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NEUROLOGIC FINDINGS OF VITAMIN B_{12} DEFICIENCY: PRESENTATION OF 7 CASES*

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SUMMARY: Kalaycı Ö, Çetin M, Kırel B, Özdirim E, Yetgin S, Aysun S, Gürgey A. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Neurologic findings of vitamin B_{12} deficiency: presentation of 7 cases. Turk J Pediatr 1996; 38: 67-72.

In this report, seven children, four males and three females, between the ages of five and 16 years with megaloblastic anemia and neuropsychiatric disorders are presented. Macrocytosis was identified in peripheral blood smears in all seven patients. Serum B_{12} levels were markedly reduced in four and were at the lower limit of normal in three patients. The Schilling test showed that B_{12} deficiency was due to specific cobalamin malabsorption in five and to inadequate dietary intake in two patients. Both neurological and hematological findings returned to normal after B_{12} replacement. This study shows that B_{12} deficiency should be considered in the differential diagnosis of neuropsychiatric disorders in children, including those with nonvegetarian habits, and that such patients should undergo a thorough hematological evaluation. *Key words: B_{12} deficiency, megaloblastic anemia, neurological disorders.*

Neuropsychiatric disorders are a well recognized aspect of cobalamin deficiency and may occur even in the absence of anemia, especially in adulthood[1,2]. However, neurological findings are considered a late manifestation of the disease, and thus reports concerning children are rare. Most reports concern infants whose mothers are strict vegetarians[3-5]. Seven children followed at Hacettepe Children's Hospital with megaloblastic anemia due to specific cobalamin malabsorption or dietary deficiency, who also had neurological findings are presented. This report shows that cobalamin deficiency should be considered in the differential diagnosis of neuropathies and neuropsychiatric disorders in children even of non-vegetarian families, and that such patients should undergo a thorough hematological evaluation.

Material and Methods

Between 1978 and 1993, seven out of 56 patients diagnosed with megaloblastic anemia resulting from vitamin B_{12} (VB_{12}) deficiency had neurological symptoms on admission to Hacettepe Children's Hospital. Diagnosis of megaloblastic anemia

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was made on the basis of macrocytosis in the peripheral blood smear, megaloblastic changes in precursor cells in bone marrow and a decreased serum VB_{12} vlaue. All patients were treated with intramuscular VB_{12}, 100 µg daily for two weeks, every other day for another two weeks, and once monthly thereafter. The diagnostic criterion for Imerslund Grasbeck Syndrome (IGS) was specific VB_{12} malabsorption shown in the Schilling test in the absence of any malabsorption syndrome. A detailed dietary history was taken in all cases. The Schilling test was performed between three weeks and three months after initiation of therapy.

A summary of some of the clinical and laboratory findings is given in Tables I, II and III. In Case 3, from the past history it was learned that one year previously the patient had been evaluated for persistent proteinuria in the Department of Pediatric Nephrology of the same hospital; during that time a kidney biopsy was performed from the propositus, and pathological changes on light microscopy were compatible with Alport Syndrome. Five months prior to admission the patient developed ataxia. A day before admission, persistent projectile vomiting started. The family history revealed that she was the second product of a marriage between cousins. The mother had undergone transplantation due to chronic renal failure, while the father, one paternal aunt and one maternal uncle had hearing problems. Hematologic examination of the parents and siblings revealed no abnormalities. Hematological data and the Schilling test result are given in Table III.

Table I: Summary of Selected Clinical Features

Case	Age/Sex (years)	Complaints on Admission	Duration of Complaint (years)	Previous Treatment	Etiology	Recovery* Period (months)
1	12/M	Weakness	9	Blood trans.	IGS	2
2**	15/M	Pallor, weakness	4	Oral iron Blood trans.	IGS	2
3	5/F	Vomiting, gait abnormalities	2	Oral iron	IGS + Alport's Syndrome	3
4	13/M	Tingling in hands and feet	7	Blood trans.	IGS	3
5**	16/M	Pallor	5	Oral iron Folic acid, Blood trans.	IGS	6
6	15/F	Ataxic gait Tingling in lower extremities	6 month	—	Dietary VB_{12} def.	2***
7	12/F	Pallor, weakness	10	—	Dietary VB_{12} def.	1 week

* Neurological findings.
** Two patients were siblings.
*** Still on therapy at the time of submission.
trans : transfusion, IGS : Imerslund-Grasbeck Syndrome, def : deficiency.

Table II: Physical and Neurological Findings of Patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Physical Findings							
Pallor	+	+	+	+	+	−	+
Growth ret.	−	−	−	−	−	−	+
Glossitis	+	+	−	+	+	+	−
Neurologic Symptoms and Findings							
Hyperesthesia	+	−	−	−	+	+	−
Tremor	+	−	−	−	−	−	−
Muscular pain	+	−	−	−	−	−	−
Basinski	+	−	−	−	+	−	−
Clonus	+	−	−	−	−	−	−
Memory loss	−	+	−	−	+	−	−
Diminished Vibration sense	−	−	−	+	+	+	−
Diminished position sense	−	−	−	+	−	+	−
Ataxia	−	−	+	−	−	+	−
Double vision	−	−	−	−	−	−	+
Agitation	−	−	−	−	−	−	+
Hallucinations	−	−	−	−	−	−	+
Paresthesia of the hands and feet	−	−	−	+	−	−	−
DTR*	I	N	N	N	I	I	N

* DTR: deep tendon reflex, N: normal, I: increased.

Case 7 was diagnosed with megaloblastic anemia at the age of seven years. Her past history revealed that pallor was first noted when she was two years old but no medical advice was sought. The patient was treated with VB12 and discharged from the hospital. At the age of 12 years this patient came to our clinic with severe megaloblastic anemia and she complained of double vision which was followed immediately by a hard-to-control agitation and visual hallucinations without a gross motor deficit. From the history it was learned that the patient had discontinued VB_{12} after discharge and had not received any therapy during the past five years.

Table III: Selected Laboratory Findings of Patients

	Case						
	1	2	3	4	5	6	7
Hb (g/dl)	4.8 (11.3)	6 (12.9)	7 (12.6)	4.2 (12)	8.2 (13.2)	10.5 (13.4)	3.5 (12.8)
Htc (%)	11 (33)	20 (37)	21 (37)	13 (36)	26 (38)	31 (41)	9 (36)
Rct (%)	1 [12.6][b]	0.4 [14]	0.6 [8.2]	1 [11]	0.4 [3.4]	0.2 [8]	4.6 [15.6]
Leukocyte (/mm^3)	2400 (5200)	3500 (4200)	3000 (5200)	2800 (5600)	4000 (4800)	5200 (5600)	4800 (5200)
Platelet (/mm^3)	340.000	220.000	200.000	310.000	320.000	330.000	91.000
MCV (fl)	95 (81.4)	117 (83.2)	125 (82)	104 (84)	115 (86.2)	129.3 (86)	103.2 (83.2)
Vit B_{12} (pg/ml)	42	258	225	42	213	80	< 20
Folic acid (ng/ml)	8.4	7.49	8.5	4.95	8.6	9.1	8.11
58Co (%)	1	5.8	0.6	4	5.4	21	12.4
57 Co + IF (%)[c]	0	5.3	0.8	6.7	5.3	21	14
Serum iron	ND	258	ND	ND	322	132	32
Iron binding capacity	ND	242	ND	ND	271	275	275
Ferritin	ND	257.2	ND	ND	198	40	ND
Proteinuria	–	–	+	+	–	–	–
D-Xylose	N	N	N	N	N	ND	ND
Methylmalonic aciduria	–	–	+	–	–	+	–
Serum IgA	ND	D	N	ND	N	N	N
EMG	N	ND	ND	ND	ND	N	ND

a : Numbers in parentheses are values obtained two months after treatment.
b : Numbers in brackets are the maximum of reticulocyte counts on the third day of treatment.
c : Vitamin B_{12}-bound intrinsic factor.
ND : Not determined, D : Decreased, N : Normal, EMG : Electromyography.

Discussion

In this report all seven cases with bone marrow smears typical of megaloblastic anemia responded promptly, both hematologically and neurologically, to VB_{12} replacement. In Cases 1 through 5, the results of the Schilling test showed defective absorption of VB_{12} that cannot be corrected by the addition of intrinsic factor, which is suggestive of Imerslund-Grasbeck syndrome in the absence of growth retardation and abnormal malabsorption tests. Proteinuria, another component of the syndrome in over 90 percent of cases[6-8] was detectable in two of our patients (Cases 3 and 4). Since Case 3 had focal glomerulosclerosis and a family history of chronic renal failure and neural hearing loss, it was thought

that proteinuria might be a symptom of Alport's Syndrome. In Cases 6 and 7 the results of the Schilling tests were normal, indicating dietary deficiency of VB_{12}. It is obvious from the dietary history that the deficiency in both cases is most likely due to inadequate intake. In our study malabsorption syndromes due to VB_{12} deficiency were excluded by performing the Schilling test long after proper treatment.

All of the patients were started on VB_{12} therapy before learning their serum VB_{12} levels. Therefore, we were not able to restudy the serum VB_{12} level in patients whose initial serum VB_{12} level was near the normal level. Complete response to VB_{12} as far as anemia and neurological findings were concerned suggested to us that the diagnosis of VB_{12} deficiency was correct in these patients. Either laboratory error or an error in handling the blood specimens might be responsible for unexpectedly high initial VB_{12} values.

Megaloblastic anemia due to VB_{12} deficiency is rare in children. Although it is well established that B_{12} deficiency may present with neurological findings even without anemia, published reports usually concern cases in adulthood[1,2]. However, the age of onset of neurological findings varies. Infants born to vegetarian mothers are devoid of cobalaminstores at birth, and neurological findings are usually noted early in infancy[3-5] along with anemia. These findings suggest that the developing brain of early infancy is very sensitive to cobalamin deficiency. This deficiency, if unrecognized, may cause permanent neurologic damage in the infant. Neurological findings have also been reported as early as four to five years of age in a patient with specific B_{12} malabsorption[9]. The symptoms of subacute combined degeneration of the spinal cord due to VB_{12} deficiency often begin insidiously; decreased vibration and position sense are usually the first objective manifestations. Therefore in patients with these types of neurological abnormalities, VB_{12} deficiency should be considered.

In six of our patients, on the other hand, anemia preceded the onset of neurological findings by many years. In two patients with dietary deficiency, we do not know exactly when the inadequate intake started. In the cases with Imerslund-Grasbeck syndrome (Cases 1 through 5) cobalamin stores are theoretically depleted by the age of one year. However it took 12-16 years for the neurological symptoms to develop except for in Case 3. These observations may imply that individual differences contribute a great deal to the susceptibility of the brain to cobalamin deficiency, which may account for the difference in ages that neurological abnormalities first appear.

Magnetic resonance imaging and computerized tomography of the brain were available in Cases 5 and 7, and were normal in both cases. Salameh et al.[9], in their report concerning a male child aged four years and nine months, showed

the presence of cerebral atrophy on cranial computerized tomography which reversed completely with treatment. This may suggest that the brain may be affected to a greater extent by cobalamin deficiency in early childhood. In all of these cases, neurological symptoms were easily attributed to B_{12} deficiency because anemia was also evident. However, in childhood it is usually not well appreciated that cobalamin deficiency may present as a neurological syndrome with no hematological component, and thus many children with a true deficiency may go unnoticed. In this report Case 6 had only mild anemia and marked macrocytosis but obvious neurological symptoms, which was the main complaint that prompted the patient to seek medical attention. It is also noteworthy that dietary deficiency may also cause this syndrome in children with nonvegetarian dietary habits.

Since the condition can easily be diagnosed and treated, cobalamin deficiency should be considered a diagnostic possibility in all cases with unexplained neurological findings.

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