A preventable disease – cobalamin-deficient encephalopathy in childhood[1]

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Summary

Objectives: Description of eight families who consciously follow a vegan lifestyle that endangers the mental and physical development of their children.

Methods: Eight children were diagnosed as suffering under cobalamin deficiency. History taking focused on the place of delivery (home vs hospital), frequency of postnatal contacts with health care providers (midwife, paediatrician, general practitioner), adherence to recommendations concerning vaccination, delivery of vitamins D and K to the infant. Observation of the child under treatment with cobalamin, vitamins and mineral nutrients. Explanation and instruction to the parents about dietary requirements of an infant taking into account specific family dietary habits. Prospective evaluation of the families' willingness to adapt their diet to their child's need.

Conclusion: A cobalamin deficient diet can lead to severe delay of psychomotor development. In the majority of cases the pursuit of a vegan diet was part of a comprehensive lifestyle that deprived the affected children of essential health care provisions. As families seem to be reluctant to accept the advice of health care providers on a change in their health habits, other forms of family guidance should be explored.

Key words: cobalamin; encephalopathy; diet; infant; reversible

Case series

Over a period of three years we had to take care of five girls and three boys who presented to us with a severe delay in their physical and mental development associated with an insufficient provision of cobalamin in their diet. Six of them were brought up on a vegan diet; two families described their diet as lacto-vegetarian although it was not clear whether animal products belonged to their diet.

All children became symptomatic around their first year of life and soon after presented to us. One child was seen in an emergency situation after more than eight years of being subjected to a cobalamin-*deficient* diet. Five of the eight children were born at home, only one had occasional contact to a paediatrician, seven of the eight children were not immunised according to standard recommendations. Vitamin D_3 prophylaxis was only provided to one child. In all children serum cobalamin was low to non-detectable and urine methylmalonic acid was distinctly increased. Most children had low vitamin D_3 and zinc serum concentration (table 1).

All parents reported difficulties in weaning their children from breastfeeding as their children were too weak to accept formula milk. As a result of malnutrition and due to repeated vomiting all of them were below the 3rd percentile in regard to weight, length, and head circumference. None of the children had achieved the age-expected motor milestones. All children showed severe psychiatric symptoms. They were not interested in their immediate surrounding and seemed estranged from their close relatives, resembling in this respect children with an autistic spectrum disorder.

A particularly severe developmental delay was seen in an eight year old boy who presented with a subacute combined degeneration of the posterior and lateral columns of the spinal cord combined with a profound cognitive delay.

In some children further examinations were performed in order to support the diagnosis and to guide specific rehabilitation therapy.

Imaging of the central nervous system by MRI, CT-scan or ultrasound revealed marked cerebral atrophy and gliosis in three children, EEG showed generalised reversible slowing in two patients, ultrasound signal density in liver tissue was increased in one patient, compound motor action potential (CAMP) of peripheral nerves was prolonged in one patient and bone marrow aspiration showed massive megaloblastic haematopoiesis in one patient. MR-spectroscopy to detect a possible decrease in N-acetyl aspartate or an increase in glutamate/glutamine, as described in the literature for detecting cobalamin deficiency, was not done.

Following diagnosis cobalamin, vitamin D_3 and zinc were substituted in all children. Parents were provided with extensive written information concerning the nutritional needs of their children and had several talks with the nutrionist and the medical doctor for metabolic diseases. As some of the involved parents were hesitant to accept a change in their diet, a close surveillance system was set up with the local GP or paediatrician. On following visits three of the eight parents were still not convinced that their children needed cobalamin substitution, four of the eight were tentatively following our diet recommendations and two of the eight had convincingly changed their own diet as well as the diet of their children. A total reversibility of the observed deficits could not be seen in a time

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Table 1 Basic and clinical data on seven children with nutritional cobalamin deficiency due to vegan or vegetarian diet.

Age at presentation in month	Gender	Delivery at	Regular contact GP/ Ped.	Immunisation	Vit. D_3	Diet	Cobalamin ng/l, Transcobal. pmol/l	MMA mol/ mol Creatinin
8	F	Home	None	None	None	Vegan	not detectable	n. m.
10	F	Hospital	None	None	None	Vegan	50 ng/l	1,200
12	F	Home	None	None	None	Vegan	57 ng/l	570
12	F	Hospital	Ped.	Some	None	Vegetarian	?	3,600
13	M	Home	None	None	Yes	Vegan	169 ng/l	260
14	M	Home	None	None	None	Vegan	<50 ng/l	850
15	F	Hospital	None	None	None	Vegetarian	4 pmol/l	2,100
?–8 y.	M	Home	None	None	None	Vegan	37 ng/l	580

F = female; M = male; Transcobal. = Transcobalamin II (nl. 19–119 pmol); Cobalamin (nl. >150–200 pmol/l);
MMA = methylmalonic acid (nl. <10 mmol/mol creatinin); n. m. = not measured.

span of one to two years following primary presentation. Regular follow up visits with the involved families were organised with the local GP or paediatrician.

Discussion

As society becomes pluralistically differentiated different diets are chosen including those that restrict or exclude animal products such as a vegetarian or vegan diet. Individual followers of such a diet feel motivated to do so by aspiring to a healthier way of life and/or as a protest against the way animals are treated in the food producing industry [1]. In contrast to adults, who are autonomous in the choice of their own diet, children are intrinsically dependent on the food intake of their mothers from the moment of perception until at least the end of the breastfeeding period. Whereas a lacto-vegetarian consumes milk products in addition to plant products, a vegan avoids all animal products.

In contrast to the belief of many vegans, cobalamin cannot be derived from plant products alone in a sufficient quantity and must therefore be substituted either through fortified food or taken as supplements. Adults need about 2.4 µg cobalamin per day rising to day 2.8 µg for nursing mothers. If a vegan mother does not consume sufficient cobalamin herself, her infant should receive 0.4 µg/day cobalamin during the first six postnatal months and 0.5 µg/day from six months onwards.

Cobalamin metabolism

Ingested cobalamin is a complex cobalt-containing molecule that must be modified through intracellular metabolism in order to be used as a co-factor in myelin formation and DNA-synthesis. Cobalamin forms the substrate for cobalamin-adenosyltransferase that converts reduced cobalamin to adenosylcobalamin which is a required co-factor for the functional activity of mitochondrial methylmalonyl-CoA mutase. A lack of cobalamin leads to an increased propionyl CoA which together, with other factors, is associated with delayed myelination [2]. Cobalamin is also a co-factor of methionine synthase, which catalyses the transfer of a methyl group from methyltetrahydrofolate to homocysteine to form methionine within the cytoplasma. A disturbed methionine metabolism can lead to reduced neurotransmitter synthesis and DNA-formation. Recently increased MMA has been described as co-occurring with disturbed episodic memory and reduced perceptual speed. Increased homocysteine has been associated with a decreased total brain volume 4.6 years after the initial laboratory exam [3].

Intrauterine cobalamin deficiency does not seem to influence duration of pregnancy or birth weight. Reports on long term development of children with cobalamin deficiency in infancy are sparse.

The severity of symptoms is more pronounced if a child is already deprived of cobalamin in utero or during the breastfeeding period compared to cobalamin deficiency later in life. Cobalamin deprived infants typically present with a loss of energy, appetite and a failure to thrive. After a long deprivation they present with signs of a subacute degeneration of the spinal cord. Some develop seizures, others show disturbances in short and long term memory and psychiatric symptoms. Bone marrow depression can manifest as pancytopaenia with hypersegmentation of neutrophils and macrocytosis. The reversibility of symptoms is dependent on the duration of malnutrition and possible secondary defects in intracellular metabolism.

Symptoms can be aggravated due to the simultaneous lack of zinc and calcium. The higher phytic acid content of a vegetarian or vegan diet can lead to a reduced bioavailability of zinc. The lack of milk products and the reduced availability of vitamin D_3 increase the risk for bone fractures. Measurement of these minerals and possibly substitution should be undertaken in affected children.

Laboratory examinations

Serum measurement of cobalamin itself is a very unreliable test to detect a deficiency. Vegans often use algae as a substitute for animal derived cobalamin; this can lead to a misleading high cobalamin serum level. Blood counts to detect a megaloblastic anaemia can give falsely normal values because a concurrent high folate intake can mask an anaemia. Measurement of serum homocysteine is a sufficiently reliable test. Levels greater than 10 µmol/l are considered pathological. The most specific and inexpensive test for cobalamin status is to

measure MMA in urine, which under a sufficient cobalamin provision, should be less than 10 mmol/mol creatinin.

Clinical course

All the children seen by us showed a considerable developmental delay. A direct correlation between their level of MMA and the severity of the acute neurological symptoms could not be observed. An improvement, as has been described in the literature, was witnessed in all children following cobalamin substitution including the boy with long-term cobalamin deficiency [4].

The prompt improvement of neurological function following cobalamin substitution can however not be attributed to an immediate reversal of the defects in myelin formation. Rectification of a supposed imbalanced cytokine ratio between the neurotoxic tumour necrosis factor-α (TNF-alpha) and the neurotrophic epidermal growth factor (EGF) could be causal for the initial clinical improvement [5]. Neither TNF-alpha nor EGF was measured in our patient group.

Future prognosis

We do not know how many children actually suffer from cobalamin deficiency. Extrapolating from our case study we assume that the number of affected children is much higher than represented in the published literature. We do not have long- term observation studies of how primarily deprived children develop under cobalamin substitution and how long such a substitution will be followed by the parents. This is probably due to the fact that families with a profound belief in the legitimacy of their particular lifestyle do not want to be under a continuing surveillance [6].

We have learnt from our experiences that identifying the underlying cause of the disease will not directly lead to a successful method of rectifying the initial disturbance. Substituting cobalamin is this context involves more than just giving a drug. It can call into question a deliberately chosen lifestyle. We had the impression that parents tend to dissociate between the positive connation of their belief system and their actual experiences of the hampered development of their children. We should therefore aim to make their emotional bond to their children compatible with their concept of life. We know from behavioural change theories that the degree of *self-efficacy* as perceived by the parents can be predictive of their willingness to change a given lifestyle [7]. Assuming that adherence to the vegan lifestyle has given these parents a high degree of self-efficacy, a comparable amount of self-efficacy will need to be found within a different field. This could be the positive experience of seeing their child catching up on growth and development. If it holds true that a change in one's behaviour is dependent on how society or any other reference group values this behaviour then support and gratification must prevail in the discourse between parents and medical professionals. Instead of activating feelings of guilt and remorse related to the illness of their child parents should be helped to cope and appreciate the benefits as a prerequisite of adherence to a new treatment protocol.

The immediate time interval following the diagnosis, while parents are witnessing the improvement of their children under a changed dietary regime, should be used for these conversations.

Conclusion

In modern pluralistic societies people increasingly use particular lifestyles to associate with others, disregarding the traditional boundaries of age, gender and nationality. Particular eating habits, such as vegetarianism, have become very popular as a way of combining a healthy life style with a criticism of modern food-producing methods. Once such a lifestyle has been adopted a departure from it is often avoided as is bears the danger of losing group membership. This is particularly so if a departure is not compensated by a more attractive new group membership. A lifestyle that restricts access to essential food components such as cobalamin puts dependent children at a particular risk.

In this report we have drawn attention to the health care habits of eight families whose children came to our attention recently with a severe cobalamin deficiency. At presentation all children were dystrophic and mentally impaired. Apart from being deprived of cobalamin, seven of the eight children did not receive the recommended vaccination, prophylactic vitamin D_3 nor had they regular access to a general practitioner or a paediatrician. Our cases series of eight children with nutritional cobalamin deficiency confirms earlier reports of severe sequelae in the mental and physical development of the affected children. We suspect that we are only seeing the tip of the iceberg and more often than expected children with developmental delay could suffer under a cobalamin deficiency. The frequency of this occurrence will be increased when parents avoid contact with medical professionals such as usually happens during visits for vaccination and vitamin supplementation. In our case series all children initially improved under a change in diet. As the reversibility of the symptoms is dependent on a lasting change in eating habits, a consideration of the motivational background of the caretakers is essential. A majority of parents however remained reluctant to change their diet despite detailed explanation about the cause of the disease. Following these experiences we recommend addressing the intrinsic belief system of families committed to a vegan lifestyle early and repeatedly. These conversations should take account of behavioural change theories.

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