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Reversibility of Neurological Deficits in Vitamin B_{12} Deficiency

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Summary. A female patient with subacute neurological deficits secondary to an hereditary vitamin B_{12} deficiency was repeatedly examined clinically and neurophysiologically. It is concluded that neurological normalization after treatment with vitamin B_{12} also occurs within the CNS. Such normalization takes place soon after initiating treatment and probably reflects other neuronal mechanisms than remyelination, i.e. recovery from conduction block in fast somatosensory pathways and/or improvement of synaptic transmission.

Key words: Vitamin B_{12} – Subacute combined degeneration of spinal cord – Visual evoked responses – Sensory evoked responses – Motor and sensory nerve conduction velocities – Neurological restitution

Introduction

Cyanocobalamin (vitamin B_{12}) is essential for the function and structural integrity of the nervous system. Deficiency, usually associated with pernicious anaemia, is characterized in terms of pathology by necrotic foci particularly in the lower cervical and upper thoracic regions of the spinal cord and by degeneration of long tracts (Brain and Walton 1969). Similar morphological changes have been described in the cerebral white matter (Adams and Kubik 1944). Disturbances of peripheral nerve function due to fragmentation of myelin sheaths and degeneration of axones add to the symptomatology of spinal cord and cerebral dysfunction.

In case of deficiency an adequate supply of vitamin B_{12} may certainly reverse the damage inflicted upon peripheral nerves. Prognosis with respect to lesions within the CNS is generally considered less favorable although the electroencephalographic abnormalities may disappear (Strachan and Henderson 1965) and spinal cord function may to some extent be restored (Brain and Walton 1969).

In the present case the reversibility of neurological deficits secondary to vitamin B_{12} deficiency was examined clinically and neurophysiologically.

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Case Report

A 59-year-old female with a history of recurrent depressions, had otherwise been in perfect health. Her family history was initially reported as unremarkable but subsequently it proved to be very much the opposite. Thus, her father died at the age of 83 from "amyotrophia", and one sibling died supposedly from leukemia at a very young age. Two sisters, still alive, have suffered from recurrent depressions; one has been treated with vitamin B_{12} since 1970 after which she has been mentally well. The other sister has been taking vitamin B_{12} supplement only for the last year.

On June 10, 1980, our patient was involved in an automobile accident and was brought to the nearby hospital in hemorrhagic shock. An exploratory laparotomy revealed massive intraperitoneal bleeding due to lacerations of the spleen. Splenectomy was performed and peroperatively she received four units of packed red cells. Postoperatively, a left-sided hemothorax was drained. Her condition stabilized and she was discharged 10 days after the accident. At that time she felt unsteady and complained of numbness in the hands and feet, and 3 weeks later the sensory symptoms had worsened and touch appreciation was altered up the thighs and lower abdominal regions. A couple of weeks later she complained of pronounced paresthesias in the hands and experienced radiating paresthesias down her back and legs on bending her head forward (Lhermitte's symptom). She easily dropped things and noticed an increasing weakness in her hands along with difficulty when walking. She had not suffered any particular pain though X-rays of the lower thoracic spine revealed a compression fracture of the vertebra Th XII. Plain X-rays of the cervical spine were normal.

Because of the worsening symptomatology the patient was admitted to the Department of Neurology, Lund. Somatic examination revealed abnormal pigmentation of the palmar folds and a marginal glossitis. Mentally there were no abnormalities, and cranial nerve functions were normal. She was uniformly weak and the distal extremity muscles were hypotrophic, stance was insecure and gait broad-based and atactic. Finger-to-nose and knee-to-heal tests showed symmetrical ataxia, and joint and vibration senses were uniformly defective with astereognosis predominantly in her right hand. Other sensory modalities were less affected. In the arms the stretch reflexes were normal while in the legs they were weak or absent. The plantar responses were flexor bilaterally and sphincter functions were normal.

Laboratory findings were as follows: sedimentation rate 25–40 mm/h, hemoglobin 110–120 g/l, red cell count 3.16–3.43 $10^6/mm^3$, mean corpuscular volume 105–106 μ^3, hematocrit 33.8%–36.5%. The bone marrow did not show any megaloblastic features although serum cyanocobalamin was 60 pmol/l (normal range for our laboratory: 110–650 pmol/l) and the folate concentration was 60 nmol/l in whole blood (normal range: 70–200 nmol/l). There was complete achlorhydria and parietal cell antibodies were present. Otherwise an extensive laboratory investigation was normal.

In the cerebrospinal fluid cytology was normal as was the protein content (0.52–0.57 g/l) with a normal ratio between immunoglobulins and albumin. Agar gel electrophoresis did not reveal any oligoclonal bands of immunoglobulins. The Queckenstedt test indicated free passage within the spinal canal.

The patient was subjected to a complete contrast (Amipaque) myelogram. Corresponding to the disc CV–CVI a protrusion was seen which to a minor extent compressed the spinal cord in the sagittal plane.

Neurophysiologial Examinations. The neurographical examinations were performed using a DISA 1500 equipment. Before the examinations the patient was warmed with heat pads until the skin temperature was 30° C. The neurographical parameters determined are listed in Table 1. Motor conduction velocities were measured in four limb nerves on the right side. The compound muscle action potentials were recorded with surface electrodes from distal muscles (thenar, hypothenar, extensor digitorum brevis and abductor hallucis) and the position was adjusted so that the initial component of the muscle response to nerve stimulation showed a monophasic negative phase. The nerves were stimulated supramaximally at the wrist-elbow and ankle-knee, respectively.

The sensory conduction velocities of the ulnar and median nerves were determined by surface recording at the wrist (inter-electrode distance 2.5 cm) with electrical stimulation of

Table 1. Peripheral neurography

	21-08-1980	05-11-1981	Δ
Motor conduction velocity (m/s)			
Ulnar	53.5	58.1	+4.6
Median	53.5	52.5	−1
Peroneal	41.0	47.5	+6.5
Posterior tibial	38.0	40.0	+2.0
Sensory conduction velocity (m/s)			
Ulnar	37.5	50.0	+12.5
Median Dig I	33.5	47.0	+13.5
Median Dig III	41.5	52.5	+11.0
Sural	—	—	—
Sensory nerve action potential (μV)			
Ulnar	8	11	+3
Median Dig I	12	22	+10
Median Dig III	9	15	+6
Sural	—	—	—

Table 2. Psychophysical thresholds

	21-08-1980	05-11-1981	Δ
Vibration threshold (μm)			
Carpus	3.6	0.3	−3.3
Tibia	>20	9	
Warm-cold difference limen (° C)			
Cheek	4.5	1.5	−3
Hand	2.0	2.0	0
Foot	8.0	3.0	−5

the 5th, 3rd and 1st fingers respectively, at strengths supramaximal for the large afferent fibers (approximately 15 mA). In addition to the conduction velocities the response amplitudes were determined. The sural nerve action potential was recorded antidromically at the lateral malleolus by stimulation of the distal calf with surface electrodes.

Psychophysical thresholds to 100 Hz vibrations were determined according to Goldberg and Lindblom (1979) and expressed as vibration amplitudes in μm at carpus and pretibially (Table 2). Warm-cold difference limens were determined for cheek, thenar and lateral edge of the foot (Table 2) according to Fruhstorfer et al. (1976).

Sensory evoked responses (Table 3) were recorded from four channels simultaneously (C3, P3, C4, P4) with a midfrontal electrode as a reference (filter frequencies 0.5–300 Hz) on stimulation (10 mA, pulse duration 0.3 ms) of the thumb by ring electrodes. Averages of 100 stimuli at randomized stimulation frequency (mean 1 Hz) were computerized in a special purpose computor (Brainlab, Digitial). Sensory-evoked responses to sural nerve stimulation were recorded from Cz relative to a frontal reference electrode. The stimulus (10 mA, 0.3 ms pulse duration) was applied immediately behind the lateral malleolus.

Visual evoked responses (Table 4) to pattern reversal stimulation by checker board or dot light emitting diodes were recorded using the stimulation and recording techniques described elsewhere (Bynke et al. 1980).

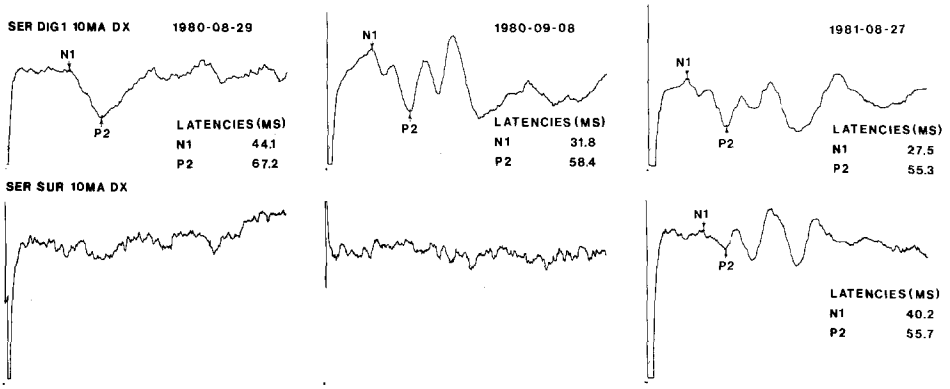

Fig. 1. *Upper row:* Somatosensory evoked responses recorded from the left parietal region (P3-ref. midfrontal electrode) on stimulation of the right thumb. For further details, see text. Note early marked reappearance of early as well as late components of the response. The same time and voltage scale was applied for the three records. *Lower row:* Somatosensory evoked responses recorded from the mid-central region (Cz-ref. midfrontal electrode) on electrical stimulation of the right sural nerve at the lateral malleolus. Note absence of response at the two first occasions and marked return of response at the third examination. Same time and voltage scale for the three records

Results

The patient was considered to be suffering from vitamin B_{12} and folate deficiency and adequate administration of these vitamins (Behepan, Folacin) was started. There was a marked improvement over several weeks. She was able to walk unaided after 3 weeks at which time gait was considerably normalized. She was discharged with a medication of 1 mg hydroxycobalamin intramuscularly once a week and 5 mg of folic acid perorally daily. She was regularly followed as an outpatient and at follow-up 1 year later her only complaints were numbness below the knees and some minor unsteadiness. Somatic examination was normal and the only persisting neurological abnormalities were slight weakness on dorsiflexion of the left foot, a right-sided missing Achilles reflex and a crossed-upgoing-toe sign (Hindfelt et al. 1976) on the left. Plantar responses remained flexor bilaterally. The warm-cold difference limen as well as the vibration sensitivity in the upper extremity showed a normalization, the pretibial vibration threshold remaining at a pathologically high level (Table 2).

Somatosensory evoked responses were recorded on three different occasions: after 2 days, 12 days and 15 months of treatment (Fig. 1, Table 3). When treatment was started the latency of the N_1 wave was greatly prolonged on stimulation of the right thumb and moderately prolonged on stimulation of the left. No response could be recorded on stimulation of the sural nerves. Even after 12 days of treatment a marked reduction in latency was observed as well as an increase in response amplitude and new response components. After 15 months there was a further normalization of the sensory evoked responses from the arms and reappearance of responses from the lower limbs (Table 3). The visual evoked responses did not change significantly during the observation period (Table 4).

Table 3. Somatosensory evoked responses

	29-08-1980	08-09-1980	27-08-1981
Stimulation site	N_1 N_1-P_2	N_1 N_1-P_2	N_1 N_1-P_2
Thumb, right	44.1 ms / 2.4 μV	31.8 ms / 5.5 μV	27.5 ms / 2 μV
Thumb, left	29.0 ms / 3.5 μV	28.0 ms / 7.4 μV	24.6 ms / 4.1 μV
Suralis, right	No response	No response	40.2 ms
Suralis, left	No response	No response	45.1 ms

Table 4. Visual evoked responses

	15-09-1980	05-11-1981
Left eye,		
checker board	118 ms / 7 μV	118 ms / 9 μV
dots	94 ms / 8 μV	95 ms / 6 μV
Right eye,		
checker board	115 ms / 7 μV	113 ms / 11 μV
dots	90 ms / 6 μV	93 ms / 12 μV

Discussion

The symptomatology, the clinical and laboratory findings and the favourable response to treatment confirmed the diagnosis of neurological defects secondary to vitamin B_{12} (and folate) deficiency. Subsequently, we learned that our patient had a sister who had suffered from vitamin B_{12} deficiency for many years and over the last year yet another sister has developed manifestation of cobalamin deficiency. So evidently, we were dealing with a familial syndrome of vitamin B_{12} deficiency and the traumatic injury only precipitated the rather acute onset of neurological symptoms. Interestingly, these sisters had all suffered from transient psychiatric symptoms i.e. depressions, which may precede the appearance of neurological abnormalities (and/or anaemia) by several years (Holmes 1956). This favors the existence of as yet little understood factors which determine the clinical presentation of vitamin B_{12} deficiency in the individual case (Strachan and Henderson 1965). Heredity is probably of major importance in this respect.

Like most patients with proven vitamin B_{12} deficiency and neurological symptoms she improved considerably over the follow-up period and particularly over the first few weeks after commencement of cobalamin/folate administration. This per se would be compatible with healing of peripheral neuropathy which is reversible. However, the findings in our patient cannot be satisfactorily explained by this alone, as the delay of the initial negative component of the somatosensory evoked responses from the right thumb was approximately 30 ms. This is far too much to be explained by demyelination of the peripheral nerves. Assuming a conduction distance from the thumb to the spinal cord of 0.7 m an increase of the peripheral sensory conduction velocity of approximately 12 m/s

(Table 1) would only reduce the latency of sensory evoked response by 8 to 9 ms (Table 3). This indicates that the normalization also involves transmission along central afferent pathways.

As can be seen from the data (Fig. 1, Table 3) much of the normalization occurs within a few weeks of treatment. A similar phenomenon has been observed for visual evoked responses after acute optic neuritis (Rosén et al. 1979; Bynke et al. 1980). This phase of rapid recovery must reflect a pathophysiological process other than remyelination. Mechanisms to be considered are recovery from conduction block in fast somatosensory pathways and/or improvement of synaptic transmission.

Our patient together with others reported in the literature indicate that vitamin B_{12} deficiency may not only affect the nervous system asymmetrically but also impair certain nervous pathways more than others and this applies in particular to the afferent systems. The optic nerves and/or tracts are frequently affected in pernicious anaemia (Troncoso et al. 1979), especially in cases with other neurological symptoms (Krumholz et al. 1980). Our patient had visual evoked responses within the upper normal range (Bynke et al. 1980) while the somatosensory evoked responses were markedly though asymmetrically affected. Treatment did not affect the visual evoked responses (Table 4) which was in contrast to the normalization of the somatosensory evoked response (Table 3).

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