Biochemical studies in Nevin-Jones syndrome

K. VALMIKINATHAN AND J. N. CUMINGS

From the Department of Chemical Pathology, Institute of Neurology, Queen Square, London

SUMMARY The lipid profiles of the brain in four cases of Nevin-Jones syndrome are described. A loss of phosphatidyl ethanolamine was found in both white matter and cortex in two cases as well as a more general loss of lipids in the cortex in one patient; there was a normal cerebroside-sulphatide ratio in myelin. These findings indicate a general loss of myelin over a period of time. The distribution of fatty acids in cerebrosides and sulphatides show a slight reduction in nervonic acid (24:1). The findings support the view that a secondary demyelination is present.

In 1954 Jones and Nevin described two cases showing clinically a rapidly fatal condition in which myoclonic epilepsy was a feature. Histologically there was cortical damage with status spongiosus; a vascular aetiology was postulated. Further cases were described six years later (Nevin, McMenemey, Behrman, and Jones, 1960) under the title of subacute spongiform encephalopathy. This condition is recognized by both neurologists and neuropathologists but no biochemical studies would appear to have been made. We have had the opportunity to examine material from four brains and the results are presented here.

MATERIAL AND METHODS

Four brains were removed at necropsy from patients aged 48, 60, 64, and 63, the two younger being males, who clinically had suffered from the typical features of the Nevin-Jones syndrome including myoclonus. Histological examination later verified the nature of the disorder. From each brain, portions of both white matter and cerebral cortex were obtained and examined by the procedures usually employed for lipid analyses. Water content, total phospholipid, total and esterified cholesterol, total cerebroside, hexosamine, and N-acetyl neuraminic acid were estimated as previously (Cumings, Grundt, and Yanagihara, 1968a). Thin-layer chromatography was performed (Müldner, Wherrett, and Cumings, 1962) and phosphorus estimations made on individual lipids, using the method employed by Cumings, Shortman, and Skrbic (1965). An analysis of the fatty acids in cerebrosides and sulphatides of the brain of one case (L.H., female, 63) was performed by the technique used by Yanagihara and Cumings (1969a).

In addition, myelin was prepared from the cerebral white matter except that the final centrifugation was 28,000 g for four hours, and sphingolipids and cholesterol

were estimated (Cumings, Thompson, and Goodwin, 1968b).

RESULTS

The results of the lipid analyses of all four cases are recorded in Table 1, showing also the findings in a normal control, examined at the same time, and which are similar to those previously reported. Relatively little abnormality is seen except in the fourth case (L.H.) where there is some loss of phospholipid and of cholesterol, more marked in the cortex than in the white matter.

Table 2 shows the relative amounts of individual phospholipids as a percentage of the total P in two cases compared with the same normal control as previously. Ethanolamine in the white matter and cortex is somewhat reduced, as has been found in other forms of demyelination (Yanagihara and Cumings, 1968, 1969b) involving the white matter.

The myelin of the white matter was examined with the results seen in Table 3 and very little difference from normal figures (Cumings, 1970) was found, but it was noted that relatively less myelin was obtained from a given amount of white matter than is usual. The cerebroside to sulphatide ratio is almost normal.

The results of the fatty acid composition of non-hydroxy and hydroxy fatty acids of cerebrosides and sulphatides of a normal control and one case of Nevin-Jones syndrome (L.H.) are presented in Tables 4 and 5, together with the findings of Svennerholm and Stållberg-Stenhagen (1968) and of O'Brien and Sampson (1965) in normals. The fatty acid pattern of cerebroside and sulphatide of the normal control is very similar to the values

TABLE 1
CEREBRAL LIPIDS IN THE NEVIN-JONES SYNDROME

	White					Cortex				
	D.S. M 48	W.F. M 60	L.T. F 64	L.H. F 63	Normal S.B. M 65	D.S. M 48	W.F. M 60	L.T. F 64	L.H. F 63	Normal S.B. M 65
Total phospholipid	26.10	27.4	22.6	19.7	24.7		23.1	21.4	16.2	22.8
Total cholesterol	10.30	10.2	11.3	6.9	12.0		5.86	6.0	4.2	5.37
Esterified cholesterol	0.24	0.66	1.2	0.14	0.35		0	0.8	0.4	0.2
Total hexose as cerebroside		12.2	11.6	7.7	12.5		4.83	4.9	2.1	4.06
Hexosamine	0.20	0.34	0.32	0.35	0.26			0.75	0.58	0.61
N-acetyl neuraminic acid						0.29	0.15	0.2	0.13	0.2
Water (%)	71.8	69.8	70.0	71.8	68.1	86.2	83.8	83.2	81.4	84.5

Results in g/100 g dry tissue.

TABLE 2
CEREBRAL PHOSPHOLIPIDS IN THE NEVIN-JONES SYNDROME

Phospholipid	White			Cortex		
	L.T. F 64	L.H. F 63	Normal S.B. M 65	L.T. F 64	L.H. F 63	Normal S.B. M 65
Cardiolipin	5.1	4.5	4.9	9.1	4.0	4.6
Phosphatidic acid	3.6	3.4	3.1	2.0	1.5	3.1
Ethanolamine	29.4	30.7	34.8	20.1	27.7	31.3
Serine	15.6	15.6	18.6	8.3	19.1	16.7
Lecithin	16.5	23.0	21.4	26.0	32.4	33.0
Lysoethanolamine	4.2	3.4	2.4	4.6	3.7	2.2
Sphingomyelin	12.6	14.6	14.0	13.9	8.0	9.0
Lysolecithin	6.0	4.8	0.7	7.0	3.6	0

Results as % of total phospholipid.

TABLE 3
MYELIN LIPIDS

L.H., F 63	
Cerebroside g/100 g myelin	24.99 (24.4)
Sulphatide g/100 g myelin	5.74 (5.4)
Cholesterol g/100 g myelin	13.3 (16.3)
Cerebroside/sulphatide ratio	4.4/1 (4.5/1)
Water content cerebral white matter	71.8%

Normal results in parentheses (Cumings, 1970).

TABLE 4
NON-HYDROXY ACIDS IN CEREBROSIDES AND SULPHATIDES
(EXPRESSED AS MOLAR %)

Fatty acids	Cerebrosides								Sulphatides							
	Case L.H.		Normal control		Normal Svennerholm and Stållberg-Stenhagen, 1968		Normal O'Brien and Sampson, 1965		Case L.H.		Normal control		Normal Svennerholm and Stållberg-Stenhagen, 1968		Normal O'Brien and Sampson, 1965	
	White	Cortex	White	Cortex	White	Cortex	White	Cortex	White	Cortex	White	Cortex	White	Cortex	White	Cortex
14 : 0	0.21	0.7	0.12	0.7	0	0	0.5	1.3	0.3	0.1	0.2	0.3	0	0	0.4	0.5
16 : 1	0.20	1.1	0.2	1.0	0	0	0	0	0.1	1.1	0.2	1.5	0	0	0	0
16 : 0	1.02	9.0	2.5	8.9	0.5	1.7	2.1	9.7	2.1	5.1	1.8	2.2	0.3	1.3	9.3	2.4
18 : 1	3.24	1.7	3.3	1.6	0.5	1.1	0.7	3.7	2.9	1.7	2.5	1.1	0.1	0.5	1.6	1.0
18 : 0	7.55	17.3	8.8	17.3	6.5	10.0	7.6	11.0	4.8	13.4	3.9	5.1	1.7	4.8	6.1	2.6
20 : 0	0	0	0	0	0	1.2	0	0.8	0	0	0	0	0	0.8	0	1.1
22 : 1	0.20	1.2	0.5	1.4	0.6	0.4	0.3	0.2	0.3	1.5	0.2	0.6	0.4	0.3	0.2	0.2
22 : 0	2.30	2.3	2.0	1.5	2.4	2.8	3.1	1.3	2.2	10.0	2.1	8.4	1.4	2.2	1.4	1.6
23 : 1	0.92	0.9	1.0	0.7	0	0	1.1	0.9	0.5	0.5	0.4	0.4	0	0	0.5	0.7
23 : 0	2.60	2.6	2.5	2.8	3.9	3.8	4.7	2.7	3.4	6.0	2.8	7.8	3.6	4.0	2.3	3.2
24 : 1	43.80	41.0	47.1	39.2	44.5	40.4	44.0	37.8	49.6	40.0	51.9	39.0	44.1	40.0	36.2	37.6
24 : 0	13.80	8.2	12.8	11.2	12.5	12.8	15.2	10.2	13.2	12.0	13.2	11.2	14.0	13.5	15.6	17.7
25 : 1	12.19	7.0	9.5	6.6	12.0	11.7	4.3	8.8	9.4	4.0	9.8	10.8	13.6	13.4	11.2	13.6
25 : 0	5.91	1.4	2.8	2.1	4.4	3.2	5.0	2.5	3.1	0.4	4.6	2.8	5.4	5.7	5.5	5.8
26 : 1	5.46	5.6	6.1	4.0	8.9	8.3	8.0	6.8	7.8	3.2	6.2	8.8	12.2	10.3	6.0	10.9
26 : 0	0.60	trace	0.7	trace	0.9	0.7	1.3	1.6	0.3	trace	0.2	trace	1.6	1.7	1.2	0.1

TABLE 5
HYDROXY ACIDS IN CEREBROSIDES AND SULPHATIDES IN
WHITE MATTER (EXPRESSED AS MOLAR %)

Fatty acids	Cerebrosides				Sulphatides			
	Case L.H.	Normal	Normal Svennerholm and Ställberg- Stenhagen, 1968	Normal O'Brien and Sampson, 1965	Case L.H.	Normal	Normal Svennerholm and Ställberg- Stenhagen, 1968	Normal O'Brien and Sampson, 1965
14 : 0	0	0	0	0.6	0	0	0	2.4
16 : 1	0	0	0	0	0	0	0	0
16 : 0	0.8	0.7	0	1.0	0.7	1.1	0	6.3
18 : 1	0	0	0	0.3	0	0	0	0.5
18 : 0	0	0	0.6	0.6	0	0	0.2	2.2
22 : 1	0	0	0	0	0	0	0	0
22 : 0	8.3	8.7	6.5	11.0	8.4	5.4	4.2	13.2
23 : 1	0	0	0	0	0	0	0	0
23 : 0	18.1	18.7	17.4	13.0	17.4	16.0	14.3	11.4
24 : 1	22.5	20.2	17.9	24.0	21.3	20.0	15.3	8.4
24 : 0	35.2	37.4	40.0	34.0	41.4	43.8	42.3	46.2
25 : 1	5.0	5.0	4.3	3.0	3.5	4.8	5.5	5.4
25 : 0	6.4	6.0	6.5	4.0	4.3	6.7	8.6	trace
26 : 1	3.8	3.4	4.8	4.1	2.5	2.7	6.5	trace
26 : 0	0.6	0.5	1.1	2.7	0.4	0.6	1.9	trace

reported earlier (O'Brien and Sampson, 1965; Svennerholm and Ställberg-Stenhagen, 1968; Yanagihara and Cumings, 1969a). No marked variation in the fatty acid pattern of cerebroside and sulphatide in the case of Nevin-Jones syndrome is noted as compared with the normal control. However, a slightly decreased ratio of nervonic acid (24 : 1) to lignoceric acid (24 : 0) is observed in the white matter cerebroside, and this is largely due to a reduction in nervonic acid (24 : 1) in cerebroside.

DISCUSSION

The importance of cerebrosides and sulphatides among the cerebral lipids is well recognized. In myelin, the ratio of cerebroside to sulphatide is remarkably constant at about 4.5 to 1, and the cerebroside levels are frequently used as an index of myelination. The composition of these two myelin lipids has been shown to be altered in conditions such as metachromatic leucodystrophy, Krabbe's disease, and multiple sclerosis (Cumings *et al.*, 1968b; Cumings and Goodwin, 1968). Structural changes as a decrease in C24 fatty acids in cerebroside and sulphatide have also been reported both in primary and secondary demyelinating diseases.

The present study with cases of Nevin-Jones syndrome has revealed certain interesting facts. In one case (L.H.) there was some loss of phospholipid and cholesterol which was more marked in the cortex than in the white matter. The ethanolamine fraction was somewhat reduced in the white matter and the cortex, as has been found in other forms of demyelination (Yanagihara and Cumings, 1968,

1969b) which involves the white matter. However, no marked abnormality was noted in the myelin of white matter as compared with normals, but relatively less myelin was obtained from the white matter than usual.

The slight reduction in such myelin lipids as cholesterol and the phospholipids, which was more pronounced in the cortex than in the white matter, indicates a primary pathology in the cortex in case L.H. This aspect is paralleled by the observed histological picture of a marked loss of neurones from the frontal cortex and a proliferation of astrocytes. Fatty acid analysis has revealed no gross variation in the fatty acid distribution of cerebroside and sulphatide as compared with the normals. There is, however, a slight reduction of C24 fatty acids, particularly nervonic acid (24 : 1) in the cerebrosides, indicating a secondary demyelination in the white matter, as shown by previous studies (Yanagihara and Cumings, 1968, 1969a).

A similar picture has been observed in Down's syndrome where there is variation in certain myelin lipids (Stephens and Menkes, 1969), as frontal lobe cholesterol content, with no alteration in the fatty acid distribution of cerebroside and sulphatide. Similarly, variations in the levels of cerebroside in the demyelinated areas of the brain associated with oedema have been reported (Yanagihara and Cumings, 1968, 1969a) when there was a slight lowering of C24 fatty acids in the white matter cerebroside.

The results of the present study with cases of the Nevin-Jones syndrome indicate some demyelination as suggested by the altered pattern of cholesterol

and ethanolamine, more pronounced in the cortex than in the white matter. The demyelination is of a secondary nature as no gross abnormality, except a slight lowering of C24 fatty acids in cerebroside, is observed in the fatty acid pattern of cerebroside and sulphatide, and this may be due to some type of metabolic disturbance which may be non-specific in character.

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