Letters to the editor

‘Benign congenital hypotonia is not a diagnosis’

SIR—I am greatly concerned that far too many children with hypotonia are being diagnosed as having ‘benign congenital hypotonia’. This has not been an appropriate diagnosis since the early 1960s following the description of central core disease in 1956,1 nemaline rod myopathy in 1963,2 myotubular myopathy in 1966,3 minicore disease in 1971,4 and congenital fibre type disproportion in 1973.5 Unfortunately, the term is sometimes used in 1956,1 nemaline rod myopathy in 1963,2 myotubular myopathy in 1966,3 minicore disease in 1971,4 and congenital fibre type disproportion in 1973.5 Unfortunately, the term is

still found on patients’ charts, in articles, and even in medical textbooks. There is also an internet group for parents whose children have this diagnosis.

It is extremely important that a specific diagnosis be made on a child with hypotonia because of the risk of malignant hyperthermia with some neuromuscular disorders, and the importance of offering genetic counseling to parents. If a specific diagnosis is not made then parents may be unaware of potential problems with a future pregnancy. In addition, some neuromuscular disorders have specific associated risks of which parents need to be aware.

The important clinical clues to the possibility of a neuromuscular disorder are: hypotonia at birth or within the first few months of life; decrease in muscle bulk and tone; lack of abnormal neurological signs except perhaps for decrease or absence of deep tendon reflexes; orthopedic problems such as hip dislocation or foot deformities; high narrow palate; long, narrow faces; and fasciculations of the tongue.

The most important neuromuscular disorders to consider are: congenital myasthenia gravis; congenital muscular dystrophy; myotonic dystrophy; Prader-Willi syndrome; spinal muscular atrophy; mitochondrial myopathies; and congenital myopathies including; central core and minicore disease, myotubular myopathy, congenital fibre type disproportion, and nemaline rod.

Congenital myopathies are now being divided into many subtypes as more is learned about the genetics of these disorders. This is also true of the mitochondrial myopathies.

In making a diagnosis it is important to take a detailed and thorough history which should include questions about the movement of the fetus during the pregnancy and the condition of the infant at birth and within the first few days or weeks of life. It is also necessary to determine if there has been improvement in muscle weakness or progression of the weakness, as would be seen with type I spinal atrophy or Werdnig-Hoffmann disease.

A family history is most important and questions should be asked about any relationship between the parents, problems that family members may have had with anesthetics, and if miscarriages or fetal deaths have occurred in any family members.

Medical investigation for a possible neuromuscular disorder does not generally have to be extensive. The two most important tests are creatine phosphokinase (CPK) and muscle biopsy, performed under local anesthesia because of the risk of malignant hyperthermia. (A muscle biopsy can be performed even under a local anesthetic). Proper staining and processing are necessary, as well as interpretation by a clinician experienced in diagnosing muscle disorders. Electron microscopy (EM) images should always be obtained unless the diagnosis is definitive on the histoch-

emical stains. EMGs are generally painful and unnecessary in children if an adequate history, physical examination, CPK, and muscle biopsy are performed.

The following case histories are typical of patients who have been diagnosed with ‘benign congenital hypotonia’.

**VA**: This 37-year-old female, who was also a member of the hypotonia internet group, was seen because of a history of difficulty with sucking and a seizure occurred at 36 hours. After discharge, it was noted that there were periodic episodes of hypotonia, as well as vomiting and diarrhea. There was also considerable proximal weakness on examination and a decrease in muscle bulk. The CPK was within normal limits and a muscle biopsy performed under local anesthetic showed variation of fiber size and an increase in type I fibers. Possible myopathy was suggested but the final diagnosis was ‘benign congenital hypotonia’.

After a review of the history, physical findings, muscle biopsy, and laboratory results it was recommended that a test for myotonic dystrophy be performed. Tests were carried out at the Center for Human Genetics at Boston University School of Medicine. A Southern blot analysis was performed using two intragenic probes. The test result was positive and a repeat test was also positive.

**FC**: This male child was first seen at two years of age having been diagnosed with hypotonia. The mother’s pregnancy had been complicated by no weight gain and decreased fetal movement. Birthweight was 2.5kg, although the infant was thought to be of 41 weeks’ gestation. The baby was delivered by Cesarean section and meconium staining was noted at birth. Apgar score was 4/9 and, subsequently, the infant was kept in intensive care for eleven days. There was difficulty with sucking and a seizure occurred at 36 hours. After discharge, it was noted that there were periodic episodes of hypotonia, as well as vomiting and diarrhea. There was also considerable proximal weakness on examination and a decrease in muscle bulk. The CPK was within normal limits and a muscle biopsy performed under local anesthesia showed variation of fiber size and an increase in fibrous tissue. EMs showed abnormal mitochondria and an unusual amount of fat. Studies were then performed at the Scottish Rite Hospital in Atlanta, USA and the diagnosis of a mitochondrial myopathy was made.

**VA**: This 37-year-old female, who was also a member of the hypotonia internet group, was seen because of a history of diffuse weakness from birth and bilateral hip dislocations detected at 5 to 6 weeks of life. The mother’s pregnancy had been complicated by some spotting at 4–5 months and decreased fetal movement. The patient’s walking was delayed because of surgery and casting for the hip dislocations.

Family history showed that there were a number of individuals on the father’s side who had ‘shallow hip sockets’ and two sisters who had dislocated hips. The paternal grandmother was apparently never very active and the paternal great grandmother had ‘shallow hip sockets’.

On physical examination, the patient was found to have moderate, diffuse weakness and a 45° lack of extension of her left leg. The joints of her hands were also hypextensive. Deep tendon reflexes were present but decreased. There were no other findings except for edema of the legs. The CPK was within normal limits and a muscle biopsy showed marked fatty infiltration. EMs showed evidence of cores and the diagnosis...
of central core/minicore disease was made.

It is, therefore, most important that a patient is not labeled with the diagnosis of ‘benign congenital hypotonia’ but that a specific diagnosis be established by information provided by a CKP test and muscle biopsy interpreted by a physician with wide experience in diagnosing neuromuscular disorders. Other laboratory studies and DNA testing may also be needed.

A specific diagnosis is important so that precautions against malignant hyperthermia may be taken in all the family members and genetic counseling offered.

Charlotte E Thompson MD
The Center for Handicapped Children and Teenagers
2001 Union Street
Suite 482
San Francisco
CA 94123, USA

References

‘Energy consumption in spasticity’

SIR–We were intrigued to read the recent publication on ‘Energy requirements of spasticity’ by Hemingway and colleagues.1 This case report described a patient treated with intrathecal baclofen in whom spasticity was reduced but whose body weight increased markedly while his calorie intake remained the same. Our team has observed a similar phenomenon in a cohort of children whose spasticity has been reduced by selective dorsal rhizotomy (SDR).

Although there has been much debate about functional outcomes after SDR, it is generally accepted that this procedure reduces spasticity.2 We have been monitoring children treated with SDR in Oswestry, UK and have noticed that the first 14 have tended to gain weight postoperatively at a rate greater than could be expected from normal growth and development. Plotted on growth charts, their weights crossed the centiles in an upward direction, on average crossing 14 centiles in the first 18 months after surgery. There was also a significant increase in walking speed across the group (0.2 m/s) and we perceived an increased level of general activity. As far as we are aware, there was no radical change in dietary lifestyle in our children, postoperatively. From the general lifestyle and activity changes alone we would have predicted weight stability or loss rather than gain. Clearly there is an additional factor at work here.

While weight gain was common to this group, it was particularly marked in four children with very low preoperative walking speeds (approximately 0.2 m/s). This small group crossed the weight centiles quite dramatically upwards (on average 30 centiles in 18 months). In this same group, postoperative walking speeds were at least double the preoperative values.

Our interpretation of these data accords with that of Hemingway and her group, namely that spasticity consumes energy and reducing spasticity by any means is likely to predispose a child to weight gain unless calorie intake is reduced. We have been so impressed by this observation that we are now careful to include control of calorie intake posttreatment in all children who undergo spasticity reducing interventions.

The link between weight gain and spasticity reduction is clearly complex and would seem to merit a prospective, controlled study. We offer our experience as further evidence that such a relationship exists.

Andrew Roberts DM FRCS
Caroline Steuwart PhD CEng MMechE
Gaynor Cole PhD FRCP FRCPPCH
Sybil Farmer MSC MCSP SRP
John Patrick FRCS

Orthotic Research and Locomotor Assessment Unit
Robert Jones and Agnes Hunt Orthopaedic Hospital
Oswestry
Shropshire
SY10 7AG, UK

References

‘Pyridoxine treatment in a subgroup of children with pervasive developmental disorders’

SIR–Pervasive developmental disorders (PDDs), including autistic disorder and Asperger syndrome, are disorders of development characterized by a triad of abnormalities in social interaction, impairments of communication, and unusual forms of repetitive behaviour.1 In the treatment of PDDs, the effects of pyridoxine (vitamin B6) remain controversial.2 Previous studies looked at patients who met the criteria for autistic disorder, which is a heterogeneous disorder.3

To date, no studies have examined the effects of pyridoxine in children with PDDs by selecting a subgroup of them according to features other than abnormal social interaction, communication impairments, and unusual repetitive behaviour. The study protocol was approved by the Ethical Committees of Saka General Hospital and Tohoku University School of Medicine. Signed informed consent was obtained from parents and from the child if over 12 years of age.

In addition to these abnormalities, a subgroup of children with PDDs demonstrates epilepsy, expressive verbal disorders, developmental motor coordination disorders, hypersensitivity to sound, hypersensitivity to touch, anxiety, agitation, sleeplessness, hypotonia, and large head circumference.4,5,6 Interestingly, autistic behaviour and all these clinical features are also seen in children with pyridoxine-dependent epilepsy, whose seizures ceased with high doses of pyridoxine.4,7

The observed similarity in these clinical features has led us to speculate that this subtype of PDDs might have a similar
pathophysiologic mechanism to pyridoxine-dependent epilepsy. Baxter and colleagues\(^6\) reported that, after receiving high-dose pyridoxine, seizures ceased and intelligence quotient (IQ) scores improved among children with pyridoxine-dependent epilepsy.

We, therefore, hypothesized that pyridoxine treatment might be effective in improving IQ scores in the subgroup of children with PDDs who exhibit clinical features similar to those of pyridoxine-dependent epilepsy but do not have a history of seizures. To test the hypothesis, we conducted a randomized, placebo-controlled, double-blind trial, focusing on expressive verbal disorders, developmental motor coordination disorders, and hypersensitivity to sound, in addition to autistic behaviour.

We recruited 15 participants through referral from the Saka General Hospital, Shiogama, Miyagi, Japan or from the newsletters of a Learning Disability Support Group. Inclusion criteria for the study were: meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)\(^7\) criteria for PDDs; having expressive verbal disorders, developmental motor coordination disorders, and hypersensitivity to sound; and aged over 6 years and under 17 years. Exclusion criteria were: history of epilepsy or an epileptiform EEG at examination. To exclude children with late onset or atypical pyridoxine-dependent epilepsy;\(^7\) – 8 use of a psychotropic agent or vitamin supplements within 3 months of the start of the study; inability to measure IQ scores; image abnormalities in the brain on MRI; or history of homocystinuria or fragile X-syndrome.

Of 15 potential participants, two were excluded because of a history of epilepsy or an epileptiform electroencephalogram at examination. Two were excluded because they were currently using B-complex vitamins. The remaining 11 children completed the baseline study. Three were excluded because their IQ scores were not measurable. Eight eligible children were randomly assigned by an epidemiologist using a table of random numbers, to either the pyridoxine group or the placebo group after being stratified by their sex and age.

The pyridoxine group comprised two males, and two females; mean age at baseline 10 years 6 months (SD 1 year 8 months). The placebo group comprised two males and two females; mean age at baseline 10 years 10 months (SD 1 year). For the two groups, mean bodyweight was 44.5 (SD 16.3) and 44.5 (SD 18.3) kg, mean verbal IQ scores, 74.3 (SD 22) and 77.5 (SD 15), mean performance IQ scores 78.8 (SD 30.8) and 68.8 (SD 5.2), and mean Social Quotient (SQ) scores 73.5 (SD 14.6) and 81 (SD 11.9), respectively.

One patient in each group was diagnosed with Asperger syndrome and three were diagnosed with PDDs not otherwise specified.\(^9\) Mean interval between IQ tests was 145.5 (SD 47.5) days in the pyridoxine group and 114.8 (SD 25.5) days in the placebo group.

Expressive verbal disorders indicate impairment in expressive language with relatively intact verbal comprehension. Relatively intact comprehension skills were assessed in terms of the ability to follow instructions for motor tasks. Assessment of impairment of expressive language included: halting and sparse speech; a limited range of vocabulary; vocabulary errors; ungrammatical speech; or shortened sentences. Assessment of developmental motor coordination disorders included: history of delay in achieving developmental motor milestones, such as tying shoelaces or buttoning shirts; difficulties with the motor aspects of handwriting; or difficulties with the motor aspects of running, playing ball, or doing mat exercises. Assessment of hypersensitivity to sound included: startle reaction to a loud sound; startle reaction to a sudden sound; or covering their ears when hearing a large number of children’s voices.

Pyridoxine was given in doses of 100 mg once a day after breakfast in the first 2 weeks. In the following 2 weeks, pyridoxine was given twice a day, after breakfast and after dinner, each in doses of 100 mg. Pyridoxine was given orally in powdered form. The placebo was supplied in a powdered form that was identical in appearance and taste to pyridoxine.

Compliance with medication was assessed by parents’ reports and by measurement of blood pyridoxine concentration after the trial. Adverse effects specific to pyridoxine toxicity were assessed on protocol by two board-certified paediatric neurologists, who observed the patients during the trial, and by blood tests after the trial. Parents were asked to complete a diary, recording any change in their child’s clinical signs or behaviour. During the trial period, treatment assignment was blinded to the patients and their parents, the clinical psychologist (MK), the medical practitioners, and a statistician.

Outcome measures were changes in IQ scores and the social quotient (SQ) scores following treatment. IQ scores were measured using the Wechsler Intelligence Scale for Children–III (WISC–III) test.\(^9\) This test assigns both verbal IQ scores and performance IQ scores. All IQ tests were conducted on each patient by the clinical psychologist both at baseline and at the end of the fourth week of medication. The standard score of each IQ has a mean of 100 and a standard deviation of 15. SQ scores were measured with the Social Maturity Scale (SM) test.\(^10\) SQ scores were calculated as social age divided by calendar age. All SM tests were assessed by the patients’ parents.

Net gains in IQ or SQ scores were calculated as follows: net gain in IQ or SQ scores = (the postintervention IQ or SQ scores of the pyridoxine group minus the baseline IQ or SQ scores of the pyridoxine group) minus (the postintervention IQ or SQ scores of the placebo group) minus (the postintervention IQ or SQ scores of the placebo group). Student’s t-tests were used to compare the net gain in IQ or SQ scores between the pyridoxine and placebo groups. Analysis of covariance (ANCOVA) was used to adjust for potential confounders. We expected an effect size of each IQ score change of 10 with 5SDs in the pyridoxine group, based on the findings of Baxter and coworkers.\(^6\) Based on this expectation, a sample size of 4 pairs would allow a significance level of 0.05 and a power of 0.65. This power calculation was based on an unpaired t-test. All statistical analysis was performed with SAS (version 6.12), and significance was set at \(p<0.05\).

Pyridoxine treatment was associated with a significant increase in verbal IQ scores. Verbal IQ scores in the pyridoxine group increased by 11.2 (from 74.3 to 85.5). Verbal IQ scores also increased by 6.0 in the placebo group (from 77.5 to 83.5). Net gain in verbal IQ scores in the pyridoxine group was relative to the placebo group showed a significant difference (5.2, 95% confidence interval 0.2 to 10.3). After controlling for sex, age, body weight, interval between IQ tests, and baseline verbal IQ scores using ANCOVA, the adjusted net gain in verbal IQ scores in the pyridoxine group compared with the placebo group still showed a significant difference (6.8, 95% CI 5.0 to 8.5; \(p=0.01\)).
Among the performance IQ and SQ scores, no significant differences were observed. All children were confirmed to have taken all their medication in accordance with the protocol of the trial. None of the children had any side effects.

A subgroup of children with PDDs exhibit clinical features similar to those of pyridoxine-dependent epilepsy patients. We, therefore, hypothesized that pyridoxine treatment might have an effect in the subgroup of children with PDDs and conducted a randomized, controlled trial. Our study demonstrated that pyridoxine was associated with improvement in the verbal IQ scores. This result suggests that the subgroup of PDDs might have a similar pathophysiological mechanism to pyridoxine-dependent epilepsy.

The results should be interpreted with caution because our study had several limitations. The main limitation was the small sample size. Because of this, the significant finding might have been a result of chance. Second, this study was a short-term study for four weeks. A long-term study of the beneficial and adverse effects of pyridoxine is necessary. It has been reported that a long-term administration of pyridoxine may induce adverse effects such as a sensory peripheral neuropathy. Third, we were unsure of the optimal dosage of pyridoxine to administer in this trial, but our use of 100 mg to 200 mg pyridoxine per day has been recommended by Baxter and colleagues for the treatment of pyridoxine-dependent epilepsy. Fourth, we did not have an objective way to measure hypersensitivity to sound. IQ and SQ tests were sufficient to measure the degree of expressive verbal disorders and developmental motor coordination disorders, but we could not objectively investigate changes in hypersensitivity to sound.

Because of the above limitations, it is premature to draw any definite conclusion from our finding. However, our results indicate that expressive verbal disorders, developmental motor coordination disorders, hypersensitivity to sound, and, perhaps, hypersensitivity to touch, anxiety, agitation, sleeplessness, hypotonia, and large head circumference may represent a clinical marker for grouping individuals with PDDs into more homogeneous subgroups. Such subgroups may be useful for further randomized, controlled trials with larger sample size and longer follow-up. This could help to define the association between pyridoxine and children with PDDs, and to assist in the search for pathophysiological mechanisms in PDDs.

Acknowledgements
The authors are grateful to Dr Kazuhisa Tsukuda and Dr Mitsuaki Nishikori for discussions; to Ms Kimiko Sasaki, Mr Hideo Shirasuna, and all the staff of Saka General Hospital for technical assistance; to Ms Yoshiko Nakata, Ms Shuko Sato, and Ms Reiko Taneichi for secretarial assistance.

References