Late onset G_{M2} -gangliosidosis

Clinical, pathological, and biochemical studies on 8 patients

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Brett, E. M., Ellis, R. B., Haas, L., Ikonne, J. U., Lake, B. D., Patrick, A. D., and Stephens, R. (1973). *Archives of Disease in Childhood*, 48, 775. **Late onset G_{M2} -gangliosidosis: clinical, pathological, and biochemical studies on 8 patients.** Eight cases of late onset G_{M2} -gangliosidosis are described. 4 presented before the age of 2 years and 4 between $3\frac{1}{2}$ and 10 years. Gait disturbance, intellectual deterioration, and fits were prominent features. Optic atrophy was seen at a late stage in 2 patients. An exaggerated startle reaction to sound and an unusual type of cherry red spot at the macula were seen for the first time in this condition. Pathological changes were similar to those described in Tay-Sachs disease. There was an increase in the amount of a ganglioside chromatographically identical with that found in Tay-Sachs disease. A partial deficiency of hexosaminidase A was found in 2 cases and a profound deficiency in 4. There was no correlation between the age of onset of symptoms and the degree of enzyme deficiency. The evidence presented is consistent with an autosomal recessive mode of inheritance.

When the lipid which accumulates in brains of patients with Tay-Sachs disease was characterized as the ganglioside G_{M2} (Svennerholm, 1962), the name ' G_{M2} -gangliosidosis' was introduced and came to be used interchangeably with the clinical term (Suzuki and Chen, 1967). From the structure of ganglioside G_{M2} it was inferred that the enzyme hexosaminidase would be involved in its normal degradation and that a deficiency of this enzyme would account for the storage of the ganglioside in patients with Tay-Sachs disease. However, normal levels of hexosaminidase activity were found in tissues from patients until Sandhoff, Andreae, and Jatzkewitz (1968) described a clinically typical case of Tay-Sachs disease in which hexosaminidase activity was absent.

After the demonstration by Robinson and Stirling (1968) that hexosaminidase activity can be resolved into two components, A and B, it was found that component A alone was absent from the tissues of most patients with Tay-Sachs disease (Okada and O'Brien, 1969; Sandhoff, 1969; Hultberg, 1969). Component B was increased to

such an extent that total hexosaminidase activity fell within the normal range or was even raised.

Sandhoff (1969) has described a third form of Tay-Sachs disease with the typical clinical features but with normal activity of both hexosaminidase components when the standard methylumbelliferyl substrate was used.

The complexity of the G_{M2} -gangliosidosis group of disorders has become increasingly apparent with the recognition of forms clinically distinct from Tay-Sachs disease. These have been described as 'late-infantile' and 'juvenile' G_{M2} -gangliosidosis, since the onset of symptoms occurs later and deterioration is less rapid. 6 cases have been reported by others (see Table I for summary and references), and 8 additional cases are presented here. The 8 children were seen between 1957 and 1972 at The Hospital for Sick Children, Great Ormond Street.

Case reports

Case 1. A female was the second child of healthy unrelated parents. Their first child, a boy, had died aged 12 years after an illness of sudden onset which lasted one year and was diagnosed as encephalitis.

The pregnancy, perinatal period, and developmental

No.	Subject	Clinical summary			
		Age at onset of symptoms (yr)	Presenting symptoms	Signs	Age at onset of fits (yr)
1 and 2	2 sisters	2	Psychic changes	Dementia; optic atrophy	
3	Patient B.H.	2	Psychomotor deterioration; ataxia	Dementia; spasticity; retinitis pigmentosa	Age not given (minor motor seizures)
4	Patient	5	Shyness and nervousness	Dementia; ataxia; increasing pyramidal signs	8
5	Patient K.L.	1½	Gait disturbance	Dementia; ataxia; spastic paraplegia; dysarthria	2½
6	Patient G.D.	5	Psychological disturbance; impaired coordination	Dementia; cerebellar ataxia	6 10/12

*Hexosaminidase activity of serum was also found to be low and his parents had intermediate values.

†She has not reached the age at which the onset of symptoms occurred in her brother.

milestones were normal. Her progress at school was average and all was apparently well until the age of 9½ when she was debarred from physical training since she seemed to lack energy, and soon was excluded from school unable to cope with her lessons. For the next 3 months she had home tuition but learned nothing. Thereafter her writing deteriorated, hand movements became slow and clumsy, and speech regressed. Fits began about a year from the onset of her symptoms with staring, crying out, and stiffening and flexing of the limbs. These attacks increased despite anticonvulsant treatment. Deterioration continued and by the age of 12 she was incontinent and unable to walk alone, apparently due to poor balance. Her speech ceased at 12½ years. At 13½ she was unable to sit without support.

On admission in 1957, aged 14 years 9 months, she was demented and speechless, with a head circumference of 51 cm and gross wasting of limbs without other neurological abnormality. The optic discs and retinae were normal. A systolic murmur was heard in the pulmonary area without thrill or cardiac enlargement. The spleen and liver were not palpable.

Investigations. Skull x-rays showed a thick vault suggesting cerebral atrophy, which was confirmed by lumbar air encephalogram. Cerebrospinal fluid (CSF) was normal. Electroencephalogram (EEG) showed a severe generalized abnormality with irregular slow activity and occasional sharp elements variably distri-

buted. Responses to photic stimulation were symmetrical but of low amplitude.

Brain biopsy was taken from the right frontal region (Mr. K. Till). The subarachnoid space was deeper and the gyri were narrower than usual. A few fits occurred after operation and she died suddenly 3 days after biopsy. Necropsy showed a small atrial septal defect, congestive cardiac failure, and pulmonary oedema. Brain weight was 1080 g (normal for age about 1400 g). The cerebral convolutions were abnormally narrow and the sulci widened.

A brief description of this case has been published (Bodian and Lake, 1963, Case 4).

Case 2. A female, the first child of unrelated parents, was born after a normal pregnancy. She walked alone at 15 months but was slow to acquire speech, with a vocabulary of only six words at the age of 2 years. A variable left-sided squint developed at 21 months, and 1 month later she became unsteady and unwilling to walk. This was at first considered a psychological reaction to the birth of a sister until continuing deterioration indicated organic disease.

When admitted in 1965, aged 3½ years, she was severely mentally retarded, speechless, grossly ataxic, and unable to stand or feed herself; she showed a marked startle reaction to sound. There was a left internal strabismus; ophthalmoscopic examination was normal. Apart from moderate hypotonia, the

blished cases

Enzyme studies						References
Family relationship	Source of enzyme	% of total hexosaminidase activity as component A				
		Controls				
			No.	Mean	Range	
Patient	Liver	41	—	—	58-75	Bernheimer and Seitelberger (1968) Volk <i>et al.</i> (1969), Klibansky <i>et al.</i> (1970), Schneck <i>et al.</i> (1970)
Patient	Brain	42	7	63	—	Suzuki <i>et al.</i> (1970), Suzuki and Suzuki (1970)
	Liver	34	5	51	—	
	Spleen	33	5	56	—	
Patient	Fibroblasts*	12	22	49	38-59	Okada, Veath, and O'Brien (1970), Menkes <i>et al.</i> (1971)
Father	"	25				
Mother	"	26				
Brother	"	29				
Sister	"	41				
Patient	Leucocytes	9	14	62	51-70	Buxton <i>et al.</i> (1972)
Father	"	55				
Mother	"	49				
Sister†	"	4				
Half-sister	"	65				

limbs showed no abnormality. The spleen and liver were not enlarged. No convulsions occurred until 1 month after admission when myoclonic jerking of the limbs began, often provoked by noise.

Investigations. Psychometric assessment showed no abilities above the 1-year level. Skull *x*-rays were normal; lumbar air cephalogram showed moderate cerebral atrophy. CSF contained 12 leucocytes/mm³ and 80 mg protein/100 ml. EEG was diffusely abnormal with no recognizable α -rhythm; no paroxysmal features were seen. The responses to photic stimulation were of low amplitude and 8 weeks later were no longer recognizable. Motor nerve conduction velocity was normal (right median and ulnar nerves). A rectal biopsy and a right frontal brain biopsy were performed.

After discharge, deterioration continued and she died aged 3 years 11 months of bronchopneumonia, 2 years 2 months from the onset of her illness.

At necropsy the brain was superficially normal apart from the biopsy site. Biochemical studies on this patient have been reported (Young *et al.*, 1970).

Case 3. The younger sister and only sib of Case 2 was normal in her early development, but from 15 months when she began to walk alone, her gait was always slightly awkward. An alternating concomitant strabismus was noticed at 19 months. By 2 years she spoke in short sentences and fed herself but never

developed sphincter control. At 3 years 4 months she developed attacks in which she stood still and looked blank for about 10 seconds. On treatment with phenobarbitone these attacks ceased. EEG showed no paroxysmal features. Marked deterioration began at the age of 4 with unsteady gait and decreasing speech. She dribbled, bit her clothes, and seemed to have poor vision.

On admission in 1965, aged 4 years 3 months, she was retarded, speechless, and drooling, and had an exaggerated startle reaction to noise. Ophthalmoscopic examination was normal, but her vision was perhaps impaired. There was moderate hypotonia in all limbs and mild cerebellar ataxia was seen when she reached out for objects and walked. No other neurological signs were found. The spleen and liver were not enlarged.

Investigations. Skull *x*-rays were normal. EEG was diffusely abnormal, resembling that of her sister at the same age. No paroxysmal features were seen. A rectal biopsy was performed.

Deterioration continued and she died aged 4½ years of a chest infection, about 3 years from the onset of her illness. At necropsy the brain appeared grossly normal apart from some reduction in size of the cerebellum, which felt unusually firm.

Case 4. A male was the first-born child of a woman

who had miscarried twice. There was no parental consanguinity. Pregnancy was complicated by vaginal bleeding at 10 weeks and pre-eclamptic toxæmia in the last trimester. Delivery, birthweight, and neonatal condition were normal. For the first 6 months he cried excessively and had feeding problems and vomiting. At 14 months he was noticed to startle markedly in response to noise. Soon after this he developed mild ptosis and squint. He was able to speak well and to walk alone at 14 months, but he walked abnormally and fell often. Fits began at 2 years of age, at first with drop attacks, and later there were more complex attacks with inappropriate laughing, raising of the arms, and phonation. Histological study of the appendix at 2½ years was considered consistent with the diagnosis of Tay-Sachs disease. At age 3 years his unsteadiness increased and he began to show intellectual deterioration with loss of speech and social responsiveness. His mother now compared him to a 6-month-old baby. By age 4 years he was immobile, blind, and unresponsive.

On admission, aged 5 years 8 months in 1970, he was semicomatose. His head circumference was 45 cm. Cherry red spots of an unusual nature were present at the maculae; there was an irregular, poorly defined area of pallor surrounding the fovea. The fovea itself was not clearly demarcated and was not circular in outline (Fig. 1). All limbs were spastic; tendon reflexes were exaggerated and plantar responses extensor. Neither spleen nor liver was enlarged.

Investigations. A bone marrow biopsy was performed. EEG was abnormal with gross poverty of rhythmic activity and an excess of slow and sharp components. Visual evoked responses (VER) from the occipital area suggested that the function of the visual pathways to the cortex was largely lost, though the electroretinogram (ERG) was normal.

Over the next 14 months progressive deterioration occurred and he died of bronchopneumonia at the age of 6 years 10 months. No necropsy examination was made.

Case 5. The younger sister of Case 4 was born in 1971 and was normal until the age of 13 months when she became unsteady in walking and fell frequently. At 14 months she became abnormally sensitive to sound. Examination at 16 months showed an alert, intelligent toddler who would jump and give a cry in response to any sudden noise. Ophthalmoscopy suggested bilateral cherry red spots. She walked unsteadily with her legs internally rotated. Tone and power in the limbs were normal, but tendon reflexes in the legs were exaggerated. Plantar responses were flexor. No definite deterioration has occurred between the ages of 16 and 21 months. Investigations so far have been limited to enzyme studies on white blood cells (Table II).

Case 6. A male was born at 37 weeks' gestation to healthy unrelated parents, and has two older normal sibs. His birth and early development were normal and at one year of age he won first prize in a baby competition. At 3½ years his right foot began to turn

inwards, and at 4 he developed a high-stepping gait. Muscular dystrophy was suspected by a paediatrician. At 4½ the left foot also turned inwards and his walking became unsteady with frequent falls. He was noticed to startle excessively in response to noise. At 5 his hands became unsteady and mental deterioration began; his speech became abnormal with omission of some consonants and, later, of whole words. He also became incontinent. He stopped walking alone at 6, but could ride a bicycle until 7, when he became unable to sit unsupported.

Seizures began at 6 years, initially with episodes of inappropriate laughing. Later attacks consisted of facial reddening, dilatation of pupils, and clenching of hands. From 8½ he also had many generalized convulsions lasting up to 5 minutes. Anticonvulsants proved unhelpful and were stopped by his mother who found him more alert off drugs.

At 5½ years ophthalmological examination under general anaesthesia showed a cherry red spot at the right macula similar to that seen in Case 4. Lumbar air encephalogram showed mild cortical atrophy and a right frontal cortical biopsy was performed.

On examination in 1969, aged 10 years, he was a demented boy with frequent myoclonic jerks of the hands. Photophobia made ophthalmological examination difficult, but mild bilateral optic atrophy and a cherry red spot on the right were seen. There was spasticity in all limbs, with hands tightly clenched and feet in equinus with shortened Achilles tendons. The tendon reflexes were normal, plantar responses flexor, and abdominal reflexes absent. The spleen and liver were not palpable.

Deterioration has continued and now, at the age of 13½, he is completely demented, wasted, and immobile with a continuous tremulous activity in the lower half of his mask-like face. Cumings has referred to this patient on two occasions (1968, 1971).

Case 7. A female was the third child of healthy unrelated parents. The pregnancy, delivery, newborn period, and motor milestones were normal. Sentences were first spoken at the age of 3. She had always run awkwardly and her gait was noticed to be unsteady at 4½. At 5½ she developed a stutter and seemed to forget what she wanted to say. At the age of 5 she could write her name and do simple sums, but at school was described as naughty, wilful, and difficult to handle.

At 6½ psychometric assessment showed IQ of 85 (verbal) and 89 (performance) and she was later seen by a child psychiatrist because emotional problems were suspected. By 7 years she had ceased to learn and thereafter deteriorated in all skills. At 9 she moved to a school for educationally subnormal children. After this she deteriorated more rapidly. She became doubly incontinent, was afraid to climb stairs, and would ask her parents which foot to put first. She lost all interest in games, spending her time watching television, but not remembering anything about the programmes. Later she stopped feeding herself. Her hearing and vision seemed normal.

Late onset G_{M2} -gangliosidosis

(a)

(b)

FIG. 1.—Photograph of left optic fundus (a) of Case 4 with late onset G_{M2} -gangliosidosis, (b) of a child with Tay-Sachs disease (absent hexosaminidase A) showing typical cherry red spot.

TABLE II
Enzyme studies on cases presented in this report

Family relationship and sex	Age at test (yr)	Percentage of total hexosaminidase activity present as component A				
		White blood cells	Serum or plasma	Fibroblasts	Rectal mucosa (from biopsy)	Grey matter (necropsy)
Case 1 (female)*	4					36
Case 2 (sister of Case 3)						
Case 3 (female)*						
Case 4 (brother of Case 5)	2	7	0			
Case 5 (female)	1	5				
Case 6 (male)	12	6	0			
Mother		40				
Case 7 (female)	12	13	1			
Father		44	32			
Mother		44	32			
Brother (R.B.)	16	44	38			
Brother (I.B.)	14	64	58			
Case 8 (male)	6	31	42	32	33	
Father		50	61	37		
Mother		51	54	39		
Older sib	8	48	51			
Younger sib	4	52	57			
Controls†		57 (48-66; no. = 53)	59 (51-71; no. = 20)	55 (44-64; no. = 7)	51 (47-56; no. = 5)	65 (no. = 1)
Cases of Tay-Sachs disease (hexosaminidase A deficient)		4 (0-9; no. = 8)	2 (0-6; no. = 5)	4 (no. = 1)	10 (no. = 1)	
Parents		34 (29-40; no. = 16)	36 (29-42; no. = 7)			
Case of Tay-Sachs disease (hexosaminidase A and B normal)		58 (no. = 1)			55 (no. = 1)	

*No enzyme studies were performed. †Control values are presented as mean (range; no. = number tested).

Examination at the age of 11 years 8 months showed a demented girl with a stutter, who walked with both feet inverted. Ophthalmoscopic examination was normal. She was tremulous in manipulation, but showed no true ataxia. Tendon reflexes were exaggerated, but no other neurological signs were found. Spleen and liver were not enlarged.

Investigations. Psychometry (WISC) showed her to function below scorable levels with an IQ of 'about 45'. Skull x-rays, CSF, and motor nerve conduction velocity (right median, ulnar, and lateral popliteal nerves) were normal. EEG showed only mild abnormality with poverty of activity over the frontal lobes. Lumbar air encephalogram showed marked cerebral atrophy. Bone marrow and rectal biopsies were performed.

For 18 months after discharge her condition seemed unchanged. Her only seizure, a generalized convulsion lasting half an hour, occurred while febrile with tonsillitis at the age of 12½. During the past 8 months she has deteriorated, losing her speech, and is now unable to walk without support.

Case 8. A male was the second of 3 children of healthy unrelated Greek parents. His 8- and 4-year-old brothers were well. His mother has had 3 miscarriages.

The pregnancy, perinatal period, and developmental history were normal. At 4 years he became anxious

and fretful when his father was in hospital. At 4½ his adenoids were removed because of frequent infections and on recovering from anaesthesia he was noticed to walk unsteadily and to have regressed in speech. From that time his condition deteriorated. Over the next 2 years recurrent episodes of fever and vomiting were associated with relapses in which he could not speak or walk and appeared worse mentally. He was said to be easily disturbed by noise.

At the time of admission in April 1972, aged 6 years 4 months, he had acute tonsillitis. He was grossly retarded and without speech. His head circumference was 47.5 cm. Ophthalmoscopic examination showed normal optic discs with increased peripheral retinal pigmentation. He played with simple toys clumsily, but without true ataxia. His feet were in equinovarus with calf muscle contractures, but he could walk unsteadily with slight support. The knee jerks were pathologically brisk; other tendon reflexes were normal. The plantar responses were extensor and abdominal reflexes were normal. No abnormal reaction to sound was noted.

Investigations. Skull x-rays showed a thick vault with an advanced diploic pattern. EEG showed patchy abnormality over both hemispheres with prolonged focal discharges of variable distribution, but maximal in the left posterior temporal region. Electroretinogram (ERG) and VER were normal. A rectal biopsy was performed.

Laboratory investigations

Pathological findings. Bone marrow films (Cases 2, 4, and 7) were stained by a routine haematological method (May-Grunwald-Giemsa) and by several histochemical methods (PAS, Sudan Black, and for acid phosphatase activity). No storage cells were present.

Cryostat sections of rectal biopsies (from Cases 2, 3, 7, and 8) were stained as described by Bodian and Lake (1963). Each biopsy contained enlarged vacuolated neurons which stained intensely with PAS (Fig. 2), weakly with Sudan Black and Luxol Fast Blue, and gave immediate strong metachromasia with Feyrter's thionin. In sections of paraffin wax-embedded tissue the neurons were unstained by PAS, but still retained their Sudan Black and Luxol Fast Blue reactions. No abnormality was found in the mucosa, muscle, or included peripheral nerves. The staining reactions and morphology were similar in each case and were identical with those of Tay-Sachs disease.

In cryostat sections of brain obtained at biopsy in Cases 1 and 2 the findings were similar to those in Tay-Sachs disease except for relatively better preservation of myelin. The enlarged and vacuolated neurons stained strongly with PAS and weakly with Sudan Black

or Luxol Fast Blue. Metachromasia was immediately apparent in the neurons using Feyrter's thionin method. Glial cells were strongly positive with Luxol Fast Blue or PAS but showed no metachromasia.

The findings in the brain obtained at necropsy examination (Cases 1 and 2) were similar to those in the biopsies. Other organs showed no abnormality.

Electron microscopy of the brain from Case 2 showed features essentially similar to those previously published by Suzuki *et al.* (1970) and Buxton *et al.* (1972).

Chemistry. Lipid extracts were prepared as described by Neville *et al.* (1973) from brain cortex in Cases 1, 2, 3,* and 6,* and from rectal tissue from Case 8. Thin-layer chromatography of the brain extracts showed a marked excess of a substance with the mobility and properties of ganglioside G_{M2} , though the excess was not as marked as that seen in Tay-Sachs disease (Fig. 3). Though the brain from Case 1 had been in formalin for 5 years before extraction, there was evidence of an excess of ganglioside G_{M2} . The ganglioside

*Cases 3 and 6 were examined by Professor J. N. Cumings of the National Hospital, Queen Square, London.

FIG. 2.—Case 8, rectal biopsy. Cryostat section, stained with PAS, showing enlarged neurons containing ganglioside in Auerbach's plexus. Scale mark 100 μ m.

FIG. 3.—Thin-layer chromatogram showing gangliosides in extracts from brain cortex. Lane 1, control (mental retardation); lane 2, Tay-Sachs disease with absent hexosaminidase A; lane 3, Tay-Sachs disease with total hexosaminidase deficiency; lane 4, late-infantile G_{M2} -gangliosidosis, Case 2; lane 5, Tay-Sachs disease with normal hexosaminidase A and B. Lipid extract, equivalent to 15 mg original tissue, was applied in each case. (Solvent, chloroform, methanol, 2.5 mol/l. ammonia (55/40/10 v/v). Spray reagent, resorcinol.)

pattern in rectal tissue was similar to that of brain and showed an excess of ganglioside G_{M2} in Case 8 (Fig. 4).

Enzyme studies. Four methods have been used to distinguish between the components of hexosaminidase activity in tissue extracts and body fluids: starch-gel electrophoresis, heat-inactivation, ion-exchange chromatography, and iso-electric focusing (Robinson, Price, and Dance, 1967; Okada and O'Brien, 1969; Sandhoff, 1969; O'Brien *et al.*, 1970; Young *et al.*, 1970). Hexosaminidase components were originally defined as bands of activity visualized after electrophoresis on starch-gel (Robinson and Stirling, 1968), and care should be taken in interpreting quantitative results when other techniques are used.

The proportion of the total hexosaminidase activity present as the heat-labile component (approximately equivalent to the electrophoretic component A) in leucocytes, fibroblasts, and tissues was determined as described by Buxton *et al.* (1972) with the following modifications. Heat-inactivation was carried out at 47.5 °C for 3 hours and 0.2% human serum albumin (Sigma Fraction V) was incorporated into the McIlvaine's citric acid-sodium phosphate buffer, pH 4.5 used for diluting tissue extracts. Heat-labile hexosaminidase activity in serum and plasma was estimated by the

method of O'Brien *et al.* (1970), except the buffer used was that described above and the methylumbelliferyl glucosaminide concentration was 1.5 mmol/l. in the final incubation medium.

Previously reported studies on the proportion of hexosaminidase component A in four cases of late onset G_{M2} -gangliosidosis are summarized in Table I, and the results on 6 of the patients described in this report are given in Table II. It can be seen that of the 10 cases in which enzyme studies have now been reported, 4 have a partial deficiency of hexosaminidase component A (30 to 40% of the total hexosaminidase activity present as component A) and 6 have a profound deficiency (0 to 13% of total activity).

Discussion

As implied by the name G_{M2} -gangliosidosis, the factor common to all types is the excessive accumulation of the ganglioside G_{M2} . They also share certain characteristic histological and electron microscopical features, but they may be subdivided either by clinical criteria or by the pattern of deficiency in the components of hexosaminidase.

The age at onset of symptoms is one of the most

FIG. 4.—Thin-layer chromatogram showing gangliosides from brain cortex (Tay-Sachs disease) and from rectal biopsies (Tay-Sachs disease, juvenile G_{M2} -gangliosidosis, and controls). Lane 1, rectum, juvenile G_{M2} -gangliosidosis, Case 8; lane 2, rectum, Tay-Sachs disease; lane 3, brain cortex, Tay-Sachs disease; lane 4, rectum control (mental retardation, 13 years); lane 5, rectum control (mental retardation, 3 years). Lipid extract, equivalent to 30 mg original tissue, was applied from each rectal biopsy; for the brain an extract equivalent to 15 mg tissue was applied. Other conditions were as in Fig. 3.

useful criteria in classifying the G_{M2} -gangliosidoses. The commonest form of this condition is Tay-Sachs disease in which symptoms appear in the 'infantile' period (within the first 8 months). Typical presenting features of Tay-Sachs disease include an abnormal startle response to sound, cherry red spots at the maculae, and failure in motor development with weakness and hypotonia. Deterioration is rapid. Fits usually begin at about 1 year. Megalencephaly often becomes apparent during the second year, and by the age of 2 the patient is in a vegetative state, blind, and hyper-tonic; frequent fits and decerebrate posturing are common. Death usually occurs between 2 and 4 years of age. Though clinically indistinguishable, three types of Tay-Sachs disease have been recognized by studies on the components of hexosaminidase, as described in the introduction.

In contrast to cases of Tay-Sachs disease, the early development of our 8 patients with the late onset forms of G_{M2} -gangliosidosis was normal.

Cherry red spots at the maculae and an abnormal startle reaction, characteristic of Tay-Sachs disease, were seen in 3 patients, though the appearance of the cherry red spots was unlike that seen in cases of Tay-Sachs disease (see Fig. 1). A further 2 patients showed an abnormal startle response alone.

The late onset cases may be subdivided according to the age of onset into late-infantile and juvenile types.

In two pairs of sibs symptoms began in the late-infantile period (the second year of life), and in each pair the age of onset and presenting symptoms were very similar. An abnormal startle reaction and gait disturbance were shown by all 4 children. Cherry red spots at the maculae were seen in one pair and a squint developed in the other pair. 3 of the 4 have had fits. Neurological signs were dementia, ataxia, and pyramidal features. 3 patients have died, death occurring between 2 and 6 years from onset.

Of 6 previously reported cases, 4 began in the

late-infantile period. Gait disturbance at the age of 1½ was the presenting symptom in the case reported by Menkes *et al.* (1971). Fits occurred in 2 patients, but the presenting symptoms are not clearly stated in all cases. Cherry red spots at the maculae are not mentioned, but 1 child showed 'the beginnings of retinitis pigmentosa' 4 years from onset.

The onset of symptoms in our other 4 cases was in the juvenile period (the fourth year or later). 3 of these patients had onset in the fourth or fifth year. They presented with gait disorder, and speech deterioration was an early feature in 2. Seizures have occurred in 2 patients. A cherry red spot was seen in only 1 child and 1 other showed an abnormal startle reaction. These 3 survive in a severely deteriorated condition.

In the fourth juvenile case the onset of symptoms was insidious and hence difficult to date precisely, but it was probably not earlier than the ninth year. This is much later than in any previously described case. This patient developed seizures about 1 year from the start of symptoms and died 4 years later.

Only 2 children with the juvenile form have previously been reported. The case of Suzuki *et al.* (1970) died at the age of 15, 10 years from onset, having had fits for 7 years. The patient reported by Buxton *et al.* (1972) developed symptoms at about the age of 5 years, and fits began about 2 years later. He was still alive about 4½ years from onset.

It is possible that the differentiation into late-infantile and juvenile categories will disappear as new cases are described.

Cases of late onset G_{M2} -gangliosidosis may alternatively be subdivided according to the degree of the enzyme deficiency. They fall into two groups: one in which the deficiency may be described as partial, and another in which it is profound and similar to that found in the common form of Tay-Sachs disease. Of the 10 cases in which enzyme studies have been performed (including 6 in the present study), 4 were found to have a partial deficiency, and in 6 it was profound. This marked difference in the degree of deficiency of the enzyme may reflect a fundamental difference in the nature of the biochemical lesion.

There appears to be no correlation between the age of onset of symptoms and the degree of deficiency of hexosaminidase component A when assayed using the synthetic methylumbelliferyl substrate. The level of hexosaminidase A in cases with the partial deficiency is, moreover, similar to that of carriers for the more common form of Tay-Sachs disease. Though the use of the natural

lipid substrate may increase our understanding of the basic defect, the variable clinical features of this disease will probably not be explained until the primary structure of hexosaminidase and the metabolic relations between its component forms are known.

An autosomal recessive mode of inheritance suggested by Okada *et al.* (1970) is substantiated by the study of our 8 cases. Among the total of 14 cases there have been 4 pairs of affected sibs; normal sibs were found in several families; males and females were affected and, in some cases at least, the parents of affected children have relatively reduced levels of hexosaminidase A. For families in which a child with the profound deficiency has been diagnosed, it seems likely that prenatal detection of an affected fetus will be reliable.

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