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LETTER TO THE EDITOR

Knuckle pigmentation, peripheral neuropathy, madness and abnormal movement: is it B_{12} deficiency?

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Dear Sir,

Cobalamine deficiency neurological syndromes are reversible if treated early. Hyperkinetic movement disorder is rarely reported in adults with cobalamine deficiency state, but in infants, they do occur after initiating cobalamine supplementation. The movement disorder is difficult to classify because of the whole of the neuraxis is involved and of the systemic involvement in this metabolic disease. In this communication, we report a case of myoclonus of spinal origin in a patient of cobalamine deficiency who presented with knuckle hyperpigmentation and megaloblastic madness, which reversed after treatment.

Case details

A 38-year-man presented with knuckle hyperpigmentation and behavioural abnormality. He was healthy until 8 months earlier when he noticed hyperpigmentation of both knuckles (Fig. 1), nail fold and distal finger of the hand and foot. After 2 months, he developed progressive behavioural abnormality in a form of depression, increase anger, irritability and inconsolable cry. He was not able to recognise family members, had a decrease in sleep and self-care and had an unsteady gait and involuntary movement of bilateral upper limbs. Once he was detained by police for his abnormal behaviour. The symptom progressed further after 3 days of diarrhoeal illness despite having provided antidepressants by local physician. He was bed-bound, incontinent and disoriented from the last 1 month. He had tremors like movements and purposeless searching and jerky movements during sleep (video 1). He was referred to our institute for his abnormal movements and hyperpigmentation. He has past history of post traumatic psychosis 10 years before that was resolved after 3 months of medications. There was no chronic gastrointestinal disease, and the patient was on a vegetarian diet with insufficient milk intake. In general examination, he was pale, vitals were stable, and there was hyperpigmentation of skin over the fingers and toes. On neurological examination, he was conscious but disoriented, the MMSE score was 10/30, the strength was 5/5, tendon reflexes were brisk except diminished in the bilateral ankle joint and plantar which were flexors. Hypoesthesia and hypoalgesia were present in sock and glove distribution. Vibration and position senses were markedly impaired in the foot. He could not stand or even sit due to ataxia and had urinary retention.

His haemoglobin was 10.9 g%, the MCV 102.37 fl, the reticulocyte count 1.68, the ESR 78 mm/1st hour and peripheral smear revealed hypersegmented neutrophils. Vitamin B_{12} level was 295 pg/ml (normal 211–911), and serum folate and ANA were normal. Bone marrow biopsy was suggestive of megaloblastic changes with reactive lymphoplasmacytosis, and serum protein electrophoresis has no 'M' spike. Electrophysiological examination disclosed motor sensory axonal polyneuropathy, bilateral P100 latency prolonged (118 and 117 ms) and absent cortical potential in tibial SEP. EEG showed generalised theta slowing. MRI spine showed increased T2 signal in the posterior column of the cervical and dorsal spinal cord. Cranial MRI revealed mild diffuse cerebral atrophy. There was no clinical feature of connective tissue or autoimmune disorder. His serum homocysteine and anti-

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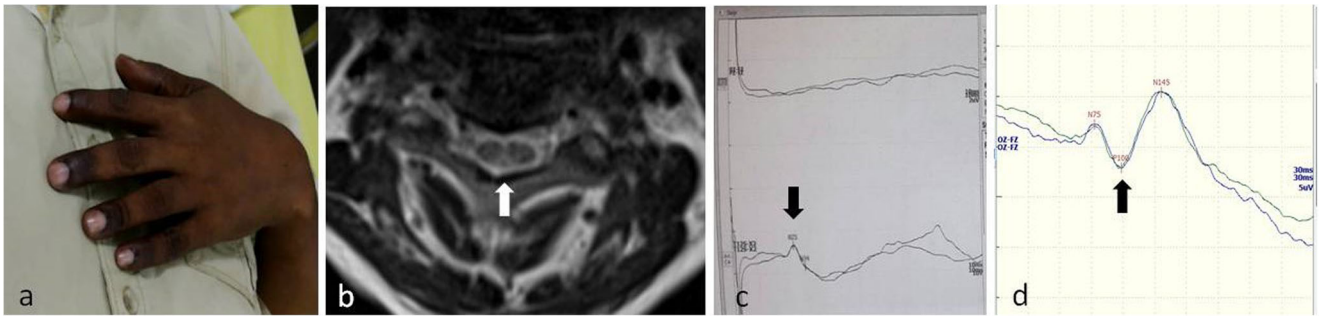

Fig. 1 **a** Knuckle hyperpigmentation. **b** Axial T2W MRI of cervical spine shows hyperintensity in the post column of spinal cord (white arrow). **c** Tibial somato sensory-evoked potential showing absent cortical potential with normal recording of lumbar potential (black arrow). **d** Visual evoked potential showing prolonged P100 latency of the right eye (118 ms) (black arrow)

parietal cell antibody were not done due to financial constraint. He was managed with 1000-μg vitamin B_{12} intramuscularly daily for 7 days followed by alternate days and then twice weekly. His behavioural symptoms improved significantly, he was able to walk independently, and hyperpigmentation and involuntary movements decreased; MMSE score was 26/30. His blood report revealed increased reticulocyte count (4.0) and EEG was normal and he was discharged after 2 weeks of cobalamine supplementation (video 2). At 3-month follow-up, he was normal with minimal paresthesia at the foot and joined his duty. His peripheral neuropathy improved at 5 months.

Discussion

The clinical and laboratory features of our patient were comparable with vitamin B_{12} deficiency. The atypical features were knuckle hyperpigmentation, megaloblastic madness and involuntary movements which reversed rapidly on B_{12} supplementation. Knuckle hyperpigmentation has been observed in about 19.0% of patients with megaloblastic anaemia and sometimes may be the only marker of vitamin B_{12} deficiency [1]. It is due to reduced intracellular glutathione leading to increased melanin synthesis as well as some degree of melanocyte pigmentary incontinence. Hyperpigmentation reverses with supplementation of vitamin B_{12} [2]. Involuntary movements occur in infants with congenital cobalamin deficiency; the phenomenology varies from tremors, twitches, chorea, and myoclonus which vary in intensity and timing [3, 4]. Some of these hyperkinetic movement disorders persisted in sleep as in the present case. Cobalamine deficiency–associated movement disorder is rare in adults and occurs after supplementation of B_{12} in infants [5]. It is difficult to classify the movement disorder in the present case which occurs prior to cobalamine supplementation; however, the pattern resembles more of myoclonus of spinal origin as it persisted during sleep. The pathophysiology may be attributed to myelopathy. Denervation hypersensitivity is the possible explanation of these movements in infants on cobalamine supplementation; however, the vitamin B_{12} dependency in the mature nervous system needs further evaluation. The present case demonstrated sequential manifestations of symptoms, i.e. knuckle hyperpigmentation, behavioural abnormality and movement disorder which suggest duration and severity of cobalamine deficiency and derangement in cobalamine-associated enzymatic reactions. There is no gold standard test for the diagnosis of cobalamine deficiency. Functional cobalamin deficiency can occur at any serum level. So, in appropriate clinical settings of vitamin B_{12} deficiency neurological syndromes, vitamin B_{12} metabolites may be helpful in diagnosis [6].

In conclusion, knuckle hyperpigmentation, behavioural abnormality and abnormal hyperkinetic can occur in an adult with cobalamine deficiency. Early diagnosis and supplementation of vitamin B_{12} reverse the symptoms. The pathogenic mechanism and the nature of the movement disorder need further research.

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Authors' contribution SKB: study concept, data acquisition, manuscript writing and critical reviewing
MJ: data acquisition and patient management
SN: data acquisition, manuscript writing and critical reviewing
GDP: data acquisition and patient management

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from the patient included in the study. "Additional informed consent was obtained the patient for whom identifying information is included in this article."

Research involving human participants and/or animals For this type of study (case report), formal consent is not required.

Abbreviations MCV, mean corpuscular volume; ESR, erythrocyte sedimentation rate; ANA, anti-nuclear antibody; SEP, somatosensory-

evoked potential; EEG, electroencephalogram; MRI, magnetic resonance imaging; MMSE, mini mental state examination

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