34. The Apallic Syndrome and Secondary Lesions of Peripheral Nerves

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Secondary lesions of certain peripheral nerves may occur in cases involving long-term unconsciousness due to cerebral damage (Gerstenbrand et al., 1971; Laederich and Bernard-Pichon, 1935; Mertens, 1961; Olsen, 1956; Tönnis, 1958); they are also found in bedridden patients (Mumenthaler and Schliack, 1965; Woltman, 1930) and under certain conditions of treatment and occupational exposure (Carr, 1957; Gerhard, cited in Mumenthaler and Schliack; Laederich and Bernard-Pichon, 1935; Sprofkin, 1958; Wilhelm, 1970). The number of patients displaying an apallic syndrome with concomitant secondary lesions of peripheral nerves is increasing. Although holistic treatment, preventive measures, attention to bedding, prophylactic measures against decubital ulcerations, and persistent physical therapy are a constituent part of modern intensive care (Krenn, 1972) secondary peripheral nerve lesions may still be observed in patients with apallic syndrome.

Clinical Data

In the past nine years (1964-1972), at the Department of Rehabilitation of the Neurological University Hospital in Vienna, 27 out of 94 patients with an apallic syndrome revealed definite damage of one or more peripheral nerves. The patients came from the intensive care units of both surgical clinics of the University of Vienna and from other surgical departments. Exact data about the time of occurrence of these nerve lesions are usually not available, because the clinical symptoms are masked by the unconsciousness, immobility, and poor general condition of the patient. Furthermore, the attending physician pays most of his attention to the function of the vital organ systems. Whenever such patients enter the phase of remission and rehabilitation, neurologic complications arising from secondary lesions attract his full attention and invariably present obstacles to rehabilitation measures. However, it is possible that in some cases the peripheral nerve lesion may already have existed some time prior to the full development of the clinical symptoms.

The localization of the secondary peripheral nerve lesions in 27 patients is shown in Table 1. According to our practical experience, local pressure is of primary importance. This is consistent with the fact that almost exclusively anatomically exposed peripheral nerves are involved. Among the patients observed, no polyneuritic symptoms were found. The following additional factors have to be included in our considerations: metabolic disturbances, endotoxins, hyperergic reactions, hypoxia during the acute phase of the apallic syndrome, anemia, and pronounced deficits in metabolic energy carriers during the long period of parenteral alimentation (Gerstenbrand and Galanti, 1972). Even loss of weight is hazardous during peroneal paralysis (Sprofkin, 1958).

Table 1. Localization of the secondary peripheral nerve lesions in 27 patients with apallic syndrome

Nerve	Left	Right	Bilateral	Isolated
Peroneus	14	10	5	5
Ulnaris	9	8	2	1
Tibialis	5	6	2	–
Medianus	4	3	1	–
Ischiadicus	5	1	1	4
Radialis	3	1	–	2

As a result of rehabilitative measures, a good prognosis can usually be given. In 21 of our 27 cases complete restitution or at least a significant improvement was observed. In six cases the lesion stayed unchanged. Two patients died and could not be reviewed. Prevention and treatment of secondary peripheral nerve lesions are of equal importance. First of all, the patients' bedding needs continuous attention by the nursing staff. Repeated and rhythmic changes of position, special stuffing and mattress covers, physical therapy with passive movements of the limbs, and use of tonus regulating reflex therapy are other recommended measures.

A high caloric and balanced diet is also required. Immediately after identification of the peripheral nerve lesion, high doses of vitamin B and electric stimulation should be administered. Sometimes it is necessary to operate and remove periarticular ossifications (Gerstenbrand et al., 1970a) or other compressive pathologic structures (Mumenthaler and Schliack, 1965; Wilhelm, 1970).

Examinations, Etiology

Muscular atrophy and lesions affecting peripheral nerves as a consequence of extended comas are well-known phenomena. However, the type of damage to the nervous and muscular structures involved and its etiology have not yet been adequately explained. In order to continue our initial study (Gerstenbrand et al., 1971), additional electrophysiologic and neuropathologic tests have been carried out.

A. Results of Electrophysiologic Examinations

Electromyography was performed on a total of 27 clinically inconspicuous muscles of nine patients suffering from an apallic syndrome of traumatic origin. The muscles involved were: the m. tibialis anterior the m. biceps brachii, the m. triceps brachii, or the m. deltoides. The electromyogram using unipolar coaxial needle electrodes revealed fibrillation potentials and monophasic positive potentials in a patchlike distribution pattern on the m. tibialis anterior (patient 3 in Table 2) and on the m. biceps brachii (patient 2 in Table 2).

The average duration of the potentials of motor units in these two patients remained in the normal range. Maximum voluntary intention always resulted in full interference pattern. In another two patients (patients 8 and 9 in Table 2), the electromyogram showed potentials of short duration, low amplitude, and polyphasic form indicating a myogenic lesion. In patients 1 and 7 (Table 2) doublets and triplets were observed on the m. triceps

brachii and the m. biceps brachii; these manifestations were nonspecific signs of a metabolic disorder (Steinbrecher, 1962), even though the electrolyte values in the serum remained normal.

Table 2. Maximum motor NCV in m/sec

Case no.	age	Ulnaris n=50		Medianus n=50		Tibialis n=44		Pernoneus n=47		Ulnaris sensory NCV n=60	
		left	right	left	right	left	right	left	right	left	right
1 S.H.	30		*32 a*			*n.c.*	*41*	*n.c.*	*49 a*		
2 Z.S.	31		*45 a*	65	*69 a*	*n.c.*		*n.c.*			
3 X.E.	11		75						*49*		87
4 H.A.	39	69		64		46		52		73	
5 B.E.	30		73		58		*45 a*				
6 C.P.	40	*55 a*									
7 B.F.	32		62				52		51	65	
8 W.J.	36			61				56			
9 S.J.	27	52		60		44		47	53	62	
10 D.M.	58					46	44	*n.c.*	*n.c.*		

NCV = Nerve conduction velocity; a = split potential; n.c. = non-conductive; n = patient's lower limit of the normal range (Method: Hodes et al., 1948).
Italics refer to the NCV of nerves with clinical symptoms.

Using the method of Hodes et al. (1948), maximum motor nerve conduction velocities (NCV) were recorded for 13 paretic and 30 clinically normal nerves. At the time the NCV was recorded, serum electrolyte values were normal in all instances. In three cases pathologic values were recorded for the paretic nerves, i.e., twice for the ulnar nerve (32 ms and 45 ms, lower limit of the normal range: 48 ms) and once for the tibial nerve (41 ms, lower limit of the normal range: 44 ms). In four cases the potentials were split and a normal maximum motor NCV was registered. The splitting of the potentials was interpreted as a lesion affecting those fibers not conducting maximally. Because of the nonexcitability of six nerves their NCV could not be measured. This was the case in two patients (patients 1 and 2 in Table 2) where both the tibial and the peroneal nerves were affected on the same side; thus a lesion above the bifurcation of the sciatic nerve had to be assumed. The other case involved a patient (patient 10 in Table 2) with an isolated bilateral paresis—clinically manifest—of the peroneal nerve. In the clinically inconspicuous nerves the nerve conduction remained within the normal range and showed a normal form of evoked muscle potentials. In four patients (patients 3, 4, 7 and 9, Table 2) the sensory NCV of the ulnar nerve was measured using the method of Buchthal (1966) (Buchthal and Rosenfalck, 1966); the values recorded were within the normal range (patients' normal range: 60-90 ms).

The most interesting phenomenon observed during the electrophysiologic examination is the electromyographic evidence of fibrillations, doublets, triplets and of motor unit potentials of short duration, low amplitude and of poliphase form in some clinically inconspicuous muscles, with the maximum motor NCV remaining within the normal range. Considering the results of the biopsy, this appears to indicate a neurogenic subclinical disorder.

No conclusions about the etiology of peripheral lesions may be drawn on the basis of our electrophysiologic examinations. Some references are made in the literature to the impact on the NCV of various individual factors which may cause peripheral lesions within the apallic syndrome. The views about the effect of electrolyte shifts on the motor NCV differ. Simpson (1958) pointed out that physiologic electrolyte shifts do not result in any changes in the motor NCV. Chaumont et al. (1964) expressed a diametrically opposed opinion. Mattson and Lecoq (1968) determined motor NCV in 25 patients who had been fasting for 14-28 days. The NCV values recorded before and after fasting did not result in any significant differences. Only in two instances, the distal latency period of the peroneal nerve was slightly extended. However, Mattson's study does not preclude the possibility that nutritional deficiencies or a catabolic metabolism—as it is found in patients with an apallic syndrome—might produce a lower NCV after a period of several months. The publication of Simpson (1958) was the only one available on the subject of the effect of insufficient oxygen saturation on NCV. Simpson states that a patient with an arterial oxygen saturation of 85% was found to have a NCV of 39.3 ms in the ulnar nerve. The last and probably still the most important causative factor is external pressure. Bentley and Schlapp pointed out in 1943 that the most prominent effect of pressure is most likely hypoxia.

Animal experiments as well as clinical studies were carried out on the NCV during pressure paralysis. It was determined that a distinct drop in NCV or even a complete loss of conductivity may occur (Gilliatt and Thomas, 1960; Meyer and Denny-Brown, 1964). A study of the literature shows that a distinct reduction of maximum motor NCV or a loss of conductivity of a nerve during the apallic syndrome may be ascribed to external pressure and concomitant local hypoxia. The formation of these lesions may be encouraged if the external pressure is exerted on nerves previously damaged due to metabolic disorders.

B. Nerve and Muscle Biopsies

These were performed in a total of seven cases for which the clinical data is depicted in Table 3. The nerve biopsies were all taken from cutaneous branches of the sensory sural nerve. In three instances the muscle biopsies were taken from the proximal m. quadriceps femoris and in four cases from the distal m. peroneus brevis. The tissues were prepared for light microscopy; parts of three nerves were also arranged for examination by electron microscopy.

1. Nerve Biopsies: In all seven cases pathologic changes in the nature of degeneration of individual fibers were observed. These changes involved myelinated fibers mostly of large diameter. The pathologic changes were always widely distributed (Figs. 1, 2).

The number of nerve fibers affected differed. In two cases only a few, in four instances (Fig. 1) several, and in one instance numerous fibers were involved. Whenever there were nerves with considerable fiber lesions, different fascia were affected to different degrees.

e 3. Nerve and muscle biopsies

no.	Age	Clinical data: Apallic syndrome	Clinical data: Peripheral nerve lesion	Biopsy performed after trauma	Nerve biopsy	Muscle biopsy
A.	39	Full stage 2 months remission stage 3 months defect stage severe	Not differentiable	6 months	Some disseminated degeneration of individual large medullated fibers, late stage of degeneration,regeneration	Proximal muscle: diffuse slight atrophy, some inflammatory infiltrates
R.	16	Full stage	Not differentiable	3 months	Isolated disseminated degeneration of individual medullated fibers, recent degenerative process	Distal muscle: neurogenic disseminated atrophy, slight diffuse atrophy
E.	11	Full stage 9 months remission stage	Doubtful lesion of n. peroneus right, n. ulnaris	4 months	Isolated disseminated degeneration of individual fibers, late phase of degeneration, small cicatrization	Distal muscle: neurogenic disseminated atrophy and slight diffuse atrophy
B.	11	Full stage	Doubtful lesion of the n. ischiadicus and ulnaris bilateral	12 months	Numerous degenerative medullated fibers, current degenerative process fascia affected to different degrees	Proximal muscle: moderate diffuse atrophy
L.	31	Full stage 8 months remission stage severe	n.peroneus and and tibialis left n. ulnaris and med.right	13 months	Much disseminated degeneration of large medullated fibers, recent degeneration	Distal muscle: neurogenic grouped atrophy and moderate diffuse atrophy
G.	17	Full stage 2 months remission stage	n. peroneus bilateral	8 months	Some disseminated degeneration of large medullated fibers, recent processes next to older ones	Proximal muscle: slight diffuse atrophy and some inflammatory infiltrates
M.	58	Full stage 3 months remission stage	n. peroneus bilateral	5 months	Some disseminated degeneration of large medullated fibers, recent degeneration	Distal muscle: neurogenic grouped atrophy and slight diffuse atrophy

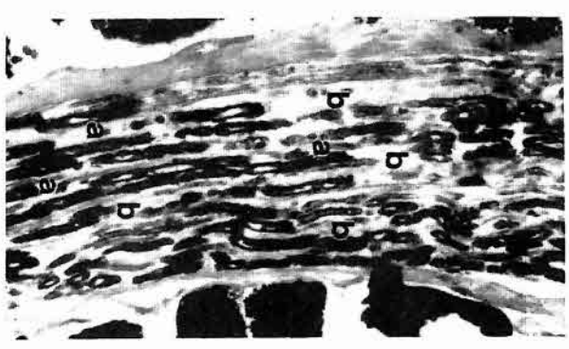


Fig. 1. Nerve biopsy. Several degenerations of individual large diameter myelinated fibers, recent *(a)* next to older *(b)* signs of degeneration. SBB x 40. (Case No. 1)

The degenerative changes of the individual nerve fibers were of a uniform nature but differed as to the stage reached. Thus, in five nerves recent fiber degeneration (Fig. 2-3) was observed. In one case the recent changes had occurred in addition to already completed processes; two nerves (one with only a few, one with several fiber lesions) revealed late stages of degeneration.

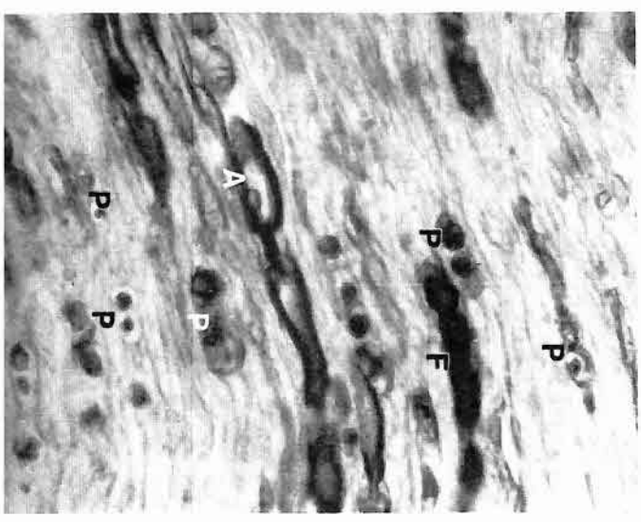


Fig. 2. Nerve biopsy, fascia section. Recent degenerations (axonal type) of myelinated fibers. Swelling *(A)* and fragmentation *(F)* of axon and myelin sheaths. Degeneration products of various sizes *(P)*. SBB

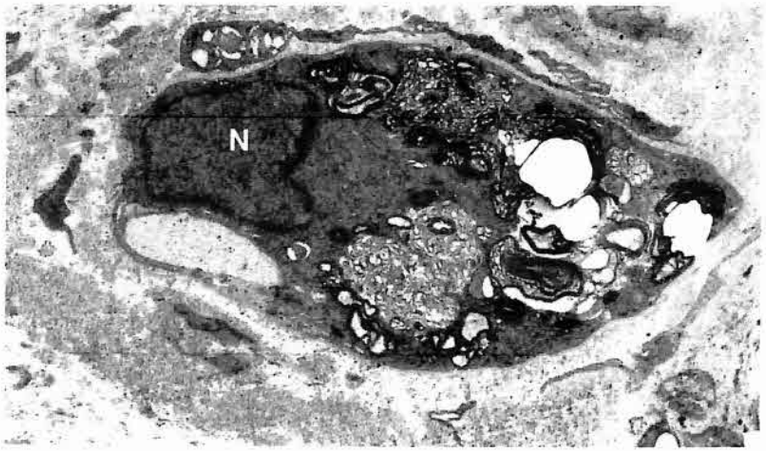


Fig. 3. Nerve biopsy, section. Degeneration of individual fiber with axon and myelin sheath disintegration. *N* = nucleus of Schwann's cell. EM magnification: x 6000. (Case No. 7)

The type of fiber degeneration was determined under the optical microscope according to swelling and fragmentation of the axon and of the myelin sheath (Fig. 2) as well as from the occurrence of fragmentation and degeneration products such as the accumulations of myelin material of varying sizes (Fig. 2). The later stages of degeneration are accompanied by a growth of the endoneurium. Depending on the extent of the nerve fiber degeneration, small cicatrical areas without fibers remained. No vascular changes were observed.

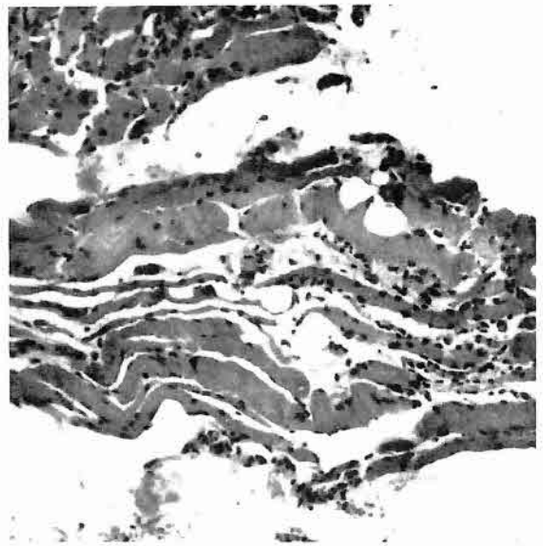
Under the electron microscope, three of the nerves disclosed disintegration of the axon and the myelin sheath structures of the nerve fibers. No selective demyelination was observed. One nerve in a late stage of the process revealed Büngner bands, indicating regeneration.

These findings reveal that the degeneration of individual fibers conforms to those from axonal lesions with a subsequent Wallerian syndrome. These studies of nerve biopsies have revealed that in all investigated cases of an apallic syndrome, peripheral nerve damage was involved. These lesions correspond to an axonal neuropathy of the myelinated fiber lesion type and are accompanied by scattered involvement of the fibers that may be slight to severe in degree.

2. Muscle Biopsies: In all cases investigated, changes were found to have taken place. In the proximal part of the muscles only slight to moderately diffuse narrowing of the fibers without considerable changes in the nuclei or the fiber diameters had occurred. In two of these muscles scattered perivascular inflammatory infiltrates were found. However, in the tested parts of the m. peroneus brevis other changes were noticed in addition to the diffuse narrowed muscle fibers. In two instances there were differences in the diameter, primarily caused by numerous scattered atrophic muscle fibers. Upon closer examination, several atrophic fibers were occasionally found next to each other.

Two biopsies, however, revealed distinct groups of atrophic muscle fibers in addition to the diffuse narrowing (Fig. 4), with a considerable increase in the number of nuclei and

Fig. 4. Muscle biopsy. Neurogenic atrophy with atrophic groups of fibers. HE x 40. (Case No. 5)



frequently with noticeable narrowing of the fibers, as well as with an occasional loss in striation. Undoubtedly, the grouping of atrophied muscle fibers corresponds to an equivalent neurogenic pattern. However, the diffuse slight narrowing of muscle fibers and considerable irregularity in their diameters were changes which at first sight signified a myopathic syndrome; only after the group patterns had been discerned was a neurogenic atrophy considered.

Taken by itself, the tissue syndrome with diffuse narrowing of the muscle fibers conforms to a bland, moderate, diffuse muscular atrophy similar to that occurring in the wake of inactivity, malnutrition or cachexia. Our studies of muscle biopsies thus demonstrate that in patients with an apallic syndrome we find a *general, moderate* loss of muscle tissue parenchyma, associated in certain regions with signs of neurogenic atrophy. In our patients these regions were found in the distal parts of the muscles investigated. The neurogenic signs may be slight to moderately severe in degree and start with a pseudomyopathic syndrome of disseminated fiber atrophies, followed later by a change to a typical, disseminated, focal fiber group atrophy.

If we take the results of the nerve and muscle biopsies together, the disseminated complete degeneration of individual fibers and the varying degrees of degeneration of the peripheral nerves explain the neurogenic lesion and the differing degree to which it is reflected in the musculature. Agreement between the extent of the nerve lesion and that of the neurogenic muscular atrophy, however, was not always present in our own investigation (viz. Table 2). This might be due to the type of nerve investigated which is sensory in nature. The possibly different effect of sensory and motor nerves could be subject to discussion. The predominant effect exerted on the distal muscles would agree with the primarily distal distribution of neuropathic processes.

In correlating the results of the nerve and muscle biopsies with the clinical data, we find that all cases with clinically manifest peripheral lesions disclose complete fiber degneration

either in several or in numerous instances. Among the cases with doubtful diagnosis of peripheral lesions one revealed severe neural damage and one only discrete involvement. Of the two cases where peripheral lesions were inconspicuous from the clinical point of view, one evidenced only discrete damage. In the other, only a few nerve fibers were completely degenerated. These correlations show that the nerves of clinically inconspicuous patients also demonstrate changes and that rather numerous nerve fiber lesions are found in patients with clinical symptoms.

Even though we cannot reduce from the case material a direct linear relationship between the number of nerve fibers affected and the manifestation of clinical symptoms (as might be expected), the impression persists that discrete nerve fiber lesions result in no clinical manifestations whereas peripheral clinical manifestations always result from a more extensive range of lesions. Thus in axonal neuropathy within the apallic syndrome we have to differentiate between clinically latent and clinically evident processes.

The correlation between duration, severity, and remission of the apallic syndrome are shown in Table 3. Both cases with nerve fiber changes that had already run their course were in an advanced stage of remission.

Discussion

Do the changes in the neuromuscular structures analyzed indicate etiologic factors? The type of neural damage shown does not provide any specific pathogenetic indications. Many causes are known for axonal myelinated fiber lesions of the wallerian type, but the distribution of damage revealed in our study precludes occlusion of the vessel supplying the nerve, a cause which seldom plays a part in peripheral nerve damage. Deficient blood supply with a particular impact on large myelinated nerve fibers may also be a cause; however, in its initial phases hypoxia—according to the degree of its severity—causes demyelination and only with increasing severity do we observe axonal lesions (Chopra and Hurwitz, 1967; Eames and Lange, 1967). In the cases investigated demyelination never occurred; even though the individual nerves revealed only very discrete damage, this factor cannot be termed a primary cause.

Pressure lesions are also frequently discussed and this phenomenon is not precluded by the pattern of damage evidenced. Thomas and Fullerton (1963) described myelinated fiber changes with diameter reduction, particularly of the large diameter regions which are caused by pressure lesions of the carpal tunnel syndrome. However, in pressure lesions in which both mechanical and ischemic factors are involved, demyelination occurs (Steinbrecher, 1962) in many instances. This was proved experimentally with tourniquet tests (Dyck, 1969).

These considerations make pressure lesions an unlikely cause of the observed discrete symptoms of neuropathy which disclose only axonal lesions and are always scattered. On the other hand, such pressure lesions may be an accidental factor in those syndromes which demonstrate numerous complete disintegrations of myelinated fibers in a rather diffuse distribution. No evidence exists for electrolyte changes being involved in the formation of axonal nerve fiber lesions.

There still remains the problem of the catabolic metabolism within the apallic syndrome which may possibly affect the large myelinated fibers since the latter are very sensitive to metabolic factors. We know from the analysis of polyneuropathies that axonal neuropathies of the myelinated fiber lesion type are frequently encountered in deficiency neuropathy or in complex metabolic disorders (Erbslöh and Abel, 1970; Sluga, 1974).

Therefore we would like to discuss the assumption that as a consequence of protracted coma with its general changes, particularly in catabolic metabolism a secondary neuropathic process develops. This process has a slight to moderate effect on the large myelinated fibers and remains on the subclinical level. Accidental factors may superimpose a marked neuropathic syndrome on this slight or moderate neural damage that apparently occurs in many and possibly in all cases, and leads finally to clinical deficiencies. Among these additional factors, pressure lesions might take first place.

Mertens (1961) described a neuropathic process in protracted coma as a disseminated neuropathy with CO intoxication; he also pointed out latent or subclinical changes and observed patch-shaped medullary failures and serous exudations. These changes do not occur in the neuropathic process of the apallic syndrome. The muscular changes are, on one hand, the direct consequence of the neurogenic lesions and, on the other, correspond to a nonspecific diffuse atrophic process of moderate severity. Diffuse, bland muscular atrophy has been described as the response pattern to inanition, malnutrition, old age, cachexia, inactivity, or consumptive diseases (Adams et al., 1962). It is likely that in the apallic syndrome it is also linked to inactivity or to reduced alimentation.

In a comprehensive study of changes due to old age or cachexia, Tomlinson et al. (1969) have described the particular features of the various stages of neurogenic atrophy in diffusely atrophic muscular tissue. Such changes were also observed by these authors in some cases of cranial traumata or cerebral disorders. The correlation with cachexia in the incidence of combined diffuse and circumscribed changes should be emphasized.

Conclusions

In patients suffering from an apallic syndrome we encounter secondary peripheral nerve failures which are particularly troublesome in rehabilitation and may complicate and prolong therapy. Electrophysiologic and bioptic tissue examinations resulted in the following findings about the course and type of peripheral nerve and muscle changes within apallic syndromes of traumatic origin:

1. Neural changes occurred even in patients without clinical symptoms and revealed patch-shaped signs of denervation whereas normal motor maximum nerve conduction velocities were maintained. At the same time, a few degenerative processes occurred in individual myelinated nerve fibers together with disseminated neurogenic muscular atrophy.

2. In doubtful or clinically manifest peripheral failures, the number of degenerating myelinated fibers increased and the neurogenic muscular atrophy occurred in distinct groups. In definite clinical symptoms the maximum motor NCV was reduced or the potentials were split while the maximum motor NCV was maintained (unless a complete loss of conductivity had set in).

3. The degeneration of individual fibers is caused by axonal lesions; the *type* of peripheral neural changes always corresponded to axonal neuropathy of the myelinated fiber type, a change that also corresponds to the extent to which the NCV is reduced. The type of muscular changes agreed with that of denervation atrophy and moderate nonspecific diffuse atrophy. The latter is known to be the consequence of inactivity, deficient nutrition, or cachexia.

4. According to the course, the type, and the distribution of the neural and muscular changes described, pathogenetic factors were discussed. For the discrete lesions, metabolic factors were assumed to be responsible whereas for the more severe neural changes the additon of accidental factors, particularly pressure lesions, were considered.

Summary

Based on these findings and the clinical experience, it may be stated that patients suffering from an apallic syndrome reveal changes in their peripheral nerves and the corresponding muscles. These changes may remain subclinical or lead to clinical manifestations, i.e., functional failure of peripheral nerves. Whereas the subclinical processes appear to be related to the general consequences of prolonged coma–perhaps with metabolic factors involved–additional damage is assumed to be responsible for the changes leading to clinical manifestations. External compression is assumed to be the predominant additional cause.

Reprint from

Monographien aus dem Gesamtgebiete der Psychiatrie / Psychiatry Series
Vol. 14 / The Apallic Syndrome

Springer-Verlag
Berlin Heidelberg New York