Pathological Changes in the Central and Peripheral Nervous System of Young Long-term Diabetics

II. The Spinal Cord and Peripheral Nerves

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Received July 10, 1967

Summary. A study of the spinal cord and peripheral nerves of 15 long-term, juvenile diabetic patients has revealed the following changes: — 1. atrophy of the spinal cord, sometimes with fibrosis of the leptomeninges; — 2. degeneration of the ganglion cells of the anterior and posterior horns; — 3. demyelination and axon cylinder loss in the posterior columns and the peripheral nerves, increasing in severity towards the periphery; — 4. severe neurogenic atrophy of the muscles; — 5. mild abnormalities in the blood vessels of the spinal cord in some of the cases, which were more pronounced in the peripheral nerves; — 6. severe hyalinosis in the muscle capillaries. — On the whole, the vascular changes were not severe enough to explain the presence of the ganglion cell and nerve fibre abnormalities observed in the spinal cord and peripheral nerves of young, long-term diabetic patients.

Modifications pathologiques du système nerveux central et périphérique de sujets jeunes, diabétiques depuis longtemps. II. La moelle épinière et les nerfs périphériques

Résumé. Une étude de la moelle épinière et des nerfs périphériques de 15 patients jeunes, diabétiques depuis longtemps, a révélé les modifications suivantes: — 1. Atrophie de la moelle épinière, parfois avec fibrose des leptoméniges; — 2. Dégénérescence des cellules ganglionnaires des cornes antérieures et postérieures; — 3. Demyélinisation et perte des cylindres des cordons postérieurs et des nerfs périphériques, devenant plus graves vers la périphérie; — 4. Grave atrophie neurogène des muscles; — 5. Légères anomalies des vaisseaux sanguins de la moelle épinière dans certains cas, plus prononcées dans les nerfs périphériques; — 6. Hyalinose grave dans les

capillaires musculaires. — Au total, les modifications vasculaires ne sont pas assez graves pour expliquer la présence des anomalies des cellules ganglionnaires et des fibres nerveuses, observées dans la moelle épinière et les nerfs périphériques de patients jeunes, diabétiques depuis longtemps.

Pathologische Veränderungen am zentralen und peripheren Nervensystem jugendlicher Diabetiker. II. Rückenmark und periphere Nerven

Zusammenfassung. Bei Untersuchungen des Rückenmarks und der peripheren Nerven von 15 jugendlichen Langzeitdiabetikern ergaben sich folgende Veränderungen: 1. Atrophie des Rückenmarks, z.T. mit Fibrose der Leptomeningen; — 2. Degeneration von Ganglienzellen der Vorder- und Hinterhörner; — 3. Markschwund und Verlust von Achsenzylindern in den Hintersträngen und, nach distal zunehmend, in den peripheren Nerven; — 4. Schwere neurogene Muskelatrophie; — 5. Bei einigen Fällen Gefäßveränderungen, die im Bereich des Rückenmarks leicht, an den peripheren Nerven stärker ausgeprägt erscheinen; — 6. Schwere Hyalinose der Muskelkapillaren. — Zusammenfassend läßt sich sagen, daß die Gefäßveränderungen nicht ausgeprägt genug waren, um die an Rückenmark und peripheren Nerven beobachteten Schädigungen von Ganglienzellen und Nervenfasern bei jugendlichen Langzeitdiabetikern zu erklären.

Key-words: Neuropathy, encephalopathy, spinal cord, peripheral nerves, juvenile diabetes, long-term diabetes, angiopathy, microangiopathy.

In an earlier report, we presented the results of histological studies of the brain in a series of juvenile, long-term diabetic patients (RESKE-NIELSEN et al., 1966). The present paper gives the results of studies of the spinal cord, the peripheral nerves and the muscles from some of the cases included in the previous report as well as from other patients in the same category. Here, as in the report on encephalopathy, we are dealing exclusively with *juvenile* diabetics dying after *many years* of diabetes.

The purpose of the present study was to elucidate the still unsettled problem of the significance of vascular abnormality in the development of diabetic neuropathy, as well as to revive the half-forgotten question of the localization of the disorder of the nervous system appearing clinically as diabetic neuropathy.

Material and Methods The Patients

Clinical observations on the 15 patients in this series are shown in Table 1. Seven of the patients were men, eight were women. The average age of onset was 11 years (range 2-29); 11 of the cases were diagnosed before puberty. The average duration of diabetes was 23 years (range 15-36 years). All the patients had severe and widespread vascular disease. Retinopathy was observed in all cases and was severe in six, four of them being blind or nearly blind. Clinical signs of nephropathy were present in 13 cases, heart disease in seven, and hypertension was found in 10. Fourteen of the patients showed signs or symptoms of neurological disease; nine had paraesthesia and four had muscle

weakness. Areflexia was present in all but one, eight revealed reduced sensitivity, nine reduced vibratory sense and eight reduced motor conduction velocity. Three patients also showed pronounced signs and symptoms of cerebral disease, which in two of them included a spastic gait.

Pathological Report

Autopsy of the brains, the spinal cords, the peripheral nerves and the muscles

All the material was fixed in four per cent neutral formalin. Nine of the spinal cords, which included the cauda equina, showed a slight atrophy and four of them had blurred leptomeninges. In nine cases inspection of the transverse section revealed a faded pattern.

For histological examination the cervical, thoracic and lumbar segments of the spinal cord, the cauda equina and the following bilateral specimens of nerves and muscles were used: nervus ischiadicus, nervus peroneus superficialis, nervus cutaneus dorsalis pedis and nervus ulnaris, musculus semimembranosus, musculus peroneus brevis, musculus extensor digitorum brevis and musculus flexor carpi ulnaris. In some cases pieces of other nerves and muscles from both the upper and lower extremities were also removed. All specimens were removed with great care, precaution being taken to avoid artificial trauma. In addition to the stains routinely used in the study of the central nervous system such as hematoxylin-eosin, VAN GIESON, gallo-cyanin-chromalum (EINARSON), toluidine blue, and Mahon, special techniques were also employed including lipid (scarlet-red) and elastic tissue stains, a modified McMANUS, a modified ZIEHL-NIELSEN, an axis-cylinder stain (DAVENPORT), and HALE's technique for demonstration of acid mucopolysaccharides as modified by RINEHART and ABUL-HAJ.

Histological Examination

Brains from patients not previously described showed essentially the same types of lesions as those seen in the cases published earlier (RESKE-NIELSEN et al., 1966).

The spinal cord

The *leptomeninges* were normal or showed slight fibrous thickening. In a few cases the anterior spinal artery and its ramifications revealed proliferation of the intima, containing phagocytes with fat droplets and PAS-positive granules in the cytoplasm. In two of the cases, vessel changes were very severe; the sub-endothelial space or the entire wall was filled with fat and the vessel lumina were narrowed, but without thrombi (No. 1 and 2). (Fig. 1)

The *anterior* and *posterior horns* showed slight or moderate loss of ganglion cells. The remaining ganglion cells revealed degeneration with swollen and/or dis-

placed nuclei. In the cytoplasm, PAS-positive and fat-positive granules were seen. A mild degree of gliosis was present. (Fig. 2, 3, 4)

In the *white matter* the myelin sheaths as well as the axons were swollen with unequal calibre, and fragmented with loss of nerve fibres. There was mild, diffuse gliosis and corpora amylacea. Most of the spinal cords revealed elective degeneration of the posterior columns with loss of axons (Fig. 5). In two of the cases (No. 2 and 3) degeneration of the lateral columns was also observed.

The *vessels of the grey and white matter* showed only mild changes. In five cases, hyalinosis of the arterioles could be seen. Only one case showed a characteristic homogeneous PAS-positive thickening of the walls of the small vessels with narrowing of the lumina. (Fig. 6)

The *anterior* and *posterior roots* showed varying degrees of loss and degeneration of myelin sheaths and axis cylinders. The myelin sheaths were swollen with varying calibre. The changes were most pronounced in the posterior roots. The degeneration of the anterior roots paralleled the alterations in the motor ganglion cells. As a rule the posterior roots were more degenerated than the posterior columns, and there was often SCHWANN cell proliferation. In few cases the small vessels of the anterior and posterior roots showed hyalinosis, but the degenerative alterations were mild. (Fig. 7, 8)

Peripheral nerves from the upper and lower extremities revealed the same pathological changes as the roots, but they were much more pronounced. In many cases, total demyelination and severe loss of fibres were seen. The large and small vessels showed mild or

Fig. 1. Small artery with fat-laden phagocytes in the intima. The lumen is narrowed and eccentrically placed (Scarletred. High magnification)

Fig. 2. Anterior horn with degenerated ganglion cells and gliosis (Gallo-cyanin-chromalum. Medium magnification)

Fig. 4. Sensory ganglion cells with degeneration (Gallo-cyanin-chromalum. High magnification)

Fig. 3. Motor ganglion cells with degeneration (Gallo-cyanin-chromalum. High magnification)

Fig. 5. Posterior columns with loss of axons and degeneration of the myelin sheaths (Mahon. Medium magnification)

Fig. 6. Small arteriole with enormously thickened, homogeneous and deeply PAS-positive wall. The lumen is nearly occluded (PAS-stain. High magnification)

Fig. 7. Spinal nerve with loss and degeneration of myelin sheaths (Mahon. High magnification)

moderate pathological changes. A considerably thickened intima with homogeneous, PAS-positive material and pycnotic nuclei was found in only one case. The nerve lesions and vascular changes gradually increased in severity from proximal to distal. (Fig. 9, 10, 11)

Fig. 8. Spinal nerve with loss and degeneration of axis cylinders (Davenport. High magnification)

The *muscle specimens* showed neurogenic atrophy with fields of varying age and size. The changes appeared to be dependent upon the degree of degeneration of the peripheral nerves. They were most pronounced in the specimens from the legs and the feet where the most severe lesions were seen. Sometimes the muscle fibres had almost disappeared and only clumps of muscle nuclei and a few very thin fibres remained. In many places the muscles were substituted by fat. Myopathy, with hyalinization and vacuolization of the muscle fibres and the presence of a few necrotic segments, was seen in only one case (No. 4), and here both upper and lower extremities were involved. (Fig. 12)

The *capillaries of the muscles* were more numerous than normal. The walls revealed both diffusely and focally thickened basal membranes with increased PAS-positivity. (Fig. 13, 14)

Fig. 9. Peripheral nerve with loss and degeneration of myelin sheaths (Mahon. High magnification)

Fig. 10. Peripheral nerve with loss and degeneration of axis cylinders. The small vessel is normal (Davenport. High magnification)

The arterioles sometimes showed fibrillar thickening. Vessel changes were extremely pronounced in the muscles of the feet.

Correlations

In Tables 1, 2 and 3 the patients have been listed according to the severity of the neurological symptoms. In spite of considerable pathological changes in both motor and sensory peripheral neurons in all the patients, only half of them had sensory symptoms (paraesthesia), and only four of them had motor symptoms (muscle weakness).

On the other hand, all of the cases except one, presented objective signs of peripheral neuropathy; 14 patients having reduced tendon reflexes and four atrophy of the muscles.

Pathological changes in the white matter of the spinal cords were, as was to be expected, most pronounced in the posterior columns.

Degeneration of the lateral columns was seen in only two cases, and was probably secondary to encephalopathy (case no. 2 and 3).

Fig. 11. Small artery with clumps of PAS-positive material in the thickened intima (PAS-stain. High magnification)

It has not been possible to demonstrate any correlation between the degree of vessel degeneration and pathological alterations in the spinal cord and peripheral nerve roots. It is striking that the changes in the nervous system were symmetrical, diffuse and remarkably uniform, whereas the alterations in the vessels were focal, variable and, in general not very pronounced.

Fig. 12. Cross-section of muscle with severe neurogenic atrophy (Hematoxylin-Eosin. Medium magnification)

Except for the fact that the two cases with severe vascular changes in the spinal cord had manifested a pronounced neuroencephalopathic syndrome during life, there was no correlation between symptoms and vascular abnormalities.

In the muscles, especially of the feet, there were very severe changes in the capillaries with enormously thickened, PAS-positive walls. In spite of this, myogen atrophy was seen in only one case, a patient who had had severe peripheral neuropathy for several years. Neurogenic atrophy on the other hand was present in every case.

Discussion

The voluminous literature on diabetic neuropathy contains surprisingly few comprehensive histological

studies that include examination of the spinal cord. Cases reported in the old literature, i.e. before the introduction of insulin, are discussed in detail in the paper by WOLTMAN and WILDER (1929). Most of these reports describe findings in only a single case. In some of these cases degenerative changes were noted in the spinal cord, similar to those of tabes dorsalis or of subacute, combined degeneration.

Fig. 13. Cross-section of muscle with severe capillary angiopathy. Muscle fibres appear as empty rings. (PAS-stain. High magnification)

WOLTMAN and WILDER's own material consisted of the spinal cord and peripheral nerves from three diabetic patients. They found that changes in the spinal cord were not very pronounced, whereas those in the peripheral nerves were severe and associated with pronounced thickening of the walls of the blood vessels. They concluded that diabetic neuropathy is a disease of the peripheral nerves — "the degenerations noted in the spinal cord are unimportant".

This conclusion was widely accepted and in the following years very little was published on the histology of the nervous system in diabetes mellitus. In the 1940's and 1950's, when it was realized that the various, so called, complications such as retinopathy, nephropathy and gangrene were in fact parts of a generalized diabetic vascular disease, the question was raised whether neuropathy was also to be accepted

under the heading of diabetic angiopathy. Many clinical facts were consistent with this concept, and FAGERBERG (1959) found a good correlation between the histological changes in the vasa nervorum of the lower

Fig. 14. Longitudinal section of muscle with numerous capillaries. The walls are enormously thickened and deeply PAS-positive. (PAS-stain. High magnification)

extremities and the symptoms and signs of clinical neuropathy. However, other evidence, clinical as well as experimental, has shown that a nonvascular element must also be present in the pathogenesis of diabetic neuropathy.

In the meantime the problem of the *localization* of the defect inside the nervous system was nearly forgotten. Except for a few case reports, only one extensive and well-documented study of the histology of the spinal cord, nerve roots and peripheral nerves in young or middle-aged patients with diabetes mellitus has appeared recently (DOLMAN, 1963). Most of the 36 patients described by this author were old, 26 being over 60, and 17 over 70 years of age. However 5 patients were younger — 27–45 years — and had suffered from diabetes for many years (18–33 years). Except regarding vascular changes, no distinction was made in the report between old patients with short or long duration of diabetes and juvenile, long-term diabetics. It appears from the tabulation of data, however, that neuropathological changes were well-marked in the

young patients. In half of the 36 cases, the spinal cord showed reduction of myelin sheaths with severe damage to axis cylinders in the dorsal columns, but not in the lateral funiculi. The posterior roots were atrophic in cases with degeneration of dorsal columns; the motor roots were normal. Patchy demyelination was seen in many peripheral nerves. Axis cylinders were also affected, but less severely. These changes increased towards the periphery. Neurogenic atrophy was seen in muscle specimens from 9 of the 25 patients. The intraneural and perineural arteries often showed cellular hyperplasia and PAS-positive hyalinization. Capillary thickening was seen only in the juvenile diabetics. Similar, although less pronounced, vascular changes were noted in 7 hypertensive, non-diabetic patients (age not mentioned).

In the present study of long-term juvenile diabetics changes which are more severe and extensive than those reported by DOLMAN have been found. The overall picture of the changes in the spinal cord is that of a diffuse, symmetrical degeneration, affecting the grey as well as the white substance. The root changes were not confined to the posterior roots. The posterior root changes were more severe than those of the posterior columns. The mild or moderate changes observed in the ganglion cells of the anterior horn might be due in part to retrograde degeneration.

The myelin sheath and axon cylinder degeneration in the peripheral nerves was even more severe than that in the spinal cord, and as in DOLMAN's cases increased towards the periphery, but we cannot conclude, as WOLTMAN and WILDER did, that in comparison the spinal cord changes are "unimportant".

Except for two cases with severe neuro-encephalopathic symptoms, vascular changes in the spinal cord were mild or absent. Vascular changes were more pronounced in the peripheral nerves, especially in the smallest vessels; and were very severe in muscles.

It is known today that nervous system abnormalities may be present at the start of clinical diabetes in young patients, and some abnormalities have been shown to be reversible (STEINNESS, 1961; GREGERSEN, 1964, 1967). Certain biochemical changes suggesting an abnormality of the sorbitol pathway of nervous tissue have been demonstrated in acute experimental diabetes in animals (GABBAY et al., 1966; STEWART et al., 1966). On the other hand, clinical signs and symptoms of diabetic neuropathy increase in incidence with the duration of diabetes and are correlated to the incidence of retinopathy and nephropathy.

Findings in the present study resemble those obtained in our study of brains from juvenile, long-term diabetics, i.e. a severe nervous system disease with relatively mild abnormalities of the vascular tree (RESKE-NIELSEN et al., 1966).

The changes observed in ganglion cells and nerve fibres cannot be due simply to ischemia alone. As in the brain, a dual pathogenesis seems likely, viz. a metabolic disturbance of nervous tissue combined with

Table 1. Clinical findings.

Retinopathy: + diabetic retinopathy, ++ proliferative retinopathy, +++ severe proliferative retinopathy or enucleated eyes. — Nephropathy: (+) slight proteinuria, possibly with slight elevation of serum creatinine, + moderate decrease of kidney function, ++ clinical uraemia. — Heart disease: + symptoms and/or signs of heart disease. — Arterial hypertension: (+) diastolic pressure ≥ 110 , + diastolic pressure ≥ 110 . — Hypoglycaemic episodes: (+) seldom, + often, ++ numerous. Neurological signs: (+) slight, + moderate, ++ severe

No	Initials	Sex	Age	Diabetes Age Onset	Duration of diabetes	Retinopathy	Visual acuity	Heart Disease	Nephropathy	Uraemia	Arterial hypertension	Hypoglycaemic Episodes	Clinical neurological picture	Reduced sensitivity	Paraesthesia	Reduced tendon reflexes	Spasticity	Ataxia	Muscle weakness	Muscle atrophy	Reduced vibration sense	Reduced motor conduction velocity
1	SVJ	M	48	29	19	+	1,0—1,0	+	+	+	+	○	Severe neuro-encephalopathic syndrome with multiple cerebral episodes.	+	+	+	○	+	+	○	+	+
2	JPCR	M	38	12	26	+	0,67—0,67	○	+	○	+	+	Severe neuro-encephalopathic syndrome with bulbar paralysis.	+	+	+	+	+	○	○	+	+
3	BGN	M	40	4	36	++	0,67—0,50	+	+	+	+	+	Severe neuro-encephalopathic syndrome with multiple cerebral episodes and dementia.	+	+	+	+	+	+	+	+	+
4	RIK	F	44	29	15	+	1,0—1,0	○	(+)	○	○	○	Severe peripheral neuropathy for the last 6 years.	+	+	+	○	○	(+)	+	+	+
5	EP ^a	F	43	9	34	++	0,67—<0,1	^b	○	○	(+)	++	Severe peripheral neuropathy.	○	+	+	○	○	○	○	○	+
6	KGL ^a	M	29	6	23	++	0,05—0	^b	(+)	○	^c	(+)	Areflexia. Paraesthesia.	(+)	○	+	○	○	○	○	○	+
7	BEH	F	39	18	21	+	0,05—0,1	○	+	+	+	+	Areflexia.	(+)	○	+	○	○	○	○	○	+
8	ESC ^a	M	21	3	18	++	0,67—0,33	○	+	○	+	(+)	Areflexia.	(+)	○	+	○	○	○	○	○	+
9	EIS	M	30	13	17	+++	blind	+	+	+	+	(+)	Areflexia. Agitated depression.	○	○	+	○	○	○	(+)	+	+
10	MMJ ^a	F	31	6	25	+++	blind	+	○	○	○	(+)	Areflexia.	+	○	+	○	○	○	○	+	+
11	EVA ^a	F	26	10	16	+++	0,67—0,67	○	(+)	○	○	○	Areflexia.	○	+	+	○	○	○	○	+	+
12	KCH ^a	M	45	16	29	+++	0,4—0,4	^b	(+)	○	○	○	Areflexia.	○	(+)	+	○	○	○	○	+	+
13	IT ^a	F	30	11	19	+++	0—0,33	○	(+)	○	○	○	Areflexia.	○	○	+	○	○	○	○	+	+
14	EAA	F	31	2	29	+++	0—0	+	+	○	+	○	Areflexia.	+	+	+	○	○	○	○	○	+
15	KMJ	F	25	5	20	+	reduced	○	+	+	+	+	No symptoms or signs.	○	○	○	○	○	○	○	○	○

^a hypophysectomized.^b died of coronary thrombosis.^c only last 2 weeks of life.

Table 2. Histological abnormalities of the vessels, the spinal cord, the roots and the peripheral nerves: (+) very slightly, + slightly, ++ moderately, +++ very severely pronounced

The spinal cord				Peripheral nerves												
No	Initials	Large vessels	Small vessels	Grey substance	White substance				Ventral roots		Dorsal roots		Upper extremities		Lower extremities	
					Myelin sheaths	Axial cylinders	Degeneration of the posterior columns	Large vessels	Small vessels	Myelin sheaths	Axial cylinders	Large vessels	Small vessels	Myelin sheaths	Axial cylinders	Large vessels
1	SVJ	++	+	+	++	++	+	+	+	+	(+)	+	+	+	+	+
2	JPCR ^a	++	++	+	+	(+)	+	+	+	+	+	+	+	+	+	+
3	BGN ^a	(+)	○	+	+	+	+	+	+	+	+	+	+	+	+	+
4	RIK	○	○	+	+	+	+	+	+	+	+	+	+	+	+	+
5	Epa	○	+	+	+	○	+	+	+	+	+	+	+	+	+	+
6	KGL ^a	○	○	+	+	○	○	○	+	+	+	+	○	○	+	+
7	BEH	○	○	+	+	(+)	+	+	+	+	+	+	(+)	+	+	+
8	ESC ^a	○	○	+	+	+	○	○	+	+	+	+	○	○	+	+
9	EIS	○	○	+	+	+	○	○	+	+	+	+	(+)	+	+	+
10	MMJ ^a	○	+	+	+	+	○	○	+	+	+	+	○	○	+	+
11	EVA ^a	○	○	+	+	+	+	+	+	+	+	+	+	+	+	+
12	KCH ^a	(+)	○	+	+	+	+	+	+	+	+	+	○	○	+	+
13	IT ^a	○	○	+	+	+	+	+	+	+	+	+	○	○	+	+
14	EAA	○	○	+	+	+	+	+	+	+	+	+	○	○	+	+
15	KMJ	○	(+)	+	+	(+)	+	+	+	+	+	+	○	○	+	+

^a hypophysectomized.

Table 3. *Histological abnormalities of the muscular vessels and muscle fibres. Third columns: neurogenic atrophy. Symbols: as in Table 2*

No Initials	Muscles							
	Upper extremities				Lower extremities			
	Large vessels	Small vessels	Musculus flexor carpi ulnaris	Myopathy	Large vessels	Small vessels	Musculus extensor digitorum brevis pedis	Myopathy
1 SVJ	+	++	++	○	+	+++	+++	○
2 JPCR	○	++	+	○	(+)	+++	+++	○
3 BGN	(+)	+	++	○	○	+++	+++	○
4 RIK	○	+++	++	+	○	+++	+++	+
5 EP ^a	○	○	+	○	○	+	+	○
6 KGL ^a	○	○	(+)	○	○	+	+	○
7 BEH	○	++	+	○	(+)	+++	++	○
8 ESC ^a	○	○	+	○	○	○	+	○
9 EIS	○	+++	++	○	(+)	+++	+++	○
10 MMJ ^a	○	+++	++	○	○	+++	++	○
11 EVA ^a	○	++	++	○	○	+++	+++	○
12 KCH ^a	○	+	+	○	+	+++	+++	○
13 IT ^a	○	+	+	○	○	+++	+++	○
14 EAA	+	+	+	○	○	++	++	○
15 KMJ	○	+	+	○	○	+	+	○

^a hypophysectomized.

a slowly developing angiopathy. Neuropathy in the clinical sense with permanent signs and subjective symptoms usually appears only after many years of diabetes when incapacitating vascular abnormalities are also present in many other organs.

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