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DEFICIENCY WITHIN THE EXTRINSIC PROTHROMBIN ACTIVATOR SYSTEM IN PATIENTS WITH ACUTE SPINAL CORD INJURY

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LIVER metabolic functions and endocrine activity are known to be affected by spinal cord injury to various degrees (O'Connell *et al.*, 1953). Several authors (Lloyd *et al.*, 1964) have reported on negative nitrogen balance with surprisingly low albumin fractions and depressed adrenal functions, especially in the acute post-traumatic stage. Impaired liver functions may be noticed at the same time (Cooper *et al.*, 1950) while endocrine disorders resulting in gynecomastia, testicular atrophy, decreased metabolic rate and low urinary output of steroids are findings that are usually related to a chronic stage beginning five to six months after the lesion. No satisfactory physio-pathological explanation has as yet been offered that correlates level and type of lesion with intensity and pattern of metabolic disturbances. Similar difficulties also arise when one attempts to dissociate possibly direct effects of spinal cord lesion from disorders secondary to non-specific trauma and immobilization.

Frequent findings of subnormal levels of vitamin-K dependent plasma factors II, VII and X, both in acute para- and tetraplegics, retained our interest and motivated the present investigation. Much of our actual knowledge concerning the effect of vitamin K upon the above-mentioned plasma factors has been derived from animal experimentation (Martius, 1967). In fact, there exist no practical and reliable methods for direct assessment of this vitamin in man. Information on its endogenous synthesis, assimilation, tissue accumulation and excretion is therefore still fragmentary.

Evidence has accumulated indicating considerable variation in the response of healthy individuals to oral or parenteral vitamin K (Zieve *et al.*, 1969). These variations may be attributed to several factors such as modifications in receptor site affinity within the hepatic tissue or fluctuations in the rate of synthesis and release of vitamin K dependent clotting factors. Recent investigations (Frick *et al.*, 1967) indicate that minimal daily requirements of vitamin K_1 for normal prothrombin complex activity hardly exceed 0·03 μg./kg. It is also known that in the absence of endogenous bacterial synthesis there exist sufficient tissue reserves of vitamin K to assure normal synthesis of dependent clotting factors for at least three to four weeks (Frick *et al.*, 1967).

Individual variation in sensitivity towards vitamin K has been reported by several hematologists (Quick, 1963) in patients previously well controlled on fixed daily doses of coumarin derivatives and who subsequently received a vitamin K

enriched diet. Some evidenced rapid and striking reversal of the anticoagulant effect while others showed only moderate antagonism with partial correction of the clotting factors after the same length of time. Coagulation studies in normal volunteers have shown that hepatic synthesis of clotting factors begins already within six hours after the oral administration of 2·5 to 5 mg of vitamin K. However, there exist considerable differences in the rate of synthesis from one person to another (Douglas, 1962).

These introductory remarks concerning normal healthy subjects should be borne in mind before we discuss some of the factors which are possibly responsible for hypoprothrombinemic states in para- and tetraplegics with recent injury to the cord.

CLINICAL RECORDS

Routine screening tests comprising Quick's one-stage prothrombin time (Rapaport *et al.*, 1960) were carried out in 94 patients recently admitted to the Paraplegic Centre of Geneva State Hospital.

Moderate to severe deficiency within the extrinsic prothrombin activator system was found in 61 cases (82·2 per cent). As evidenced by further analysis, this deficiency was essentially related to subnormal levels of vitamin K dependent clotting factors VII and X; factor V, which may be regarded as an indicator of normal hepato-cellular function (Rapaport *et al.*, 1960; Satake, 1963), was slightly affected in five cases only (5·3 per cent).

All patients have been analysed with regard to their sex, age, level and type of lesion as well as lapse of time between the spinal cord injury and laboratory assessment of prothrombin activity. After eliminating 14 cases with a former history of slight hepatic dysfunction or intestinal disorders and another group of 42 patients, receiving medication possibly interfering with coumarine-like anticoagulants, we retained 26 para- and 12 tetraplegics for our investigation. Their average age at the onset of the study was 33½ years (Table).

Among the 26 paraplegics, seven had complete flaccid lesions, 11 complete and eight incomplete spastic lesions. Among the 12 tetraplegics, nine had complete and three incomplete spastic lesions. Considering the relatively small number of cases that remained after initial pre-screening, neither the level nor type of lesion can be safely related to the coagulation defect. The same also applies to the time interval between the onset of the lesion and the discovery of abnormally low prothrombin complex activity. In 31 cases factor VII and X deficiency was evidenced within the first month after injury while the patients were either still in a state of spinal shock or just recovering some reflex activity. In the remaining seven cases the clotting defect became apparent between the fourth and sixth week after the lesion. The physiopathological mechanism responsible for the above-mentioned modifications of the clotting mechanism appears to be of a rather complex nature since it affects both spastic and flaccid, complete and incomplete cases with traumatic spinal cord injury.

Occasionally similar observations can be made in the chronic state, *i.e.* more than six months after the lesion. However, on statistical grounds these findings are not significant.

TABLE—Coagulation studies

Case No.	Age (years)	Level and type of lesion	Before treatment			Vitamin K oral (30 mg. daily for 4 days)			Vitamin K i.v. (20 mg. daily for 3 days)		
			Quick	V	VII + X	Quick	V	VII + X	Quick	V	VII + X
		Complete flaccid paraplegia									
1	39	L3-L4 bilateral	75	100	65	100	—	—	—	—	—
2	43	Th12-L1 right/L2-L3 left	45	100	20	60	100	55	100	—	—
3	22	L3-L4 bilateral	70	90	35	70	—	—	100	—	—
4	40	L4 right/L2-L3 left	80	—	—	80	—	—	90	—	—
5	42	Th2-Th3 bilateral	80	100	60	90	—	—	—	—	—
6	21	Th11-Th12 bilateral	65	—	60	65	100	70	100	—	—
7	24	L4-L5 bilateral	70	—	—	75	—	—	90	—	—
		Complete spastic paraplegia									
8	21	Th5 bilateral	55	100	65	60	—	—	100	—	—
9	23	Th10-Th11 bilateral	80	100	70	100	—	—	—	—	—
10	56	Th7-Th8 bilateral	60	100	50	55	100	60	90	—	—
11	42	Th5 bilateral	65	—	—	60	—	—	100	—	—
12	18	Th7 bilateral	70	80	65	80	—	—	100	—	—
13	25	Th8-Th9 bilateral	80	100	70	100	—	—	—	—	—
14	20	Th4-Th5 bilateral	65	—	—	70	—	—	100	—	—
15	38	Th4-Th5 bilateral	65	100	45	65	100	50	100	—	—
16	21	Th8 bilateral	80	100	70	100	—	—	—	—	—
17	28	Th11-Th12 bilateral	55	80	60	60	100	55	100	—	—
18	18	Th10-Th11 bilateral	50	100	35	65	—	—	90	—	—
		Incomplete spastic paraplegia									
19	25	Th4-Th5 bilateral	80	100	60	85	—	—	—	—	—
20	39	Th6 bilateral	60	—	40	70	—	—	100	—	—
21	14	Th4-Th5 bilateral	20	100	50	60	—	—	90	—	—
22	49	Th5-Th6 bilateral	65	90	50	—	—	—	100	—	—
23	59	Th5-Th6 bilateral	75	—	—	80	—	—	—	—	—
24	56	Th4-Th5 bilateral	80	75	—	85	—	—	—	—	—
25	40	Th11 bilateral	65	100	70	100	—	—	—	—	—
26	61	Th5 bilateral	80	100	75	100	—	—	—	—	—
		Complete spastic tetraplegia									
27	33	C5 bilateral	75	70	85	75	70	80	70	65	60
28	26	C6 bilateral	70	100	60	100	—	—	—	—	—
29	46	C7-C8 bilateral	60	90	—	70	—	—	100	—	—
30	32	C6-C7 bilateral	70	100	65	70	—	—	95	—	—
31	19	C7 bilateral	80	100	70	100	—	—	—	—	—
32	25	C6-C7 bilateral	65	60	50	70	—	—	65	60	55
33	45	C7-C8 bilateral	50	100	45	60	100	50	90	—	—
34	40	C7-C8 bilateral	75	100	—	65	100	55	100	—	—
35	53	C5-C6 bilateral	65	90	50	60	—	—	100	—	—
36	20	C6-C7 bilateral	80	100	—	100	—	—	—	—	—
		Incomplete spastic tetraplegia									
37	27	C6-C7 right/C7-C8 left	65	100	70	70	100	65	90	—	—
38	19	C4-C5 bilateral	75	100	60	80	—	—	100	—	—

Normal range—Quick: 80-100 per cent; Factor V: 80-110 per cent; Factors VII + X: 80-110 per cent.

METHODS OF INVESTIGATION AND RESULTS

The following tests have been carried out on all patients with spontaneous subnormal levels of prothrombin complex activity: complete hemogram; liver function tests; electrophoresis of plasma proteins; thrombelastogram; Quick's one-stage prothrombin time (Quick, 1963); Bachmann's method (Bachmann *et al.*, 1957) for combined dosage of factors VII and X; Dacie-Lewis (Dacie *et al.*, 1963) test for assessment of factor V; complete analysis of the feces.

Correction of factor VII and X deficiency was first attempted by oral administration of high doses of Konakion, a water-soluble, synthetic preparation of vitamin K. The patients received 30 mg. per day on four consecutive days. Reevaluation of the clotting factors 24 hours after the last dose showed total correction in nine (25 per cent), partial improvement in two (5·5 per cent) and no effect in 25 (69·5 per cent) of the cases. Considering the possibility of deficient intestinal resorption, we thereupon treated all 25 refractory cases intravenously with 20 mg. of Konakion per day on three consecutive days. Normalisation of factors VII and X was subsequently observed in 23 cases; two patients only showed no response to intravenous vitamin K. In order to avoid possible drug interactions, no other medication was given throughout the trial. No particular restrictions were made concerning the patient's diet. Besides a fairly regular tendency towards moderate hypoalbuminemia and hyper-alpha-1-globulinemia, all other parameters, such as liver function tests, TEG-curves and chemical and microscopic analysis of the stools, gave invariably normal results.

DISCUSSION

Quick's one-stage prothrombin time expresses the combined activity of factors V, VII and X. Among these, factor VII and X have many physical and chemical properties in common: they both are present in normal serum, stable at room temperature, destroyed at 56°C, adsorbed by aluminium hydroxide and barium sulphate and dependent upon the presence of vitamin K. Their differentiation is, however, possible through their different coagulation properties. Thus, factor VII is not required for intrinsic thromboplastin formation while factor X is essential. From a practical point of view, such differentiation has hardly more than an academic interest, all factors tending to decrease together in acquired deficiency states. Isolated marked deficiency of either one factor is rare and usually genetically determined.

Subnormal levels of vitamin K dependent factors may be encountered in various situations such as during the neonatal period, in cases with hepatic insufficiency (Butt *et al.*, 1938; Warner *et al.*, 1938) or intestinal malabsorption (Moore *et al.*, 1956) and evidently during treatment with coumarin-indanedione anticoagulants. The effects of oral anticoagulants may, as it is well known, be potentiated by a large number of substances: oral administration of large-spectrum antibiotics is likely to alter the intestinal flora and to prevent sufficient endogenous synthesis of vitamin K; other drugs, such as prophylthiouracyl, phenylbutazone and salicylic acid prevent its normal action within the hepatocyte probably through their competitive combination with the apoenzyme.

Little is as yet known about the potentiating effect of clofibrate, a hypolipemic agent, and about the anabolic steroids which also have been shown to influence

the plasma levels of factors VII and X. Chronic infection and hyperpyrexia may lower the prothrombin complex because of higher requirements and a more rapid turn-over of the vitamin (Wilson *et al.*, 1940). Vitamin K being a liposoluble substance, its intestinal absorption may be interfered with in the event of steatorrhea or prolonged diarrhoea. In spinal cord injury patients, regular absorption of paraffin oil during bowel training may interfere with normal intestinal uptake of vitamin K, the latter remaining bound to the mineral oil. Occasionally patients on prolonged parenteral feeding show signs of vitamin K deficiency which may gradually worsen due to concomitant insufficient endogenous synthesis (Berthoud *et al.*, 1966).

In our final group of 36 patients all these aetiological factors have very carefully been ruled out. Since normalisation of prothrombin complex activity could be achieved either by very high oral or low intravenous doses of vitamin K in all but one of our cases, there presumably exists an intestinal barrier for the resorption of lipo-soluble material. Clinical and laboratory investigations with tritium-labelled vitamin K would allow for a more refined analysis of the exact mechanism underlying factor VII and X deficiency in acute spinal cord injury.

Summary

Routine laboratory investigations carried out in 94 cases with acute spinal cord injury indicated moderate to severe deficiency within the extrinsic prothrombin activator system in 82·2 per cent of the patients. The clotting defect could be shown to be related to subnormal levels of vitamin K dependent plasma factors VII and X. There were 25 drop-outs in this study due to drug interference, irregular administration of vitamin K, intercurrent disease, etc. In the remaining group of 36 patients, none of the common etiological factors of acquired hypoprothrombinemia could be incriminated—such as poor intestinal resorption due to lack of bile salts, hepato-biliary disease, broad-spectrum oral antibiotherapy, drug interaction, hyperpyrexia, prolonged parenteral feeding, etc. In nine (25 per cent) of the cases total correction of factors VII and X was achieved after oral administration of vitamin K; in two (5·5 per cent) partial correction was similarly attained; in the remaining group of 25 (69·5 per cent) who proved to be resistant to oral vitamin K all but two normalised their factors after intravenous administration of the vitamin. These observations support the hypothesis that in acute spinal cord injury intestinal uptake of lipo-soluble substances may temporarily be impaired.

Résumé

Les examens de laboratoire de routine effectués chez 94 patients atteints d'une lésion médullaire aiguë ont révélé l'existence d'une déficience modérée à sévère du système extrinsèque de l'activation prothrombinique dans 82,2% des cas. Il s'est avéré que ce défaut de la coagulation était lié à un taux particulièrement bas de facteurs vitamino-K-dépendants VII et X. 25 patients ont dû être éliminés de cette étude à cause d'une interaction médicamenteuse, d'une administration irrégulière de la vitamine K ou d'une maladie intercurrente. Dans le groupe restant, comportant 36 patients, aucun des facteurs étiologiques habituels d'une hypoprothrombinémie acquise n'a pu être retenu,—tel qu'une mauvaise résorption intestinale due à un manque de sels biliaires, une affection hépato-biliaire, l'antibiothérapie à large spectre par voie orale, une éventuelle interaction médicamenteuse, une alimentation par perfusion i.v. pendant un long laps de temps, etc. Dans neuf cas (25%), l'administration orale de vitamine K a permis d'obtenir une correction totale des facteurs VII et X; dans deux autres cas (5,5%), une correction partielle a pu être

enregistrée. Parmi les 25 patients, (69,5%) restés réfractaires au traitement oral tous, sauf deux, ont entièrement corrigé leurs facteurs après l'administration intraveineuse de la vitamine. Ces observations appuient l'hypothèse salon laquelle la résorption intestinale de substances liposolubles serait temporairement inhibée en cas de lésion médullaire aiguë.

ZUSAMMENFASSUNG

In routinemässig durchgeführten Laboruntersuchungen an 94 Patienten mit akuter Querschnittslähmung wurde in 82,2% der Fälle eine mittelschwere bis starke Störung des externen Prothrombinaktivator-systems festgestellt. Der betreffende Koagulationdefekt konnte in Verbindung gebracht werden mit subnormalen Plasmawerten der vitamin-K-abhängigen Faktoren VII und X. 25 Patienten mussten aus der Untersuchung ausscheiden infolge von Arzneimittelinterferenzen, zusätzlichen Krankheitsgeschehen, unregelmässiger Verabreichung von Vitamin K, usw. In den übrigen 36 Fällen konnte keine der üblichen Aetiologien erworbener Hypoprothrombinämia nachgewiesen werden,—wie z.B. schlechte Darmresorption bei Mangel an Gallensalzen, Hepatopathien, Verordnung oraler Breitbandantibiotika, Arzneimittelinterferenzen, Hyperpyrexie, langfristige, exklusio parenterale Ernährung, usw. In neun Fällen (25%) konnte mit oraler Verabreichung von Vitamin K eine totale, in zwei weiteren (5,5%) eine partielle Korrektur der Faktoren VII und X erzielt werden. Die übrigen 25 Patienten (69,5%), welche auf diese Therapie nicht ansprachen, normalisierten die betreffenden Faktoren,—mit 2 Ausnahmefällen, nach intravenöser Injektion von Vitamin K. Diese Beobachtungen unterstützen die Hypothese, wonach bie akuten Querschnittsläsionen die Darmresorption fettlöslicher Stoffe vorübergehend gestört sein kann.

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