		
Case 3	2.2	2.7
<i>Biopsy</i>		
Control	81.5	—
GLD, late-onset		
Case 3	3.7	—

*Activity expressed as n moles substrate hydrolysed per g wet weight of tissue per hr at 37 °C.

levels of galactocerebrosidase activity were found in leucocyte preparations from a case of infantile GLD and two cases of late-onset GLD (Table II). The families of the late-onset cases were investigated and all three parents tested had levels of activity intermediate between those of affected children and of normal adult controls. The value for the younger brother of Case 6 was reduced

TABLE II
*Galactocerebrosidase Activity of Leucocytes**

Subject	Range (and Mean)
<i>Controls</i>	
Adults (14)	0.67-2.76 (1.44)
Children, aged 6-12 yr (6)	0.53-3.70 (1.60)
aged 1-6 yr (11)	0.56-4.00 (1.43)
aged 0-1 yr (7)	0.23-1.42 (0.78)
<i>GLD</i>	
Infantile	
Case 4, aged 1 yr	0.02
Late-onset	
Case 5, aged 10½ yr	0.03
Mother	0.32
Case 6, aged 9 yr	0.02
Father	0.45
Mother	0.29
Sister, aged 14 yr	1.21
Brother, aged 2½ yr	0.24

*Activity expressed as n moles substrate hydrolysed per mg protein per hr at 37 °C.

Comment

Although the clinical presentation of globoid cell leucodystrophy in the histologically proven case (Case 3) and in his sister (Case 5) was markedly different from that observed in Krabbe's disease, the deficiency of galactocerebrosidase was similar. The clinical findings in Case 5 closely resemble those in Case 6, and these patients would in other circumstances perhaps have been unsatisfactorily diagnosed as 'Schilder's disease' but must now be presumed to be examples of late-onset GLD. It is likely that, as in metachromatic leucodystrophy, the infantile and late-onset forms of GLD are genetically distinct, but this differentiation cannot be explained at present on the basis of varying degrees of enzyme deficit. With current assay procedures the deficiency of galactocerebrosidase was equally pronounced in brain and leucocytes of both infantile and late-onset forms.

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