QUEBEC COOPERATIVE STUDY
OF FRIEDREICH'S ATAXIA

Lysosomal Enzymes in Ataxia: Discovery of Two New Cases of Late Onset Hexosaminidase A and B Deficiency (Adult Sandhoff Disease) in French Canadians

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ABSTRACT: We have measured in leukocytes the following lysosomal enzymes in 11 Friedreich disease cases, 11 "atypical" recessive ataxias, 13 neurological controls and 16 normal controls: hexosaminidase A and B; β-galactosidase and neuraminidase (labile and cold stable, or A and B). The lysosomal enzyme deficiencies known to produce certain forms of spinocerebellar degeneration were not present in Friedreich's disease or the Charlevoix-Saguenay syndrome. The very small scale survey of "atypical" recessive ataxias revealed 3 cases of severe deficiencies in hexosaminidase activity. Two adult brothers presenting with the clinical phenotype of Kugelberg-Welander disease (one also with ataxia), were shown to have a severe deficiency of both HEX A and HEX B activity (Sandhoff biochemical pattern). This is the first such report. A further adult female patient, unrelated to the others, had a severe isolated deficiency of HEX B and presented with a very slowly progressive and mild ataxia with severe internal strabismus. These patients and their families are being studied clinically and biochemically in greater detail and will be reported elsewhere. However these preliminary findings justify screening for such lysosomal defects in all cases of "atypical" recessive ataxia.

RÉSUMÉ: Nous avons mesuré dans les leucocytes les enzymes lysosomiales suivantes: Hexosaminidase A et B, β-galactosidase et neuraminidase A et B (stable au froid). Pour ce, nous avons étudié 11 patients avec maladie de Friedreich, 11 avec des ataxies récessives "atypiques", 13 témoins neurologiques et 16 témoins normaux. Les insuffisances enzymatiques du lysosome qui produisent parfois certaines formes de dégénérescence spino-cérébelleuse ne se retrouvent pas dans la maladie de Friedreich, ni dans le syndrome de Charlevoix-Saguenay. Parmi les ataxies récessives atypiques, nous avons trouvé 3 cas de déficience sévère en Hexosaminidase. Deux frères à l'âge adulte se présentent avec le phénotype clinique de la maladie de Kugelberg-Welander et l'un d'eux a également de l'ataxie. Ces deux frères ont une importante diminution de l'activité de l'Hex A et B (patron biochimique de la maladie de Sandhoff). Il s'agit de la première publication sur cette situation. Une autre patiente adulte, non reliée aux deux autres, présentait une baisse importante, mais isolée,de l'activité Hex B. Son tableau clinique était marqué d'une légère ataxie très lentement évolutive et d'un strabisme interne sévère. Nous poursuivons l'étude détaillée de ces familles, mais il est d'ores et déjà permis de proclamer qu'une étude biochimique systématique de ces cas familiaux atypiques d'ataxie s'impose dorénavant.

Can. J. Neurol. Sci. 1984; 11:601-606

One of the important discoveries of the last 30 years was the presentation of the lysosomal theory by De Duve and his collaborators (De Duve and Wattiaux, 1966). As stated by Philippart (1978), lysosomal storage disorders reflect an impairment of cellular digestion. Lysosomes are ubiquitous organelles equipped with an extensive complement of hydrolytic enzymes capable of digesting proteins, lipids, polysaccharides and nucleic acids. If a specific enzyme is missing as a result of a mutation, the membrane or molecule which cannot be degraded is trapped inside the lysosome and then accumulates. The non degradable substance is often a lipid: GM_1-ganglioside, sulfatide or sphingomyelin. The gangliosidoses refer to the group of disorders characterized by the accumulation of the sialic acid containing lipids, usually GM_1 or GM_2. In cells that do not divide, like the neurons, the storage is directly additive and the cells continuously enlarge. Eventually this interferes with cell physiology and survival (Philippart, 1978). It is of interest that many hydrolases are found as two or more molecular species that can

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be separated by electrophoresis or chromatography. For example Hexosaminidase exists under two major forms (Robinson and Stirling, 1968). Hexosaminidase A (Hex-A) is acid and heat labile, whereas hexosaminidase B is stable under the same conditions. Hex A consists of two different polypeptide chains, α and β, in the combination $\alpha_1\beta_2$. Hex B is a tetramer containing only β-chains with the structure $\beta_2\beta_2$. Expression of the ***α-chain*** is determined by a locus on ***chromosome 15***. The ***β-chain*** locus is on ***chromosome 5*** (Gilbert et al., 1975). In Tay-Sachs disease, Hex B activity is normal. The mutation is thought to be in the α-chain locus on chromosome 15. Similarly in Sandhoff disease the mutation is believed to be in the β-chain locus on chromosome 5 and to involve failure of synthesis of that β-chain (Kolodny and Raghavan, 1983). Finally, in the so-called "AB variant", both Hex A and Hex B are increased, probably because of a mutation in the activator protein. Similarly neuraminidase has also been shown to have freeze labile and freeze-stable components (Suzuki et al., 1981). The activity of these hydrolases is usually determined using artificial substrates (4-methyl-lumbelliferyl derivatives) that substitute for the natural one which is difficult to isolate, but confirmation should be obtained with the natural substrate.

Approximately 10 years ago, it was realized that lysosomal storage disorders may masquerade under various phenotypes, such as dystonia, motor neuron disease or as spino-cerebellar degenerations, including the various forms of ataxia deriving from lesions at different levels of the central nervous system: cerebellum, posterior columns, spino-cerebellar tracts and peripheral nerves or anterior horn cells (Johnson, 1981). Ataxia will be present in those patients in whom the nervous system impairment is still compatible with some motor function (Philippart, 1978). It will probably be marked by pyramidal and extrapyramidal features in early, severe, cases, but will tend to be more evident when the lesions is slowly progressive. A similar pattern of associated symptoms is predicated upon age of onset and severity in the autosomal dominant hereditary ataxias like Machado-Joseph disease (see Barbeau and Roy, 1984, this issue). The full range of the phenotypes is listed in Table 1 from data by Johnson (1981).

Since the first report by Rapin et al. (1976) who described two adult Ashkenazi Jewish siblings deficient in Hex A activity with slowly progressive deterioration of gait and posture from early childhood, distal to proximal muscle atrophy, pes cavus, foot drop, spasticity, mild ataxia of limbs and trunk, dystonic features and dysarthria, many other similar cases have been identified. These cases were called juvenile or chronic GM_2-gangliosidoses. By 1980 (Johnson et al., 1980) at least 21 such families had been reported, 18 with α-locus mutations, and 3 with β-locus mutations. In addition, genetic compounds of hexosaminidase have been reported in at least seven families, five with α-locus mutations and two with β-locus mutations. The compound had the phenotype of infantile Tay-Sachs disease in one family, infantile Sandhoff disease in another, and the normal phenotype in the rest (Dreyfus et al., 1975; Lane and Jenkins, 1978; Kelly et al., 1978). In most cases, like the first one, Hex A activity was markedly decreased in serum, leukocytes and fibroblasts but not to the degree that was found in Tay-Sachs disease. Some of these patients even had the Friedreich phenotype (O'Neil et al., 1978; Navon et al., 1981; Willner et al., 1981; Musarella et al., 1982; Johnson, 1982; Johnson et al., 1982). In a few cases both the A and B forms of Hexosaminidase were deficient, like in Sandhoff disease (Sandhoff et al., 1968; Johnson and Chutorian, 1978; Oonk et al., 1979; Wood and MacDougall, 1976; MacLeod et al., 1977; Goldie et al., 1977).

Similar cases of late onset disease are also known in GM_1-gangliosidosis and in neuraminidase deficiency, the "sialidoses", some with cerebellum or spino-cerebellar phenotypes (Lowden and O'Brien, 1979).

In a few instances, the phenotypes and the enzyme deficiencies (β-galactosidase and neuraminidase) are combined (galactosialidosis). This has been particularly evident in cases from Japan where lysosomal sialidase activity is nearly absent while the deficiency in β-galactosidase is only partial, thus probably secondary (Kuriyama et al., 1980, 1982; Mueller and Shows, 1982; Tsuji et al., 1982, 1984; Wenger et al., 1978; Yamada et al.,

Table 1: Phenotypic Variations in Hexosaminidase Deficiencies

[adapted from Johnson (1981)]

PHENOTYPE	USUAL DENOMINATIONS
I - INFANTILE ENCEPHALOPATHY	
Alpha-locus	— Tay-Sachs disease
	— Tay-Sachs disease — genetic compound with residual HEX A
Beta-locus	— Sandhoff disease
	— Sandhoff disease — genetic compound
Activator locus	— AB variant
II - LATE INFANTILE OR JUVENILE ENCEPHALOPATHY	
Alpha-locus	— Juvenile Tay-Sachs disease
	— Juvenile Tay-Sachs disease compound
Beta-locus	— Juvenile Sandhoff disease
Activator locus.	—
III - CEREBELLAR ATAXIA	
Alpha-locus	— Atypical spinocerebellar degeneration
Beta-locus	— Juvenile cerebellar ataxia *(Ramsey-Hunt phenocopy)*
	— Adult onset spinocerebellar ataxia
Activator locus	—
IV - MOTOR NEURON DISEASE	
Alpha-locus	— ALS phenocopy
	— Kugelberger-Welander phenocopy
Beta-locus	— Kugelberger-Welander phenocopy with ataxia (this report)
Activator locus	—
V - ADULT ONSET ENCEPHALOPATHY	
Alpha-locus	—
Beta-locus	—
Activator locus	— Adult GM_2-gangliosidosis with dementia, seizures and normal pressure hydrocephalus
VI - ASYMPTOMATIC OR PRE-SYMPTOMATIC ADULTS	
Alpha-locus	— "Total" HEX A deficiency
	— "Near total" HEX A deficiency
Beta-locus	— HEX A and B deficiency
Activator locus	—

https://doi.org/10.1017/S0317167100035125 Published online by Cambridge University Press

1983; Yamaguchi et al., 1983; Sakuraba et al., 1983; Federico et al., 1980). In addition to the spino-cerebellar symptoms many of these cases have myoclonus and a macular cherry-red spot, with or without progressive mental deterioration.

The above occurrences are reasons enough to screen all atypical forms of hereditary ataxias for a possible lysosomal enzyme deficiency, particularly of Hexosaminidase, β-galactosidase and neuraminidase. Previous studies by others in the French Canadian population had indicated that these mutations did exist in that particular group. Andermann et al. (1977), Andermann and Andermann (1982) described typical (infantile) Tay-Sachs disease in French Canadians from 5 families living in Eastern Quebec; and Sandhoff disease in a further 2 families from the Eastern Townships. None of these, however, had the juvenile or adult (chronic) forms of gangliosidosis. One of the latter families had been reported in detail by Melançon et al. (1974), the other partially by Aronson, (1964). Andermann et al. (1977) also report the results of a screening program for Hexosaminidase deficiency carriers in French Canadians. In Montreal, French Canadian controls had a heterozygote frequency of 0.3% while Jews of Ashkenazi origin had a frequency of 4.2%. However in the French Canadian deme (area of high incidence) in Eastern Quebec, the heterozygote frequency was 18% (six times higher than in the Ashkenazi Jews). This figure increased to 20.4% in the Tay-Sachs relatives and was still 7.6% in "unrelated" spouses. Such results justify the present enquiry.

Subjects and Methods

Leukocyte hexosaminidase, neuraminidase and β-galactosidase activities were measured in a consecutive series of 11 patients with typical Friedreich's disease as defined by Geoffroy et al. (1976). These patients were compared to 3 control groups, matched for age range: 11 patients with closely related recessive ataxia (Acadian subtype of Friedreich; Charlevoix-Saguenay syndrome and unclassified others) (Bouchard et al., 1978); 13 neurological controls (8 with recessive dystonia musculorum deformans and 5 with familial spastic paralysis). Finally 16 normal subjects also served as controls. All the patients and controls were French Canadians (ie: all four grandparents were French Canadians from Quebec).

Leukocytes were isolated by the dextran differential sedimentation procedure as previously described (Barbeau et al., 1980; Snyder and Brady, 1969). Proteins were measured with the method of Lowry et al. (1951). Hexosaminidase total, A and B activities were measured using a modification of the method of O'Brien et al. (1970) for serum as described in the Laboratory Manual for Biochemical Genetics Jan. (1982 revision) from Hayward Genetics Center, New Orleans, kindly given to us by Dr. E. Shapira.

4-methyllumbelliferyl-N-acetyl-β-D-glucosamide (Suzuki et al., 1971) was used as the artificial substrate. Determination of β-galactosidase activity and of neuraminidase activity in leukocytes was done according to the methods of Hong et al. (1980) and Sakuraba et al. (1983) using the fluorogenic substrates 4-methyllumbelliferyl-α-D-N-acetyl neuraminate and 4-methyllumbelliferyl-β-D-galactopyranoside. Measurement of the cold stable form of neuraminidase was done after 5 successive thawings and freezings. For the purpose of this report we have called neuraminidase A the labile enzyme and neuraminidase B the cold-stable form.

Results

The primary purpose of this investigation was to verify the state of these lysosomal enzymes in the classical form of Friedreich's disease (Geoffroy et al., 1976). Control groups were included to rule out other contributing factors which could have played a role, had the values in Friedreich been found abnormal. This study was not intended as a screening procedure in hereditary ataxia among the French Canadians.

As seen in Table 2 the activity of the three enzymes was entirely normal in typical Friedreich's disease. In the neurological controls, equally, no significant deviation from normal could

Table 2: Leukocyte Lysosomal Enzymes in Friedreich's Disease and Controls

(Mean ± SEM)

ENZYME		NORMAL CONTROLS	FRIEDREICH	ATAXIC CONTROLS	NEUROL. CONTROLS
		(16)	(11)	(10) + (1*)	(13)
(1) **HEXOSAMINIDASE**					
(nM/mg Prot/hr)	A:	225 ± 25	238 ± 21	288 ± 40 (38)	257 ± 31
	B:	146 ± 16	183 ± 19	147 ± 28⁺ (7)	133 ± 23
	% A:	64 ± 2	57 ± 2	69 ± 3 (85)	64 ± 3
	Total:	401 ± 39	421 ± 37	435 ± 40 (45)	390 ± 28
(2) **NEURAMINIDASE**					
(nM/mg Prot/min) x 10^{-3}	A:	13 ± 1	11 ± 1	14 ± 2 (11)	16 ± 2
	B:	6 ± 1	6 ± 1	6 ± 1 (7)	8 ± 1
	% A:	70 ± 2	68 ± 2	71 ± 3 (60)	67 ± 3
	Total:	19 ± 2	17 ± 1	20 ± 2 (18)	24 ± 2
(3) **β-GALACTOSIDASE**					
(nM/mg Prot/hr)	Total:	85 ± 7	87 ± 5	109 ± 10 (90)	98 ± 8

*separated from other controls because of clearly abnormal values
⁺includes one patient with value of 22.5 (see text)

be found, *ie* familial spastic paralysis and dystonia musculorum are not due to a deficiency in these three enzymes. Both these neurological control groups were purposely chosen to rule out the contribution of two components often observed in hereditary ataxia: dystonic postures and spasticity.

In the ataxic control group, normal values were found in all patients but two. In particular the patients with Charlevoix-Saguenay syndrome had entirely normal activities of the three enzymes and their isosymes. One man, however, with a very atypical form of ataxia turned out to have extremely low activity of both the A and the B form of Hexosaminidase, thus to possibly suffer from an adult form of Sandhoff disease. Further studies were carried out in the family, as seen below. Another patient, a 39 year-old woman with a mild form of recessive ataxia had a low total Hexosaminidase activity (202nM/mg Prot/hr). Hex A activity was only slightly decreased (180nm/mg Prot/hr), but Hex B activity was markedly decreased at 22.5nm/mg Prot/hr, thus 80% of the enzyme activity is in the A form. β-galactosidase (90nm/mg Prot/hr) and neuraminidase activities (total: 21.4; A: 14.1; B: 7.3 (nm/mg Prot/hr) x 10^{-3}) were entirely normal in that woman.

Discussion

It is very unlikely that "typical" Friedreich's disease would ever be confused clinically with any of the entities caused by a lysosomal enzyme deficiency. For example knee-jerk reflexes are always absent in Friedreich, whereas they are normal or increased in all of the late onset lysosomal disorders with ataxia. Evidence of more widespread CNS involvement is also the rule in lysosomal disorders. The three enzymes studied are the only ones where mutations have been known to produce a progressive spino-cerebellar syndrome in adolescence or adulthood, therefore it is unlikely that a lysosomal disorder will turn out to be the cause of Friedreich's disease. Enzyme activity was never increased, thus an activator protein defect can also be eliminated. These negative result are to be added to the mosaic of data gathered on this disease in the course of the Quebec Cooperative Study. It is hoped that each piece of the puzzle will gradually help in unraveling the mystery and in focussing on the basic defect.

Meanwhile, the discovery of two possible cases of lysosomal enzyme deficiencies among only 11 cases of "atypical" recessive ataxias studied, certainly would appear to recommend the institution of a screening program for such cases. In the same period we had the occasion to study another 12 cases of "atypical" recessive ataxia, from ethnic origins other than French Canadian. One of these, a young girl from South America, was also seen at the Montreal Neurological Institute where a Hex A deficiency was confirmed. Thus from 10 to 15% of atypical recessive inherited ataxias in adolescent and adults could be lysosomal enzyme deficiencies. This surprising finding would again justify the establishment of a screening program for adults in any large population basin.

Case 1 (R.C.) (IRCM no 3981). The patient with possible adult Sandhoff disease is a 44 year-old man, one of 5 children of a non consanguinous marriage. He was born in Montreal but his parents were from Joliette and region. His birth and early years were normal until the age of 6 when tremor of the hands was noted. Shortly afterwards the mother noted a progressive dysarthria. The patient is tall (6'3") and extremely thin (140 lbs) with long, thin fingers and was always taller than his friends. This is probably why his ungainly and hesitant gait was ascribed by his parents and doctors to "growth problems". There is a pectus excavatus but no laxity of ligaments, no hyperelasticity and no ectopic lens. The heart and vessels are normal. After the age of 20 the hand tremors became worse and were accompanied by large amplitude abnormal movements of the limbs with changes in posture. The legs were also weaker. A wide angle scoliosis developed at that time and the dysphagia became worse, very dystonic in tone. Gait became gradually stiffer, but not markedly more ataxic. At the age of 22 the patient was seen by a neurologist who diagnosed dystonia musculorum deformans. At the age of 30 (in 1971) the patient was investigated for the first time by the senior author at the Hôtel-Dieu Hospital. At examination the above noted features were confirmed. The neurological examination also revealed the dystonic postures on active voluntary contraction and dysarthria but no dysphagia. The cranial nerves were otherwise normal except for frequent action grimaces. No cherry-red spots were seen. Fasciculations were present at the level of the shoulders and arms and in the legs and there was a coarse, rapid tremor of both hands. All limbs were stiff, but no extrapyramidal rigidity or cogwheeling were found. Deep tendon reflexes were brisk (2 +) in the upper limbs but normal or decreased in the legs. The plantar response was bilaterally flexor. There was clear atrophy present distally in hands and legs and marked weakness of triceps and biceps. No atrophy of paraspinal muscles. Sensations were slightly decreased to touch bilaterally, but vibration and position sense were normal. Psoriasis was present over the knees and elbows. Finally finger to nose and heel to knee tests were slightly ataxic and dysmetric (score 1.5/3). The clinical diagnosis at that time was Kugelberg-Welander syndrome, a diagnosis confirmed by the electromyographic and nerve conduction examinations (Drs. A. Aguayo and J.M. Peyronnard). Conduction velocities in sensory and motor nerves were normal. The other laboratory tests were all normal except for a slightly increased but constant calciuria.

The patient was lost to follow-up for 5 years. When seen again in 1976, he was weaker and the fasciculations were more widespread. The psoriasis, however, had progressed. In 1979, the tremors spread to the trunk and the dystonic postures were worse in the left hand. The dysarthria was also worse. Because of the important dystonic component a ceruloplasmin determination was done but was normal at 28 mg % (N: 15-60 mg %). In the last few years, the gait difficulties increased and explained why he was included in the "atypical" ataxia group of patients which we studied. Myoclonic jerks were often seen recently but no seizures. The mental status is normal with a low-normal I.Q.

The proband is the oldest of 5 children. He has one neurologically normal brother who has psoriasis and one brother (**case 2**) who suffers from an identical disease and psoriasis. Both sisters refused to be examined, but are said to be neurologically normal except for the youngest who has psoriasis. The father died at age 67 from intestinal adenocarcinoma. He had no neurological symptoms or signs. The mother, now 71, is entirely normal. The parents were not related as far as they knew.

Case 2 (J.C.) (IRCM no 3981.01). This patient is now 39 years old. His history and neurological examination are absolutely identical to that of his brother (case 1). On the telephone the dysarthria is so identical that it is impossible to distinguish them. The patient was never hospitalized under our care. At examination he has the dystonic postures of head, face and neck, the fasciculations, the muscle weakness, the tremor of the hands, the pectus excavatus, the scoliosis of his brother. The deep tendon reflexes and the plantar responses are normal. There are no sensory signs or symptoms. However, it is impossible to detect ataxia in finger to nose, gait or heel to shin tests. This is in contrast to his brother.

Some of the members of the family could be examined biochemically. The results of these tests are given in Table 3. It is seen that case 2 has an even more severe deficiency in both Hex A and Hex B and that he also has the Sandhoff biochemical profile. The mother (G.T.C.) is obviously an heterozygote carrier with enzyme activities approximately half of the normal values. Interestingly the normal phenotype brother (G.C.) has a decreased (−58%) activity of Hex A, but an increased (+18%) activity of Hex B in the leukocytes. If these changes are confirmed in fibroblasts, it is possible that the family may be a genetic compound with respect to hexosaminidase. These and other studies are being carried out and will be reported elsewhere.

Table 3: Adult Sandhoff Disease Hexosaminidase Activity

RELATIVES	LEUKOCYTES (nM/mg Prot/hr)				SERUM (nM/ml/hr)			
	TOTAL	A	B	% A	TOTAL	A	B	% A
RC - **PROBAND** (case 1)	44.4	37.6	6.7	84.8	63.6	13.2	50.4	20.7
GTC — MOTHER	194.2	137.0	57.2	70.6	—	—	—	—
GC — BROTHER (normal)	279.3	106.0	173.3	37.9	1080.0	570.0	510.0	47.2
JC — BROTHER (case 2)	37.0	23.4	13.6	63.2	16.5	16.5	0	100.0
NORMAL CONTROLS (our laboratory N = 16)	401 ± 39	255 ± 25	146 ± 16	64 ± 2	792 ± 24	505 ± 13	287 ± 25	64 ± 2

It is of interest that in this family the Kugelberg-Welander phenotype is present in both affected brothers, but that the ataxia is only present in one. To our knowledge the Kugelberg-Welander phenotype has only been reported in two families (Johnson et al., 1982; Karpati, G. — personal communication). In both of these the alpha-locus (Hex A) was the culprit. The present family would be the first with a biochemical Sandhoff profile and the phenotype Kugelberg-Welander ± ataxia.

Case 3 (H.G.) (IRCM no. 6180). A word should be said about the patient whose leukocyte Hex B activity was markedly decreased (− 85%) while Hex A was at the very lower limits of the normal range (2 SD) (− 29%). These results are from duplicate tests. This patient was only examined once in the field and no fibroblasts have yet been grown. This is a 39 year-old woman who had walking difficulties from age 2 or before. She is said to have walked on her tip-toes most of her childhood. Presently her ataxia is moderate on finger to nose and gait. Alternating movements are slow. The fundi are pale and there is no retinitis. A severe internal strabismus is present on the right. Dystonic postures are not evident. Speech is only slightly hesitant. The patient is said to have a 9 year-old son who has internal strabismus of the right eye and some speech hesitancy. Two of her sisters also have some ataxia and strabismus. Further biochemical and clinical investigations will be carried out when the family grants permission.

Conclusion

Our studies revealed first that lysosomal enzyme deficiencies known to be associated with some spino-cerebellar degenerations are not present in Friedreich's disease or the Charlevoix-Saguenay syndrome. Secondly, a very small scale survey of "atypical" recessive hereditary ataxias turned up 3 cases of severe deficiencies in Hexosaminidase activity. Two adult brothers presenting with the clinical phenotype of Kugelberg-Welander disease (one also with ataxia), were shown to have a severe deficiency of both Hex A and Hex B activities (Sandhoff biochemical pattern). This is the first such report. A further female patient, unrelated to the others, had a severe isolated deficiency of Hex B and presented with a very slowly progressive and mild ataxia, with severe internal strabismus. These patients and their families are being studied clinically and biochemically in greater detail and will be reported elsewhere. However, these preliminary findings justify screening for such lysosomal defects in all cases of "atypical" recessive ataxia.

Acknowledgements

The studies reported in this paper were made possible through a grant from "L'Association Canadienne de l'Ataxie de Friedreich". Thanks are due to Mrs. Nicole Guay-Poirier for typing the manuscript.

References

Andermann F, Andermann E (1982) Neuroepidemiological studies in Eastern Canada—Genetic aggregates in specific population, including three newly described autosomal recessive syndromes. *In:* Fukuyama Y (ed). Child Neurology, Excerpta Med Foundat ICS 579, pp 351-365.

Andermann E, Scriver CR, Wolfe LS, Dansky L, Andermann F (1977) Genetic variants of Tay-Sachs disease: Tay-Sachs disease and Sandhoff's disease in French Canadians, juvenile Tay-Sachs disease in Libanese Canadians, and a Tay-Sachs screening program in the French Canadian population. *In:* Kabak MM, Rimoin DL, O'Brien JS (eds). Tay-Sachs disease: screening and prevention. New York, A.R. Liss, pp 161-188.

Aronson SM (1964) Epidemiology. *In:* Volk BW (ed). Tay-Sachs disease. New York, Grune and Stratton, pp 118-153.

Barbeau A, Charbonneau M, Cloutier T (1980) Leukocyte glutamate dehydrogenase activity in various hereditary ataxias. Can J Neurol Sci 7: 421-424.

Bouchard JP, Barbeau A, Bouchard R, Bourchard RW (1978) Autosomal recessive spastic ataxia of Charlevoix-Saguenay. Can J Neurol Sci 5: 61-69.

De Duve C, Wattiaux R (1966) Functions of lysosomes. Annual Rev Physiol 28: 435-492.

Dreyfus JC, Poenaru L, Svennerholm, (1975) Absence of Hexosaminidase A and B in a normal adult. New Engl J Med 292: 61-63.

Federico A, Cecio A, Battani GA, Michalski JC, Strecker G, Guassi GC (1980) Macular cherry-red spot and myoclonus syndrome — juvenile form of sialidosis. J Neurol Sci 48: 157-169.

Geoffroy B, Barbeau A, Breton G, Lemieux B, Aubé M, Léger C, Bouchard JP (1976) Clinical description and roentgenologic evaluation of patients with Friedreich's ataxia. Can J Neurol Sci 3: 279-286.

Gilbert F, Kucherlapati R, Creagan RP, Murnana MJ, Darlington GJ, Ruddle FH (1975) Tay-Sachs' and Sandhoff's disease: the assignment of genes for Hexosaminidase A and B to individual human chromosomes. Proc Nat Acad Sci 72: 263-267.

Goldie WD, Holtzman D, Suzuki K (1977) Chronic Hexosaminidase A and B deficiency. Ann Neurol 2: 156-158.

Hong VN, Beauregard G, Potier M, Belisle M, Mameli L, Gatti R, Durand P (1980) Studies on sialidoses — Properties of human leukocyte neuraminidases. Biochem Biophys Acta 616: 259-270.

Johnson WG (1981) The clinical spectrum of hexosaminidase deficiency diseases. Neurology (N.Y.) 31: 1453-1456.

Johnson WG (1982) Hexosaminidase deficiency: a cause of recessively inherited motor diseases. Adv Neurol 36: 159-164.

Johnson WG, Chutorian AM (1978) Inheritance of the enzyme defect in a new hexosaminidase deficiency disease. Ann Neurol 4: 399-403.

Johnson WG, Chutorian A, Miranda A (1977) A new juvenile hexosaminidase deficiency disease presenting as cerebellar ataxia. Neurology 27: 1012-1018.

Johnson WG, Cohen CS, Miranda AF, Waran SP, Chutorian AM (1980) α-locus hexosaminidase genetic compound with juvenile gangliosidosis phenotype: clinical, genetic, and biochemical studies. Am J Hum Genet 32: 508-518.

Johnson WG, Wigger HJ, Karp HR, Glaubiger LM, Rowland LP (1982) Juvenile spinal muscular atrophy: a new hexosaminidase deficiency phenotype. Ann Neurol 11: 11-16.

Kelly TE, Reynolds LW, O'Brien JS (1976) Segregation within a family of two mutant alleles for hexosaminidase A. Clinical Genetics 9: 540-543.

Kolodny EH, Raghavan SS (1983) GM_2-gangliosidosis-Hexosaminidase mutations not of the Tay-Sachs type produce unusual clinical variants. Trends in Neurol Sci 6: 16-20.

Kuriyama M, Miyatake T, Owada M, Kitagawa T (1982) Neuraminidase activities in sialidosis and mucolipidosis. J'Neurol Sci 54: 181-187.

Kuriyama M, Okada S, Tanaka Y, Umezaki H (1980) Adult mucolipidosis with β-galactosidose and neuraminidase deficiencies. J Neurol Sci 46: 245-254.

Lane AB, Jenkins T (1978) Two variant hexosaminidase β-chain alleles segregating in a South African family. Clin Chimica Acta 87: 219-228.

Lowden JA, O'Brien JS (1979) Sialidosis: a review of human neuraminidase deficiency. Am J Hum Genet. 31: 1-18.

Lowry OH, Rosebrough NJ, Farr AL, Randall RJ (1951) Protein measurement with the folin phenol reagent. J Biol Chem 93: 265-275.

Macleod RM, Wood S, Jan JE, Applegarth DA, Dolman CL (1977) Progressive cerebellar ataxia, spasticity, psychomotor retardation, and hexosaminidase deficiency in a 10 year-old child: Juvenile Sandhoff's disease. Neurology 27: 571-573.

Melancon SB, Potier M, Geoffroy G, Dallaire L (1974) Maladie de Sandhoff: étude clinique et génétique chez une enfant canadienne-française. Union Méd Can 103: 1218-1222.

Mueller OT, Shows TB (1982) Human β-galactosidase and α-neuraminidase deficient mucolipidosis: genetic complementation analysis of the neuraminidase deficiency. Hum Gent 60: 158-162.

Musarella MA, Raab EL, Rudolph SH, Grabowski GA, Desnick RJ (1982) Oculomotor abnormalities in chronic GM_2 gangliosidosis. J Ped Ophth Strab 19: 80-89.

Navon R, Argov Z, Brand N, Sandbank U (1981) Adult GM_2 gangliosidosis in association with Tay-Sachs disease: a new phenotype. Neurology (NY) 31: 1397-1401.

O'Brien JS, Okada S, Chen A (1970) Tay-Sachs disease: detection of heterozygotes and homozygotes by serum hexosaminidase assay. N Engl J Med 283: 15-20.

O'Neill B, Butler AB, Young E, Falk PM, Bass NH (1978) Adult-onset GM_2 gangliosidosis — Seizures, dementia, and normal pressure hydrocephalus associated with glycolipid storage in the brain and arachnoid granulation. Neurology 28: 1117-1123.

Oonk JGW, van der Helm HJ, Martin JJ (1979) Spino-cerebellar degeneration: hexosaminidase A and B deficiency in two adult sisters. Neurology 29: 380-384.

Philippart M (1978) Clinical and biochemical pathophysiology of ataxia in the sphingolipidoses. Adv Neurol 21: 131-149.

Rapin I, Suzuki K, Suzuki , Valsamis MP (1976) Adult (chronic) GM_2 gangliosidosis - atypical spinocerebellar generation in a Jewish sibship. Arch Neurol 33: 120-130.

Robinson D, Stirling JL (1968) N-acetyl-β-glucosaminidases in human spleen. Biochem J 107: 321-327.

Sakuraba H, Suzuki Y, Akagi M, Sakai M, Amano N (1983) β-galactosidase — neuraminidase deficiency (galactosialidosis): clinical, pathological, and enzymatic studies in a postmortem case. Ann Neurol 13: 497-503.

Sandhoff K, Andreae Y, Jatzkewitz H (1968) Deficient hexosaminidase activity in an exceptional case of Tay-Sachs disease with additional storage of kidney globoside in visceral organs. Life Sci 7: 283-288.

Snyder R, Brady RO (1969) The use of white cells as a source of diagnostic material for lipid storage diseases. Clin Chim Acta 25: 331-338.

Suzuki Y, Berman PH, Suzuki K (1971) Detection of Tay-Sachs disease heterozygotes by assay of hexosaminidase A in serum and leukocytes. J Pediatr 78: 643-647.

Suzuki Y, Sakuraba H, Potier M, Akagi M, Sakai M, Beppu H (1981) β-galactosidase-neuraminidase deficiency in adults: deficiency of a freeze-labile neuraminidase in leukocytes and fibroblasts. Hum Genet 58: 387-389.

Tsuji S, Yamada T, Ariga T, Toyoshina I, Yamaguchi H, Kitahara Y, Miyatake T, Yamakawa T (1984) Carrier detection of sialidosis with partial β-galactosidase deficiency by the assay of lysosomal sialidase in lymphocytes. Ann Neurol 15: 181-183.

Tsuji S, Yamada T, Tsutsumi A, Miyatake T (1982) Neuraminidase deficiency and accumulation of sialic acid in lymphocytes in adult type sialidosis with partial β-galactosidase deficiency. Ann Neurol 11: 541-543.

Wenger DA, Tarby TJ, Wharton C (1978) Macular cherry-red spots and myoclonus with dementia: coexistent neuraminidase and β-galactosidase deficiencies. Biochem. Biophys Res Commun 82: 589-595.

Willner JP, Grabowski GB, Gordon RE, Bender AN, Desnick RJ (1981) Chronic GM_2 gangliosidosis masquerading as atypical Friedreich's ataxia: clinical,morphologic, and biochemical studies of nine cases. Neurology (NY) 31: 787-798.

Wood S, MacDougall BG (1976) Juvenile Sandhoff disease: some properties of the residual hexosaminidase in cultured fibroblasts. Am J Hum Genet 28: 489-495.

Yamada T, Tsuji S, Ariga T, Miyatake T (1983) Lysosomal sialidase deficiency in sialidosis with partial β-galactosidase deficiency. Biochim Biophys Acta 755: 106-111.

Yamaguchi H, Okamoto K, Shooji M (1983) A case of adult type sialidosis with partial β-galactosidase deficiency without myoclonus. Clin. Neurol. 23: 1-8.