

## Optic neuropathy in ketogenic diet

CREIG S. HOYT AND FRANK A. BILLSON

*From the Department of Ophthalmology, University of California, and the University of Sydney, Australia*

**SUMMARY** A symmetrical, bilateral optic neuropathy is reported in 2 patients being treated with ketogenic diets for seizure control. Laboratory tests suggested a thiamine deficiency, and both patients recovered normal visual function after several weeks of treatment with thiamine. The risk of optic nerve dysfunction occurring during the treatment with a ketogenic diet can be minimised if routine vitamin B supplements are given and periodic evaluation of optic nerve function undertaken.

The ketogenic diet is now widely accepted as an effective alternative treatment for children whose seizure disorder is not controlled by standard anticonvulsant medications (Dodson *et al.*, 1976). In general, patients have not been treated by dietary therapy alone but in conjunction with standard anticonvulsant drugs. Moreover, most authorities have restricted ketogenic diet therapy to those patients in whom standard anticonvulsant therapy has not been efficacious (Dodson *et al.*, 1976; Gordon, 1977). However, since the diet has proved to be highly effective, and its reported adverse effects have been limited to infrequent abdominal pain, vomiting, and diarrhoea, a wider prescription of this form of anticonvulsant therapy has been recommended (Gordon, 1977).

Here we report the occurrence of bilateral, symmetrical optic neuropathies in 2 patients being treated with a ketogenic diet. It appears that the optic nerve dysfunction in these patients was the direct consequence of a nutritional disorder related to the diet. A thiamine deficiency appears to be the most plausible causative factor in these cases. We recommend that emphasis be placed on the need for routine vitamin supplements when instructing parents about the details of a ketogenic diet. We further suggest that a periodic assessment of optic nerve function should be an integral part of the routine medical evaluation of these children.

### Patients and methods

#### CASE 1

This was a 5-year-old white boy. His mother's pregnancy and delivery were normal and the family

history gave nothing unusual. The child was in good health in all respects until 28 months of age, when he began to have minor seizures in the form of myoclonic or akinetic attacks. Their frequency gradually increased to over 30 to 40 a day. He was treated with various drugs (barbitones, phenytoin, succinimides, and primidone) with only slight effect on the frequency and intensity of his attacks.

Examination when the boy was 38 months old showed a well-developed child, and the findings of a general physical and neurological examination (including a neuro-ophthalmic evaluation) were normal. Routine laboratory studies, skull *x*-rays, cerebrospinal fluid, and computer-assisted tomography scan were all normal. The electroencephalogram showed frequent epileptiform discharges in the form of generalised spikes, polyspikes, and spike-and-wave complexes; most of these were bilaterally synchronous.

At the age of 43 months he was begun on a 4:1 ratio high-fat diet. Over the next 2 months his seizures decreased in frequency, until at the age of 46 months he was essentially free of all seizures. He continued on a ketogenic diet in conjunction with phenytoin and primidone. At 56 months of age his parents were advised by his kindergarten teacher that he had poor vision as detected on a routine preschool examination.

On ophthalmological examination the patient read 6/24 with either eye and could not be corrected with lenses. His pupils were equal and responsive to light. He was unable to detect any of the red-green hues in the H-R-R colour test plates with either eye. The patient was not very reliable in his responses to visual field examination, but bilateral centrocecal scotomas with poorly-defined borders were noted. The ocular media were clear. The ocular fundi appeared normal even with a careful evaluation of the nerve fibre detail with red-free light. Neuro-

Address for reprints: Dr Creig S. Hoyt, Department of Ophthalmology, University of California Medical Center, 400 Parnassus Avenue, Suite 751-A, San Francisco, California 94143, USA.

logical examination revealed no abnormality other than the visual deficit.

Normal laboratory studies included a complete blood count, red blood indices, and serum electrolytes. Skull x-rays with optic foramina views were normal. Serum folate level was 18 ng/ml (normal 4 to 20 ng/ml); and vitamin B<sub>12</sub> was 260 pg/ml (normal, greater than 200 pg/ml). Serum transketolase was 56 µg/100 ml (normal 100 to 160 µg/100 ml). Examination of the cerebrospinal fluid was entirely normal. Urinary screening for heavy metals gave a negative result.

The parents were questioned on the details of the patient's diet. They admitted that although they strictly adhered to the 4:1 ketogenic diet they did not routinely give the patient the recommended vitamin or calcium supplements. Treatment with 50 mg of thiamine daily in addition to vitamin B supplements was therefore instituted. He remained on his anticonvulsants and ketogenic diet. Six weeks after beginning treatment the patient's vision was 6/12 in either eye. He remains on a 4:1 ratio ketogenic diet and vitamin B supplements without any further visual problems.

#### CASE 2

This patient was a 7-year-old girl who had a history of normal development until aged 3 years, when she had abrupt onset of seizures. There was no known precipitating cause, and the family history is negative for convulsive disorders. After a few weeks of frequent grand mal seizures the patient developed akinetic seizures, myoclonic jerks, and automatisms. Routine blood studies, cerebrospinal fluid examination, skull x-rays, and a computer-assisted tomography scan were entirely normal. The electroencephalogram showed frequent bursts of generalised high-voltage spike-wave activity on a background of diffuse high-voltage slow waves. Over a period of 3 years various combinations of barbitones, phenytoin, primidone, ethosuximide, and acetazolamide were ineffective in treating the seizures. At the age of 6 years she was started on a 4:1 ketogenic diet, which had a dramatic effect within 6 weeks. The patient intensely disliked the diet and periodically refused to eat. However, her parents insisted on continuing the dietary therapy since it rendered the patient essentially free of seizures.

About 1 year after initiation of the ketogenic diet the patient complained of a gradual diminution in vision. On examination her best corrected visual acuity was found to be 6/36 in the right eye and 6/24 in the left eye. She read the red-green hues of the H-R-R colour test plates with extreme difficulty. The pupils were equal in size and reactivity to light. The ocular motility, media, and fundi were entirely

normal. The visual field examination showed centrocecal scotomas in both eyes to a 5/1000 white test object.

Routine laboratory studies included a complete blood count, electrolytes, and urine analysis; these were all normal. Skull films with optic foramina views, a computer-assisted tomography scan, and examination of the cerebrospinal fluid were also normal. Serum transketolase was 50 µg/100 ml (normal 100 to 160 µg/100 ml). Serum folate level was 35 ng/ml (normal 4 to 20 ng/ml); and vitamin B<sub>12</sub> was 240 pg/ml (normal greater than 200 pg/ml). Urinary tests for heavy metals showed nothing unusual.

In questioning the parents about the details of the patient's diet they admitted they had thought the prescribed vitamin and calcium supplements were unimportant. They had not given these to the patient for more than a year. The patient was therefore given thiamine 50 mg daily in addition to the routine vitamin B supplements. She remained on a ketogenic diet. After 6 weeks she stated she thought her vision had improved, though no change in visual acuity could be detected. After 11 weeks the visual acuity was 6/9 in both eyes. Colour vision was normal and no field defects could be demonstrated. After 3 months of treatment with thiamine and B vitamins the visual acuity was 6/5 in each eye. The patient remains on 4:1 ketogenic diet and supplemental vitamins.

#### Discussion

Wilder (1921) introduced the ketogenic diet for the control of childhood seizures. Despite the availability of an increasing variety of drugs the ketogenic diet remains an important alternative form of anti-convulsant therapy. The 2 major indications for it are resistance to drug therapy and/or drug toxicity. However, results of ketogenic dietary therapy have been good enough to encourage its more general use (Gordon, 1977). About 30% of properly selected children with epilepsy will have their seizures controlled while on the diet, and an additional 30% will show partial improvement in the frequency of seizure (Dekaban, 1966). Although the diet is usually restricted to the treatment of seizure disorders in childhood, some adult epileptics have benefited from it as well (Dodson *et al.*, 1976).

Ketosis is produced by giving the patient a diet consisting of a 3:1 or 4:1 fat ratio (Signore, 1973). That is, the patient is given 3 or 4 g of fat for every 1 g of nonfat. The nonfat portion is composed of variable proportions of carbohydrate and protein. An alternative diet consisting of 50 to 70% medium chain triglycerides appears to be equally efficacious

and more palatable (Huttenlocher *et al.*, 1971). After 10 to 21 days the therapeutic effect of the diet becomes apparent. Some authorities (Hendley *et al.*, 1948; De Vivo *et al.*, 1973) have correlated the therapeutic effect with the degree of ketosis. However, Huttenlocher (1976) has presented evidence that the anticonvulsant action of ketogenic diets is mediated by the direct action of ketone bodies on cerebral excitability. Furthermore, it has been shown that during fasting the central nervous system can utilise ketone bodies for a large part of the substrate requirement for cerebral oxidative metabolism (Owen *et al.*, 1967). The greater effectiveness of the ketogenic diet in controlling seizures in children may be related to the fact that children seem to have a greater capacity than adults to oxidise ketone bodies (Krause *et al.*, 1974).

It is noteworthy that despite the significant metabolic alterations that occur as a consequence of a ketogenic diet serious complications have been infrequent. Mild gastrointestinal disturbances such as abdominal pain, vomiting, and diarrhoea may occur, but they rarely cause trouble. Hyperuricaemia and hyperlipidaemia may develop, and the long-term effects of these disturbances have been cited as potential hazards requiring further investigation (Gordon, 1977). A more serious complication has been the development of dehydration and severe metabolic acidosis in some mentally retarded children treated with a ketogenic diet during intercurrent febrile illnesses (Dodson *et al.*, 1976).

In this paper we report 2 patients who, while being treated with ketogenic diets, developed bilateral, symmetrical optic neuropathies. The presence of symmetrical optic neuropathies with bilateral centrocecal scotomas should prompt the consideration of a nutritional or toxic amblyopia (Harrington, 1971). We believe the most likely cause of optic nerve dysfunction in these 2 patients is thiamine deficiency.

The role of thiamine deficiency in our patients' optic neuropathies is suggested by: (1) The fact that a ketogenic is deficient in B vitamins (Dodson *et al.*, 1976); (2) the failure of both sets of parents to administer the prescribed B vitamin supplements; (3) the low serum transketolase levels, strongly suggesting significant thiamine deficiency in both patients (Dreyfus, 1965); (4) the reversal of the visual defects as a consequence of treatment with thiamine supplements despite continuation of the ketogenic diets and anticonvulsants; and (5) the fact that a pure thiamine deficiency has been shown to cause optic nerve degeneration in experimental animals (Rodger, 1953).

We specifically investigated other potential metabolic causes of optic nerve dysfunction. Serum folate

and vitamin B<sub>12</sub> levels were normal in both patients. There was no history of exposure to toxic substances, including those most commonly associated with this kind of optic neuropathy. Urinary tests for heavy metals were negative. We considered the possibility that the anticonvulsants were responsible. However, although it is well recognised that visual blurring may occur during acute intoxication with some anticonvulsants (Patel and Crichton, 1968), we are unaware of any data correlating optic neuropathy with standard anticonvulsants in therapeutic doses. The prompt recovery of both patients after treatment with thiamine and B vitamin supplements strongly suggests a vitamin deficiency as the cause of the optic nerve disturbance in both patients.

A recent report of a comparable type of optic neuropathy occurring in patients adhering to a low-carbohydrate high-protein diet for weight reduction also implicated thiamine deficiency as the cause of optic nerve dysfunction (Hoyt and Billson, 1977). Thiamine deficiency is involved in several disorders of the central nervous system. It is well established as the cause of the Wernicke-Korsakoff syndrome (Cogan and Victor, 1954). However, optic nerve dysfunction is uncommon in this disorder. It seems likely that thiamine deficiency is involved in the aetiology of alcohol amblyopia (Dreyfus, 1965). The production of optic nerve degeneration in rats fed a thiamine-deficient diet lends support to the thesis that pure thiamine deficiency can cause optic nerve dysfunction (Roger, 1953).

Clinically significant thiamine deficiency has become an uncommon condition in non-alcoholic patients since the introduction of enriched breads and cereals (Lane *et al.*, 1942). However, the ketogenic diets used in the treatment of childhood seizures and the low-carbohydrate/high-protein weight reduction diets are both thiamine deficient. Although thiamine requirements decrease as carbohydrate intake decreases, a thiamine deficiency may develop after long-term use of either of these diets. Therefore, optic nerve dysfunction is a potential complication of the diets if supplemental vitamins are not taken. We suggest that when prescribing the diets physicians should place special emphasis on the necessity of B vitamin supplements. In addition, periodic evaluation of optic nerve function should be incorporated into the examination of these patients.

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