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Dystonia and Dyskinesia in Glutaric Aciduria Type I: Clinical Heterogeneity and Therapeutic Considerations

M. Kyllerman, *O. H. Skjeldal, †M. Lundberg, ‡I. Holme, §E. Jellum, ‖U. von Döbeln, *A. Fossen, and ¶G. Carlsson

*Department of Pediatrics II, University of Gothenburg, Göteborg, Sweden; *Department of Pediatrics, Oslo University, Oslo, Norway; †Department of Pediatrics, Huddinge University Hospital, Huddinge, Sweden; ‡Department of Clinical Chemistry, Sahlgrenska Hospital, University of Gothenburg, Göteborg, Sweden; §the Institute of Clinical Biochemistry, Oslo University, Oslo, Norway; ‖Department of Clinical Chemistry, Huddinge University Hospital, Huddinge, Sweden; and ¶Bräcke Östergård Regional Child Habilitation Center, Göteborg, Sweden*

Summary: Glutaric aciduria type I (GA-I) is an inborn error in the degradation of lysine, hydroxylysine, and tryptophan due to a deficiency of glutaryl-CoA dehydrogenase. Glutaric, 3-OH-glutaric, and glutaconic acids are excreted in the urine, particularly during intercurrent illness. The enzyme may be assayed in leukocytes, cultured fibroblasts and chorionic villi. Twelve new cases, 9 months–16 years of age, are reported, comprising all known cases of GA-I in Sweden and Norway. Ten had a severe dystonic–dyskinetic disorder, one had a mild hyperkinetic disorder, and one was asymptomatic. Two children died in a state of hyperthermia. Carnitine deficiency and malnutrition developed in patients with severe dystonia and dysphagia, which necessitated substitution and gastrostomy. A slowly progressive dyskinetic disorder developed in spite of adequate early dietary treatment in one subject. Macrocephaly was found in three. Computed tomography and magnetic resonance investigations in 10 showed deep bitemporal spaces in 7. Neuropsychological testing of 8 of 12 subjects demonstrated receptive language function to be superior to expressive language and motor function. Cognitive functions were obviously less affected than motor functions. A review of 57 pooled cases showed that a severe dystonic syndrome developed in 77%, a mild extrapyramidal syndrome in 10%, and 12% were asymptomatic. This disorder may pass undetected in the cerebral palsy and mentally retarded child and adult populations. Repeated urine examinations of organic acids in the urine and enzyme assay may be necessary to confirm GA-I. **Key Words:** Glutaric aciduria type I—Dystonia—Dyskinesia—Extrapyramidal disorder.

In glutaric aciduria type I (GA-I), a deficiency of glutaryl-CoA dehydrogenase causes defective degradation of tryptophan, lysine, and hydroxylysine, with excretion of glutaric acid, 3-OH glutaric acid, and glutaconic acid in the urine (1–3). A severe and permanent dystonic–dyskinetic syndrome usually develops in clinically affected patients after metabolic derangements during the first year of life (4,5). This disorder may pass undetected in populations of children and adults with cerebral palsy and mental retardation. Slowly progressive courses and asymptomatic homozygotic cases have been observed (6).

Speech functions may be severely affected due to dysarthria, necessitating various modes of sign and symbolic communication. Intellectual functions appear to be well preserved, considering the severe motor handicap (4).

Characteristic deep bitemporal spaces on computed tomography (CT) have been described (7–11),

A videotape segment accompanies this article.

Address correspondence and reprint requests to Dr. M. Kyllerman, Department of Pediatrics II, Östra Sjukhuset, S-416 85 Göteborg, Sweden.

and in severely dystonic cases, dominating neuropathological changes have been detected in the basal ganglia, especially in the caudate and putamen (12–14).

The complete spectrum and degree of neurologic abnormality is not known. No overview of a large number of cases addressing this issue has as yet been published. The purpose of this article is to report all 12 diagnosed Swedish and Norwegian cases and to review these patients together with those in four recent series reported in 1989–1991 (6,15–17), comprising a total of 57 cases. In addition, neuropsychologic findings are published for the first time in this disorder.

MATERIAL

All parents were nonconsanguineous and ethnic Scandinavian. There were five boys and seven girls, including two pairs of siblings (Table 1). All had normal birth weights and were products of full-term pregnancies. The mean birth weight was 4,002 g (range 3,090–4,410) and the mean head circumference was 36.7 cm (range 36–38). Five had head circumferences of ≥37 cm. Two of the 12 children died at the ages of 9 months and 2⁹⁄₁₂ years, respectively, both in hyperthermia and shock without recovery of any infectious agents or convincing laboratory evidence of infection.

The neurologic outcome was evaluated in 10 patients who were 2 years or older (median age 13 years, range 2–16 years). Four typical case histories are presented below.

Patient 1

A 16-year-old girl with a severe dyskinetic–dystonic syndrome was the fifth reported case in 1977 of glutaric aciduria (4). Psychomotor development was normal until 12 months of age, when she started to walk without support, could speak a few single words, and had pincer grasp and bimanual functions.

By 12 months, 3 days after the onset of a common cold with a high temperature, she had slight diarrhea and anorexia, and there was a sudden deterioration with convulsions, short episodes of respiratory arrest, and loss of mental contact for half a day. There was a mild metabolic acidosis but no hypoglycemia. She improved with intravenous rehydration and glucose infusion. After this episode, she had a severe head lag, trunk hypotonus, choreoathetotic movements, loss of expressive speech, and a developmental delay at the 3-month level.

When she was 24 months old she had another bout of febrile gastroenteritis. On the 2nd day of illness there was another sudden deterioration, which left her with a permanent tetraparetic dyskinetic–dystonic syndrome with complete loss of voluntary motor control and expressive speech.

GA-I was diagnosed on high levels of glutaric, glutaconic, and 3-hydroxyglutaric acids in the urine and trace levels of glutaryl-CoA dehydrogenase activity in fibroblasts. Protein restriction and riboflavin supplementation caused a reduction of urine metabolite excretion but no clinical improvement. Despite several febrile episodes she has had no further compromise after the age of 2 years.

Major dysphagia successively caused malnutrition, manifest by the age of 15 years. Gastrostomy was performed and the patient's weight increased rapidly. With increased comfort and satisfaction, there was an impressive reduction of dystonia and attacks of profuse sweating. By the age of 16 years

TABLE 1. *Age at onset, diagnosis, follow-up, and dominating neurologic abnormality in 12 Swedish and Norwegian patients with glutaric aciduria type I*

Patient no.	Sex	Age at onset (mos)	Age at diagnosis	Age at follow-up (n = 10) (yrs)	Dominating abnormality
1	F	12	24 mos	16	Dystonia–dyskinesia
2	M	6	30 mos	15.5	Dystonia–dyskinesia
3	F	10	16 mos	14	Dystonia–dyskinesia
4	F	6	6 mos	3	Normal
5	F	6	6 mos	+⁹⁄₁₂	Dystonia–dyskinesia
6	F	9	28 mos	14	Dystonia–dyskinesia
7	M	8.5	9 mos	7	Dystonia–dyskinesia
8	M	18	0.5 mos	8	Slight hyperkinesia
9	M	7	11 yrs	13	Dystonia–spasticity
10	F	13.5	25 mos	5	Dystonia–dyskinesia
11	M	7	32 mos	+2⁹⁄₁₂	Dystonia–dyskinesia
12	F	4	15 yrs	15	Dystonia–dyskinesia

the tendon reflexes were brisk, there was no foot clonus, and she had an essentially pure extrapyramidal syndrome with anarthria. She was wheelchair bound and communicated by eye movements. She had a large head and a CT scan demonstrated bitemporal subdural spaces (Fig. 1) and some frontal cerebral atrophy. On testing her verbal IQ was 68 and her performance IQ was 50.

Patient 8

A 6-year-old boy was born at full term after an uneventful pregnancy. His 2-year-older brother had a severe dystonic syndrome and had GA-I diagnosed when he was 2 years old. Because of this, the patient was examined for the same disorder when he was 7 days old. The urine glutaric acid level was high and he had only trace levels of glutaryl-CoA dehydrogenase activity in fibroblasts. CT of the head showed deep bitemporal subarachnoid spaces. From the start he was treated with a low-protein diet and riboflavin supplementation.

His psychomotor development was only slightly retarded. At the age of 1½ years he walked and ran with a mild gross motor incoordination, giving the impression of a clumsy child. His language expression and comprehension were appropriate for age and there was a mild dysarthria. Muscle tone at rest was somewhat low and the tendon reflexes were brisk. The plantar reflex was extensor on the right and flexor on the left. A psychological examination indicated that he had an attention deficit disorder and functioned at the borderline to normal IQ range. He had been given methylphenidate, and had some improvement of attention.

Patient 4

A 3-year-old girl had normal early psychomotor development. By 6 months she could crawl, by 12 months she could walk with support, and by 14 months of age she walked unassisted. She had pincer grasp at 10 months and spoke 5–10 single words at 15 months of age.

When 6 months old, she refused feedings for 2 days but did not vomit. The third morning she was obtundated and could hardly be awakened. On admission to the hospital she ran a high temperature and had a mild metabolic acidosis and hypoglycemia (0.4 mmol/L). She was given intravenous glucose, buffer, and fluids. She was comatose, hypotonic, and tachypnoic for half a day. She had no convulsions. On the 2nd day of admission she was restored and had neither lost development nor acquired abnormal neurologic signs. Investigation subsequently disclosed a high urinary glutaric acid and 3-hydroxy-glutaric acid excretion. A diet low in tryptophan and lysine was begun and she was given L-carnitine supplementation.

By 3 years of age she was an alert little girl with well-developed language and normal gross and fine motor function. She had a large head and a CT scan showed deep bilateral temporal spaces and wide frontal subarachnoid spaces.

Patient 9

A 13-year-old boy had a normal neonatal period and early development. When 7 months old, a few days after becoming ill with a slight cold, he suddenly deteriorated and was referred to the hospital for presumed encephalitis. Cerebrospinal fluid (CSF) was normal and he had no laboratory signs of infection. After this he could no longer sit unsupported, and he had muscle hypotonus and a total head lag. A CT scan demonstrated wide bitemporal spaces. At the age of 10½ years GA-I was first detected in a younger sister and then in the patient

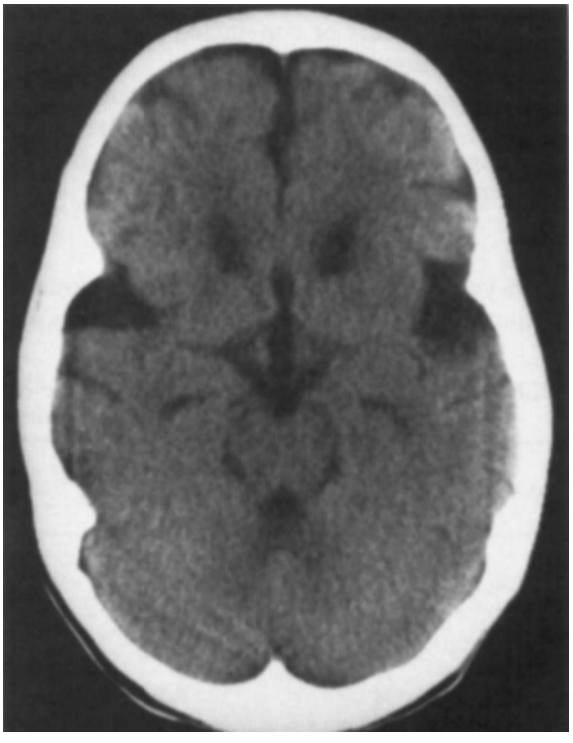

FIG. 1. Computed tomography of a 16-year-old patient with glutaric aciduria type I demonstrates central and cortical atrophy. The changes are most prominent at the caudate head and in the insular region.

because of a high urinary output of glutaric acid and trace levels of glutaryl-CoA dehydrogenase activity in fibroblasts. A magnetic resonance (MR) scan confirmed the previous CT findings. A severe dyskinetic–dystonic syndrome with loss of purposeful motor function and expressive speech gradually emerged. Protein restriction and riboflavin supplementation reduced urinary glutaric acid but had no effect on the clinical condition. He was dystonic with attacks of profuse perspiration.

Because of feeding problems and manifest malnutrition, gastrostomy was performed at the age of 13 years. During the following 6 months the improved nutrition and fluid balance caused a marked improvement and weight gain. Decreased muscle tension and a reduction of dystonia paralleled the impression of an improved well-being.

METHODS

This series of 12 cases was collected from several clinics and was diagnosed in ordinary practice (Table 1). No specific population search procedure was performed. Because of the relatively small populations, the organization of health care, the limited number of laboratories, and close collegial connections, we are sure that these are all the diagnosed GA-I cases at present in the two countries.

The neurologic impairment was classified as severe with generalized dystonia, notes on tetraparesis, diplegia, or choreoathetosis, and as slight with motor incoordination or notes on clumsiness or developmental delay. Macrocephaly was accepted with head circumference +2.0 SD or more of normal (18).

Biochemical Assays

The diagnosis was based on analyses of organic acids in urine by gas chromatography–mass spectrometry performed at the Departments of Clinical Chemistry at Sahlgrenska Hospital and Huddinge Hospital in Sweden, and the Institute of Clinical Biochemistry at Rikshospitalet in Norway. Glutaryl-CoA dehydrogenase activity was assayed as previously described (19) on cultured fibroblasts in nine subjects (patients 1–3,5–9, and 10) or leukocytes in one (patient 12) at Sahlgrenska Hospital, Sweden.

Psychologic Assessments

Eight children (patients 1–3,5–8, and 9), ages 3.8–16 years (mean 10.5 years), took part in the neuropsychological investigation. Because of the extensive gross and fine motor deficits in most of the children, nonverbal and nonmotor tests were selected, i.e., the Peabody Picture Vocabulary Test, the Coloured Progressive Matrices, and the Motor-free Visual Perception Test (MVPT) (20). For six of the subjects an adapted version of the test material was used. The test material was cut into pieces and affixed to a wooden frame. Five of the children responded by eye-pointing, whereas one child answered by pressing an indicator level with the chin. Because of mental and physical exhaustion, the test session was discontinued after a few trials, and no test results could be reported for this child. Three children with less pronounced motor deficits were tested with the standardized test booklet forms.

RESULTS

Ten of the 12 patients had severe dystonia with a tetraparetic distribution (Table 1). This was also quite obvious in the youngest child, who died at 9 months of age. The dystonia and dyskinesia increased on action and postural change. All demonstrated some side predominance. In one patient (patient 9) there were clinical signs of spasticity in addition to the extrapyramidal signs. One 8-year-old boy (patient 8) had a slight choreoathetosis and was hyperactive. He had been treated for GA-I since the neonatal period. One child (patient 4) was also treated and was neurologically normal at 3 years of age. There was neither dysmetria nor dyssynergia, indicating unaffected cerebellar functions. Three were macrocephalic, with head circumference +2.0, +2.5, and +2.8 SD scores of normal (18), respectively.

The functional neurologic impairment in the 11 patients who were 2 years and older was severe in nine, slight in one, and one patient was nonimpaired (Table 2). Eight children were wheelchair bound and needed assistance to move.

Nine patients had had an acute encephalopathic onset, usually associated with infection during the 1st year of life. Eight of these developed a dystonic syndrome with severe impairment. One patient had escaped clinical neurologic damage and functional impairment in spite of 12 h of unconsciousness at 6 months of age. Two patients insidiously developed dystonia and choreoathetosis, respectively, in both manifest by the age of 4 years.

Neuropsychological Investigation

Test results could be evaluated in seven subjects. Most of the children performed with great efforts

TABLE 2. *Mode of onset (acute or insidious) of glutaric aciduria type I or quiescent disorder and neurologic impairments in 49 subjects*

	Impairment						
	Acute onset			Insidious			
	S	SL	N	S	SL	Quiescent	All
Amir et al., 1989	3	—	—	—	—	3	6
Haworth et al., 1991	6	—	—	1	3	—	10
Hoffmann et al., 1991	4	—	—	4	—	1[a]	9
Morton et al., 1991	8	—	1[b]	3	1	—	13
Kyllerman et al., 1993	8	—	1	1	1	—	11
Total	29	—	2	9	5	4	49

S, severe; SL, slight; N, none.
[a] Treated from infancy, present age 2 5/12 years.
[b] Died at onset 36 months of age.

during the test procedure as evidenced by increased dystonia, dyskinesia, and profuse sweating. The extensive problems with verbal speech and motor performance prevented a fully standardized test procedure for most of the children, and the test results were negatively affected by lack of endurance. Three subjects were found to have normal verbal comprehension and logical reasoning ability as shown by Ravens Progressive Matrices and MVPT. Four were found to have a verbal comprehension in the mild mental retardation range (IQ 50–70) and one in the severe mental retardation range (IQ <50). Three subjects had a performance IQ in the mild and three in the severe mental retardation range. The two physically best-functioning children with a fully developed verbal speech showed signs of attention deficits and performed at a borderline to normal level (IQ 70–90). Four subjects had a higher verbal than performance IQ, three had the same IQ level in both, and one had a lower verbal than performance IQ.

Neuroradiologic Findings

CT scanning of the brain was performed in 10 patients. Three were examined with MR imaging in addition. In seven of the patients, enlarged CSF spaces lateral to the temporal lobes were detected (Fig. 1). This was observed in severely impaired, in less affected (patient 8), and in asymptomatic cases (patient 4). All investigated children had a slightly dilated ventricular system, and in one child there was a decreased attenuation of the cerebral white matter. The neuroradiologic findings in four patients in this series were reported earlier by Hald et al. (8).

Treatment

Specific therapy comprised protein restriction (1–2 g protein/kg) with a low lysine intake (corresponding to 50–100 mg/kg). Riboflavin supplementation (50–100 mg/day) was given to all patients except one (patient 4) after diagnosis. With this treatment, a decreased output of metabolites could be demonstrated in the urine. However, in already symptomatic cases this treatment could not be shown to reverse or improve the clinical situation.

Two patients were given specific treatment after diagnosis before onset of any neurologic signs. One patient who was treated from the neonatal period (patient 8) had insidiously developed a hyperkinetic attention deficit disorder by the age of 4 years with onset at about ~18 months. One (patient 4), who had a severe acute onset at the age of 6 months, developed normally by the age of 2 years, after 18 months of continuous therapy.

One boy (patient 2) had one additional minor deterioration by the age of 14 years during adequate treatment. One child (patient 5) died at 9 months of age while receiving full dietary treatment.

Early L-carnitine supplementation with 50–100 mg/kg/day was given to seven of our patients. Late L-carnitine supplementation with the same amounts was given to four patients (patients 1, 2, 3, and 6) at ages 13–14 years, after workup that showed subnormal serum carnitine levels in four patients and low muscle carnitine levels in the three patients assayed. No clinical improvement could be observed during 1 year of supplementation.

Nonspecific metabolic treatment included securing an anabolic situation with adequate energy and water balance in both the acute and chronic conditions. Requirements were difficult to meet and assess due to the pseudobulbar dysfunction with severe feeding difficulties, and the high energy needs secondary to muscular tension and increased water loss due to perspiration. Emaciation gradually became obvious in five long-term survivors (patients 1, 3, 6, 9, and 12) between the ages of 10 and 15 years. Percutaneous gastrostomy was therefore performed in three (patients 1, 6, and 9). Within months a dramatic nutritional improvement could be substantiated, with a rapid weight increase in two. Concomitantly with this, the dystonia was greatly improved and there was a marked reduction of the dystonia. The psychologic effects on the fam-

ilies and the care load were markedly relieved at the same time.

Pharmacological treatment did not eliminate dystonia or dyskinesia. L-Dopa was tried without effect. Baclofen reduced hypertonus marginally and sodium valproate was reported to reduce dysphagia in one patient. Gamma-vinyl-GABA caused the extremely low CSF γ-aminobutyric acid levels to rise to supranormal levels in one patient but had no clinically noticeable effects. Diazepam was used by several patients, with some relief of dystonic swings.

REVIEWED SERIES

Presently there exist four series of patients with GA-I, all published in 1989–1991 (6,15,16,17). To study the clinical spectrum of GA-1, the Swedish-Norwegian series of 12 cases was pooled with the other four series comprising 45 subjects, making a total of 57 reviewed patients. The majority, 38 (67%), had had an acute, encephalopathic onset. With few exceptions, this had occurred during the 1st year of life. A minor group, 14 (25%), had had an insidious onset and 5 subjects (9%) were asymptomatic, two of whom had been given specific diet, riboflavin, and carnitine from infancy. Nine (16%) had died, between 6 months and 7 years of age.

The dominating neurologic signs reported were reviewed in those 2 years or older, n = 49 (Table 2).

Severe impairment was described in 38 (77%). The oldest patient was a 37-year-old man who had spastic quadriplegia, dystonia, choreoathetosis, and used a Bliss board to communicate (15). Twenty-four had notes on a dominating generalized dystonia, frequently combined with dyskinesia and dysarthria. Spasticity was reported in 11, in all but one by the same author (17), who probably applied a different nomenclature. Three were reported to have seizures.

Slight impairment was described in five (10%). The oldest reported patient, who was 9 years old, developed in the low normal range and had hypotonia and incoordination but no involuntary movements (15). The dominating abnormality in the group was motor incoordination, mild dyskinesia, and mild developmental retardation. Six subjects were *nonimpaired* (12%). One child died at onset at 3 years of age. The oldest reported asymptomatic homozygote was a 37-year-old man. This man has also fathered children with a heterozygous woman (6). There are also examples of parenthood in symptomatic cases with slight impairment (17).

Macrocephaly was reported in 26 subjects and had been observed both at birth and as a result of a rapidly growing head circumference during the first months.

Outcome by type of onset was studied in a restricted group comprising 45 symptomatic cases of the 49 subjects who were 2 years or older (Table 3). Thirty of 31 (97%) patients had had an acute onset that resulted in severe impairment, and one had escaped clinical damage. Nine of 14 (64%) had had an insidious onset and had developed severe impairment, and 5 of 14 (36%) had slight impairment.

DISCUSSION

At the present time, ~100 cases of GA-I have been described in short case reports or small series of cases (3,6,15,16,17,21). Our 12 Swedish and Norwegian patients comprise all diagnosed cases encountered in ordinary clinical practice since 1977 in a total population of ~10 million. This nonsystematic collection of subjects and the evolving picture of a disease with an extremely variable course could indicate that GA-I is an underdiagnosed metabolic disorder in both the child and adult populations. No reliable prevalence figures are available. Our early assumption that the prevalence may be on a par with that in phenylketonuria (21) may still be reasonable, although not enough cases have in fact been diagnosed. In restricted ethnic groups, the prevalence may, however, be considerable (15,17). The largest accumulation of cases appears to be in the Amish Lancaster population, with 38 diagnosed cases at present (R. I. Kelly, unpublished observations), 14 of which have been reported in some detail. Even within this genetically homogeneous group of subjects, the whole spectrum of outcomes has been encountered. By 1992, 11 cases from various ethnic groups had been diagnosed in Israel (O. Elpeleg, unpublished observations). Four of these, 12–46 years of age, are asymptomatic.

By pooling our cases with 45 others from recent

TABLE 3. *Outcome by type of onset; review series (n = 45)*

			Impairment					
			Severe		Slight		No	
Onset	n	%	n	%	n	%	n	%
Acute	31	100	30	97	0	0	1	3
Insidious	14	100	9	64	5	36	0	0
	45		39		5		1	

clinical series, we had the opportunity to study various types of onset and the marked clinical heterogeneity within sibships and to define the major neurologic subtypes.

The characteristic acute encephalopathic onset occurs during the second part of the 1st year of life in two-thirds of cases of GA-I. An acute onset is usually followed by severe impairment and a dystonic–dyskinetic syndrome. Occasional cases exist with acute onset followed by a mild hyperkinetic syndrome. At least two reported cases seem to have escaped clinical neurologic damage in spite of a severe first attack. A diagnosis of sequelae secondary to encephalitis is frequently made. This fact, and the stable course after early, severe brain damage, makes occasional GA-I cases prone to be hidden within the cerebral palsy and mental retardation populations. Case 12 seems to corroborate this statement. She was long accepted as having a postaphyic cerebral palsy syndrome and was diagnosed as GA-I at the age of 15 years in the course of preparation of this article. A slowly progressive dyskinetic–dystonic disorder, usually a choreoathetosis or motor incoordination syndrome with an attention deficit disorder, develops in 25% of cases of GA-I.

Macrocephaly (12) is not an obligatory sign but has been reported in approximately half the patients. There is no definite correlation between macrocephaly and clinical neurologic signs. Some of our Swedish and Norwegian patients were normocephalic from the start and had severe impairment. Others with equally poor outcome had severe macrocephaly and rapidly growing head circumference during the 1st year of life, leading to subduroperitoneal shunt operations in two. Macrocephaly and characteristic CT findings occurred in an asymptomatic case. The cause of the macrocephaly has not been adequately explained but may be associated both with brain edema and with obstruction of the arachnoid villi outflow.

Asymptomatic cases with quiescent GA-I were detected in <10% of the accumulated review series. These were diagnosed in family investigations and prompt the practice of conscientious investigation of all siblings of clinical cases. Undiagnosed asymptomatic cases may exist even in small sibships and the disorder may also be considered in children with macrocephaly or bitemporal wide subdural spaces or hygromas on CT scans. In fact, this combination appears to be so specific as to be considered highly indicative of GA-I (3,9,12,15,16,17).

The presence of all clinical presentations in large families with the same gene mutation (17) raises the difficult problem of pathogenesis. The basal ganglia, in particular the putamen, bear the brunt of damage, with almost complete loss of neurons in advanced cases (12). It is reasonable to assume toxic local damage as a result of acute metabolic decompensation, mainly during vulnerable developmental periods. Whether the metabolites exert a direct neurotoxic effect or are mere indicators of a deranged neurometabolism is not possible to state with certainty. Intrauterine damage seems to occur because babies with GA-I have been born with large heads (22) and the characteristic CT findings and white matter hypodensities. If the damage to the fetal brain were to be caused by toxic metabolites, these substances would then have to be confined to the fetal brain compartment. This is difficult to accept because these low-molecular compounds would easily pass compartment boundaries and be eliminated by the placenta. In addition to local toxic effects, compromise of mitochondrial energy production and other possibilities have to be considered.

One of the basic theses about neurometabolic diseases is that they should be diagnosed and treated before the onset of permanent neurologic damage. Early treatment has been shown to be effective in that the wide bitemporal subdural spaces and white matter lucencies have dissolved with time in young patients who seem to develop well (6,16). Presymptomatic treatment could not be relied on to prevent the development of a hyperkinetic attention deficit disorder, as demonstrated by one of our patients.

Once neurologic signs have been established, our experience shows that adequate dietary treatment, coenzyme riboflavin replacement, and L-carnitine substitution are not able to reverse the clinical condition. On the other hand, the treatment may provide the patient with extra safety margins for sudden metabolic derangements. L-carnitine should be given because carnitine deficiency seems to develop in long-term survivors without replacement therapy (23–26). Normal outcome without any treatment whatsoever has been reported by Amir et al. (6).

In view of these observations, we believe that no definite conclusions can at present be drawn regarding the preventive effect in all cases of this type of treatment. It seems likely, however, that early treatment may prevent a severe course of the disease and help avoid development of the severe, generalized dystonic form.

Nonspecific treatment with percutaneous gastrostomy to secure adequate nutrition in patients with severe dysphagia was very successful. In children with mental and motor disabilities, oral–motor dysfunction and prolonged assisted feeding significantly reduce energy intake (27). In our patients, gastrostomy improved the nutritional situation and, what was more remarkable, also the extrapyramidal signs. This type of treatment should be considered when feeding times exceed 20–30 min and when the weight increase is subnormal in patients with GA-I.

The extensive communicative and motor problems prevented a standardized testing procedure and only tentative conclusions can be drawn. All the children seemed to be able to understand verbal instructions. The ability to treat verbal material was less damaged than the general motor function in this group of children. One particular feature was the heavy involvement of expressive speech functions. The dysarthria was so severe as to quality for anarthria in several cases. Speech expressive function was closely linked to gross motor impairment and was judged to be predominantly motor in quality. Associated expressive linguistic dysphasia was difficult to evaluate but of minor importance, to judge from the capacity to cope with Bliss and other verbal symbolics of expression. A surprisingly good cognitive capability was found. This is not usually encountered in children with severe brain damage but is similar to that found in dystonic and choreoathetotic children with cerebral palsy (28).

The diagnosis of GA-I rests first on clinical suspicion of the disorder. This review demonstrates that GA-I has a much larger clinical variation than just severe dystonia, and should be looked for in slowly or stepwise progressive hyperkinetic disorders, attention deficit disorders with motor dyscoordination, macrocephaly, CT findings with the characteristic wide bitemporal spaces, and also in asymptomatic siblings of index cases. It is not a disorder confined to infants and toddlers but may also be found in adolescents and in the adult population. Urinary excretion of metabolites may be intermittent and low and only found during intercurrent infections. Enzyme assays of glutaryl Co-A dehydrogenase define the disorder and constitute the proof that ultimately should be sought in suspected cases. Prenatal diagnosis is preferably made by enzyme assay of chorionic villi (29) and has made it possible for several couples to undertake the risk of another pregnancy and so to expand the family with healthy children.

LEGEND TO VIDEOTAPE

Each subject is identifiable by number in the tables of the article. The first three segments demonstrate severe dystonia in 14 and 15-year-old patients with GA-I. The fourth segment shows a mild dyskinetic syndrome in a 3-year-old boy.

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