The first report of pyridoxine-deficiency convulsions in humans was by Synderman in 1950. He showed that apathy, failure to gain weight, anemia, and convulsions occurred on a pyridoxine-deficient diet and that administration of pyridoxine corrected the condition.

The 1951 edition of New and Nonofficial Remedies mentioned for the first time that infant convulsions might be caused by pyridoxine deficiency. Finally, the A. M. A. Council on Pharmacy and Chemistry reported in The Journal for Sept. 22, 1951, the whole subject in detail and warned that convulsions in infancy could be produced by pyridoxine deficiency.

Thus the mystery of this peculiar convulsive disorder of young infants occurring during 1952 has been solved. It is our purpose in presenting these clinical case reports to acquaint physicians of the solution of this problem so that they may reopen cases in which a diagnosis of seizures of unknown etiology was made and determine if they were due to accidental pyridoxine deficiency. The pleasure and relief afforded the parents of our six cases through a simple explanation for what appeared to be an ominous condition was very gratifying.

The situation we have described is just another instance of the dangers involved in attempting to copy human milk by blind reliance on laboratory analysis. There probably are several properties of human milk we have not yet learned to discern by laboratory methods. Human milk, it may be noted, has a high level of pyridoxine.

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CONVULSIVE SEIZURES IN INFANTS WITH PYRIDOXINE-DEFICIENT DIET

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In the fall of 1951, four young infants with hyperirritability and recurrent seizures were admitted to the pediatric department of the Saint Joseph's Hospital. Extensive clinical and laboratory evaluations were made, including complete blood cell counts, urinalysis, blood urea nitrogen, electrolyte determinations, glucose tolerance test, x-ray survey, phenylpyruvic acid test, spinal tap, and electroencephalogram. All laboratory procedures on each patient were within normal limits. During their hospital stay, all of the infants clinically improved, with rapid decrease of their hyperirritability and cessation of their seizures. Without benefit of medication, all have remained free from seizure throughout the succeeding two years. The appearance of this small group of unexplained seizures prompted a review of the cases, with the revelation of one pertinent observation. From birth each infant had been fed on liquid SMA formula, which consists principally of defatted cow's milk, vegetable and animal fats, and vitamins, plus iron. Furthermore, the only definitive therapeutic measure undertaken was that of changing diet of each from the liquid SMA to the hospital routine evaporated milk formula, the use of which was continued after discharge from the hospital. Since these original observations in 1951, an additional 50 cases have come to my attention and have provided the basis for this report. No cases were encountered in infants receiving SMA powder formulas.

METHODS AND MATERIAL

The infants reviewed in this study were uniform in the pattern of their problem, varying only in the degree of severity of their symptoms. Clinical observation therefore became the main tool of this investigation. The extensive laboratory work-up originally undertaken was abandoned after a number of patients had shown no appreciable changes from normal. It was felt that of the procedures available, the electroencephalogram was the most likely to provide the desired data on the status of the central nervous system. Wherever possible, electroencephalographic studies were made, with the paraldehyde method of sleep induction previously described. Tracings were done under the usual conditions of normal room temperature, noise level, and reduced illumination with the patient recumbent on a sponge mattress. A standard six channel electroencephalograph was used with the sensitivity set at 7 μV per mm. Twelve electrode placements were used of the bentonite type (all reading 3,000-5,000 ohms); tracings of all areas of the brain were obtained by both scalp-to-ear and scalp-to-scalp techniques.

RESULTS

The clinical observations in these cases provided much important information. All of the infants had been fed liquid SMA from birth and had received no supplemental feedings of solid foods. Some of them had been given additional vitamins in the form of multiple vitamin preparations, none of which contained pyridoxine (vitamin B6). Their ages ranged from 5 weeks to 4 months, with the average about 2½ months. The onset of the syndrome was usually subtle, with an apparent gastrointestinal phase of colic with abdominal distress, spitting up, and hyperirritability. Parents described the infants' activities as becoming increasingly alarming with episodes of crying out, stiffening of the body and extension of the head, staring, and periods of rolling the eyes upward. In most of the cases, these changes became progressively more severe with resultant generalized convulsive seizures of short duration. These seizures occasionally became as frequent as six to eight per day with variations of duration from a few minutes to 10 or 15 minutes. At no time was it possible to demonstrate any evidence of injury, infection, or abnormality that might have contributed to their appearance.
Between seizures electroencephalographic studies were done, on repeated occasions with no clear-cut abnormality evident in any tracing. The well-known lack of established patterns of activity of the very young perhaps obscured some changes so that they were not recognizable; however, comparison of the observations in this group with known normals of the same age did not reveal any significant difference in patterns. Therapeutically, it was possible to control the syndrome either by sedation or by change in diet. Phenobarbitol in doses of 1/8 grain three times a day controlled all symptoms of patients maintained on liquid SMA, but episodes would recur soon after medication was stopped, suggesting that the sedation masked a more deeply based problem.

A change of diet to evaporated milk formulas provided a ready cure for the phenomena with disappearance of symptoms. A return to liquid SMA caused exacerbations within 48 hours. It could be further demonstrated that with patients continued on liquid SMA, the addition of cereal would produce definite improvement.

It was apparent, therefore, that the liquid SMA of 1951 either contained some substance or lacked some element of nutrition to a degree that hyperirritability and convulsive seizures could be produced in some very young infants. Extensive studies failed to reveal any toxic material in the formula. Apparent correlations of the seizures with changes in water supplies induced by drought and with the fatty acid components of the formula were found to be invalid. Vitamin assays, however, showed the formula to contain less than 60 mcg. of pyridoxine per liter following the rigorous autoclaving of the formula. This manufacturing precaution against any possible contamination had, therefore, apparently destroyed much of the pyridoxamine and pyridoxal, the naturally occurring forms of pyridoxine. While no minimum daily requirements have been established for pyridoxine, this level of the vitamin, associated with its previously described effects on the nervous system, suggested that pyridoxine was probably the etiologic agent. Since cases were reported from Texas, Arkansas, and Illinois, a general notice to all physicians was issued by Wyeth, Inc., describing the possible hazard of a pyridoxine deficiency in some infants. This led to the use of the vitamin intramuscularly or orally in at least nine cases of seizures, with definite clinical improvement. The follow-up has of necessity been short, but these patients probably will not have exacerbations if their pyridoxine ingestion is kept above minimal requirements.

**ROLE OF PYRIDOXINE**

The relationship of convulsive seizures to pyridoxine deficiency has been well established in rats, chicks, and pigs; on the other hand, studies in humans have been limited to isolated instances, such as that of Snyderman and associates. They reported a case of a mentally defective child of 4 months who had been maintained on a pyridoxine deficient diet for 76 days with a resultant severe seizure episode. Addition of pyridoxine to the diet prevented recurrences. Stokes and associates have also made some interesting observations on a patient with an apparent congenital metabolic defect of pyridoxine metabolism with resultant need for continued maintenance dosage of pyridoxine to prevent seizures. Therapeutically, Ernsting and Ferwerda have reported some favorable results in the use of pyridoxine in the treatment of epilepsy. One of the patients in the group treated with pyridoxine has provided perhaps the most clear-cut clinical and laboratory evidence of the relationship of pyridoxine to this whole problem.

**REPORT OF A CASE**

The baby had been a full-term newborn infant delivered without difficulty and with no neonatal distress. Feedings had consisted of liquid SMA entirely. At 4 weeks of age, the baby was noted to be irritable and to have supposed colic pains, with tossing of his head and stiffening of his whole body. Progressive changes with staring episodes and generalized seizures were noted. The infant was admitted to the pediatric department of St. Joseph's Hospital at the age of 2½ months. The physical examination was not remarkable. Laboratory studies, including an electroencephalogram, were within normal limits. Feeding of liquid SMA was continued in the hospital with no evidence of seizures; however, it was discovered that a relief nurse had been giving him cereal. Feedings were then limited strictly to liquid SMA with reappearance of symptoms in five days. On the fifth day, the infant became more evidently affected and went into status epilepticus. The eyes remained fixed and staring, pupils contracted with no reaction to light. The body was held rigid with the head thrown back. Generalized convulsive seizures recurred repeatedly with occasional outbursts of an abnormally high-pitched monotone cry. There was some evi-

**Fig. 1.** Electroencephalogram of convulsive seizure during status epilepticus, while the infant was on a liquid SMA diet. In this scale, five vertical lines equal one second and 2 mm. in amplitude equal 50 µv.

**Fig. 2.** Electroencephalogram taken five minutes after injection of 100 mg. of pyridoxine intramuscularly during status epilepticus, while the infant was on a liquid SMA diet. In this scale, five vertical lines equal one second and 7 mm. in amplitude equal 50 µv.
dence of cyanosis about the lips, and there was no response to painful stimuli. Pulse was rapid and regular at 180 per minute. Respiration were gasping at 40 per minute. The patient was placed in oxygen with some improvement of color but no effect on the seizures. He was removed to the electroencephalograph laboratory and connected to the electroencephalograph apparatus. Continuous recording was undertaken with great technical difficulty due to the child's muscular activity. Successful tracing, however, was obtained with evidence of markedly increased voltage of 200 μv and slowing to 2-3 waves per second, which appeared in bursts with recurrently accompanying spikes and lasted 4 to 6 seconds. The bursts were interspersed with 40 μv, 20-per-second fast activity of 3 to 4 seconds' duration (fig. 1). On occasion, during prolonged rigidity, runs of high voltage 3-per-second waves lasting 20 to 30 seconds were obtained. This pattern of activity with accompanying clinical seizures was well established when 100 mg. of pyridoxine was given intramuscularly. For about one minute following injection, there was little change in the electroencephalogram; however, by three minutes, activity had definitely diminished, and by four or five minutes after injection, the electroencephalogram became a normal sleep record (fig. 2). Clinically, without added oxygen, the infant had good color, slept peacefully, and showed no evidence of tremor or rigidity. He was removed to the child's ward and within 24 hours was much improved. In 48 hours, there was little evidence of previous difficulties. A third electroencephalogram, which compared favorably with the preseizure record and did not show any evidence of abnormal pattern, was taken 36 hours after the seizure episode.

The dramatic improvement in this baby in the presence of status epilepticus was most impressive. The rapid absorption and utilization of pyridoxine has been evident from other studies; however, it is felt that this is probably one of the first actual recordings of neurological response to pyridoxine under these circumstances. The infant has been free from seizure on a continued formula of the liquid SMA with supplemental pyridoxine.

TEACHING INTERNAL MEDICINE AT UNIVERSITY OF OKLAHOMA SCHOOL OF MEDICINE

A PROGRAM FOR UNDERGRADUATES

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Recently, those concerned with medical education have been reexamining their aims and methods. The deficiency of technology emphasized is a lack of effective coordination and integration in teaching. Suggested remedies have included relaxing departmental barriers, eliminating some departments, or combining them. Perhaps the need for change may best be brought into focus by a brief review of earlier steps that have led to present forms of medical teaching. With the rapid and imposing accumulation of data pertaining to the functions of organs and organ systems in experimental animals and in man, clinical teachers were left deficient in many of the sciences basic to medicine. This led to the establishment of the "preclinical" departments that now have jurisdiction over a certain number of hours of the student's life. During this same era, the most pressing medical problems were infectious diseases for which effective therapy was unavailable. The all-important bedside care melded the clinical teacher's attitude, and it also limited his horizon. More recently, with the striking reduction in the number of fatal or even serious infections, and with increasing interest in the problems of ageing and of social and emotional adaptation, exclusive emphasis on bedside teaching has given way to a growing interest in the ambulatory patient. The research interests of medical faculties have also changed. The "preclinical" teacher is now more inclined to observe experiments in man, and the clinician is becoming more physiologically minded. These developments call for a closer integration of the subject matter of the various departments and raise the question as to whether the departmental approach to medical education has become outmoded, arbitrary, and uneconomical.

SUMMARY AND CONCLUSIONS

A review of the sequence of events in the 1951-1953 study of a syndrome of hyperirritability and convulsive seizures in young infants is presented. The evidence at hand appears to prove conclusively that these observations occurred in infants fed a liquid SMA preparation, which consists principally of defatted cow's milk, vegetable and animal fats, and vitamins, plus iron and contains insufficient pyridoxine (vitamin B\textsubscript{6}). The manufacturer has added thermostable pure pyridoxine to the new (June, 1953) liquid SMA in an attempt to solve this problem; so far no cases of the syndrome have been reported in infants fed this formula. An interesting group of 54 patients clearly demonstrated the need for pyridoxine in infant nutrition. Those who received pyridoxine with observed clinical improvement supplied valuable empirical evidence of their need for the vitamin. However, the one patient who experienced status epilepticus that was clinically and electroencephalographically demonstrable and improved after pyridoxine intramuscular injection provided the final link in the chain of evidence supporting the syndrome as being the result of a specific deficiency. The ramifications of this problem are numerous and are beyond the scope of this paper. Additional work seems indicated in order to provide a more specific determination of minimal daily requirements for pyridoxine in infancy. Furthermore, a better understanding of the role of pyridoxine in nerve cell metabolism would no doubt be of value in answering some of the questions of its significance in transamination, in the metabolism of glutamic acid, and in the process of myelination.

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