PostScript

LETTER

Nutritional infantile vitamin B12 deficiency: pathobiochemical considerations in seven patients

In infants with nutritional vitamin B12 deficiency, early clinical symptoms follow a consistent pattern with irritability, failure to thrive, apathy and anorexia, accompanied by consistent refusal of solid foods and developmental regression. Vitamin B12 acts as a cofactor in the remethylation of homocysteine and the degradation of methylmalonyl-CoA. The biochemical mechanisms by which vitamin B12 deficiency leads to neurological damage are poorly understood. We report on seven breast fed infants with nutritional vitamin B12 deficiency due to maternal vegan diet. Tables 1–3 give clinical, radiological, and laboratory findings. Increased excretion of methylmalonic acid in the urine as well as increased total homocysteine in the plasma were found in all the patients. There was no clear correlation with the severity of acute neurological symptoms. Accumulation of methylmalonyl-CoA is known to interfere with the biosynthesis of lipids needed for myelin sheaths. Delayed myelination was observed in patient 4, and reversible brain atrophy was seen in all patients examined.

Disruption of the methionine cycle and lack of *S*-adenosylmethionine, the most important methyl group donor, may lead to accumulation of neurotoxic guanidinoacetate.[1] We found normal plasma concentrations of guanidinoacetate in three patients examined. It has been speculated in a single case report whether the thermolabile MTHFR polymorphism C677T aggravates neurological damage or leads to delayed recovery by further impairing the folate cycle.[2] Molecular analysis of the MTHFR gene was normal in six of our patients making it impossible to assess the relation to clinical severity or recovery.

The early presentation and adverse outcome in patient 3 would support the

Table 2 Laboratory data of patients

	1	2	3	4	5	6	7
Erythrocytes ((3.7–5.3) × 10^6)	2.71	2.12	3.33	2.57	2.3	1.6	1.95
MCV (70–86 fl)	112.5	89.2	90.4	108	106	88	88.9
Haemoglobin (115–135 g/l)	102	63	101	89	78	61	58
Vitamin B12 (180–914 pg/ml)	<45	<45	113	<45	122	<45	<45
Homocysteine (<14 μmol/l)	120	117	150	–	111	–	65.6
MMA (<25 μmol/mmol creatine)	7663	7500	525	308	5300	383	801
GAA (1.21–4.33 μmol/l)	1.5	1.37	1.46	–	–	–	–
MTHFR mutation	–	–	–	c.h.	–	–	–

Values in parentheses represent age matched controls.
MCV, mean corpuscular volume; MMA, methylmalonic acid; GAA, guanidinoacetate; MTHFR, methylene tetrahydrofolate reductase gene; c.h., compound heterozygous for thermolabile variant C677T and A1298C.

Table 1 Basic and clinical data on seven breast fed infants with nutritional vitamin B12 deficiency due to maternal vegan diet

	1	2	3	4	5	6	7
Sex	Male	Male	Male	Male	Female	Female	Male
Age at onset (months)	5	6	4	6	6	6	9
First symptoms	Failure to thrive, refusal to wean	Failure to thrive, refusal to wean	Focal seizures	Failure to thrive, refusal to wean	Failure to thrive	Failure to thrive	Refusal of solid foods, pallor, weakness
Patient's history	Vomiting, weight loss, constipation	Irritability, muscular hypotonia, loss of milestone	Seizures	Psychomotor retardation, muscular hypotonia	Severe psychomotor retardation	Vomiting, weight loss	Psychomotor retardation
Mother' s diet	Vegan	Vegan	Vegan	Vegan	Vegan	Vegan	Diabetic
Diagnostic delay (months)	7	1	–	5	3	2	3
Age at diagnosis (months)	12	7	4	11	9	8	12
Weight/ length at diagnosis	<3rd centile	<3rd centile	50th centile	<3rd centile	<3rd/10th centile	<3rd centile	50th centile
Presentation at diagnosis	No ability to sit, muscular hypotonia, poor social contact, no vocalisation	Apathy, no ability to sit, muscular hypotonia, poor social contact	Focal seizures	Apathy	Apathy, muscular hypotonia	Apathy	Apathy
MRI at diagnosis	–	–	Mild brain atrophy	Brain atrophy, retarded myelination	Brain atrophy	Brain atrophy	Brain atrophy
EEG at diagnosis	Normal	Normal	Hypsarrhythmia	Moderate diffuse encephalopathy	Normal	–	Normal
Follow up	Improvement of social and motor activity, weight gain	Improvement of social and motor activity, weight gain	Therapy resistant seizures	Improvement of social and motor activity, weight gain	Slow recovery, weight gain	Slow recovery, weight gain	Improvement of social and motor activity, weight gain
MRI follow up	–	–	Brain atrophy	Retarded myelination	Normal	–	Normal
Outcome at age/months	Lost to follow up	Complete recovery /30	West syndrome, mild hemiparesis, no active speech/24	Complete recovery/24	Slight psychomotor retardation, impaired fine motor skills/19	Psychomotor retardation/12	Slight muscular hypotonia/26

MRI, Magnetic resonance imaging; EEG, electroencephalogram.

Table 3 Laboratory data of mothers

	1	2	3	4	5	6	7
Erythrocytes ((4–11) × 10^6)	3.9	–	5.0	–	4.0	3.8	4.3
MCV (80–93 fl)	95.4	–	83.5	–	91	64	88.9
Haemoglobin (120–160 g/l)	122	–	132	–	135	71	122
Vitamin B12 (180–914 pg/ml)	98	212	145	75	232	92	102
Homocysteine (<14 μmol/l)	37.8	31.2	16	–	22	–	3.7
MMA (<25 μmol/mmol creatine)	1.7	17	–	–	8	19	7
GAA (1.21–4.33 μmol/l)	1.69	1.55	2.0	–	–	–	–
MTHFR mutation	–	–	–	–	–	–	–

Values in parentheses represent age matched controls.
MCV, mean corpuscular volume; MMA, methylmalonic acid; GAA, guanidinoacetate; MTHFR, methylene tetrahydrofolate reductase gene.

hypothesis that the prognosis of infantile vitamin B12 deficiency is related to the age of onset.[3] As patient 3 showed no other clinical signs of vitamin B12 deficiency at the time of diagnosis, a coincidence of idiopathic BNS epilepsy leading to the diagnosis of vitamin B12 deficiency by chance cannot be ruled out.

In our opinion the severity and prognosis of infantile vitamin B12 deficiency cannot be related to a single biochemical variable. Additional measurement of methionine and *S*-adenosylmethionine in plasma and methyl tetrahydrofolate in cerebrospinal fluid should be performed. Paediatricians should be aware of nutritional vitamin B12 deficiency in breast fed infants, as immediate and appropriate treatment is mandatory.

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References

1 **Stöckler S**, Marescau B, De Deyn PP, *et al*. Guanidino compounds in guanidinoacetate methyltransferase deficiency, a newborn inborn error of creatine synthesis. *Metabolism* 1997;**46**:1189–93.
2 **Zschocke J**, Schindler S, Hoffmann GF, *et al*. Nature and nurture in vitamin B12 deficiency. *Arch Dis Child* 2002;**87**:75–6.
3 **Graham SM**, Arvela OM, Wise GA. Long-term neurologic consequences of nutritional vitamin B12 deficiency in infants. *J Pediatr* 1992;**121**:710–14.

BOOK REVIEW

Assisted ventilation of the neonate, 4th edition

J P Goldsmith, E H Karotkin. Published by Saunders, Philadelphia, 2004, $99.00, hardback, pp 578. ISBN 0721692966.

Since its first publication in 1981, this book has been regarded by many as one of the foremost reference books on ventilation of the neonate. In the 22 years from that edition to this, many new modalities and strategies have been added to the clinician's repertoire. However, while this fourth edition continues to cover those modalities in great detail, it has also evolved an editorial style in keeping with the drive to deliver evidence based medicine. The failure of numerous randomised controlled trials to define the optimum ventilatory modality is probably due to our inability to accurately delineate appropriate treatment groups. The trainee and practitioner can be left with a bewildering number of treatment options and endless opinions. This book succeeds in describing those options, as well as using the evidence available to direct their use in such a way as to minimise iatrogenic lung damage. Then difference between evidence and opinion is made reasonably clear.

New chapters have been added which widen the scope of the book. Despite the fact that the chapter on ethical and legal issues has, not surprisingly a US legal focus, it contains issues that should be reviewed by all delivering care to premature and sick neonates. It is refreshing in a book about ventilation to find a chapter near the beginning dealing with whether we should ventilate at all and if so for how long. It is too easy to be swept away by what can be done without first asking if it should be done.

Buying the first edition (although not in 1981) gave me a better understanding of what I was doing and made me feel I had an edge. Whether that was true or self delusion, it was the chapters on physiology and control of breathing that formed the foundation for my feelings of superiority. These subjects are still often neglected partly because the word ''physiology'' puts many to sleep. However, in this edition the text is succinct and clear and essential reading. Similarly the chapter on pulmonary function and graphics is both clear and practical, using case studies to illustrate their application. This approach is also evident in the last chapter, where eight cases are worked through applying the lessons of the rest of the book.

Are there any weaknesses to be found? The chapter on resuscitation is not weak but I suspect it is present in its current form for historical reasons. Few would buy this book to use it as reference for resuscitation of the neonate. The chapter could have been focused on those aspects of delivery room care that may influence later ventilation and respiratory outcomes such as the use of oxygen, CPAP, volutrauma, and atalectotrauma to mention but a few. I also found the chapter on cardiovascular aspects disappointing. It needs to be either expanded with a wider remit or focused to neonates without complex congenital heart disease. There was little about assessment of cardiac function. Also between this chapter and those on pulmonary graphics and volume controlled ventilation, one could come up with three different, but overlapping, target ranges for tidal volume delivery. Last but not least, the quality of the paper might be better, as I suspect that it will be subject to a lot of use.

Overall then this is another excellent edition of this series. Perhaps the most telling recommendation is that we already have three copies on our unit, and, if you want a comprehensive reference book on ventilation of the neonate for nurses, trainees, and consultants alike, I would suggest you do likewise.

J P Wyllie