CASE REPORTS

Glutaric Aciduria Type I Misdiagnosed as Leigh's Encephalopathy and Cerebral Palsy

P. Stutchfield
Mary Anne Edwards
R. G. F. Gray
P. Crawley
Anne Green

There are many metabolic diseases which present with neurological dysfunction in infancy. A large number of these, particularly the storage disorders, present with regression and the degenerative process often leads to intensive biochemical investigations. It is not uncommon for a patient with chronic neurological handicap to be labelled with a 'tentative' diagnosis which is unproven. The case described here illustrates this problem.

Case report

This nine-year-old boy was born at full term to unrelated caucasian parents. Birthweight was 2·95kg. There were no neonatal problems. He developed normally until five months of age when he had a series of focal seizures involving his right arm and leg. Investigations at this time, including plasma electrolytes, glucose, CSF microscopy and culture, congenital infection screen, skull X-ray and urinary amino-acid chromatography, were all negative.

At seven months, following an upper-respiratory tract infection, he was admitted to a local hospital with further focal convulsions, severely dehydrated and acidotic (lowest pH 7·14, bicarbonate 10·2 mmol/l). He had no diarrhoea or vomiting. The infection screen, including lumbar puncture, was negative. An EEG showed changes compatible with an encephalitis. Following rehydration and correction of the acidosis, he was transferred to our regional paediatric unit for further investigation.

The only abnormal results at this time were a minimally elevated fasting plasma lactate level of 2011μmol/l (normal range up to 1700μmol/l) with pyruvate concentration 140μmol/l (normal range 40 to 70μmol/l).

At this time he was unable to sit and had generalised central hypotonia with very poor head control. He tended to turn his head to the right. He appeared aware of his surroundings and attempted to reach for objects. However, he made no babbling noises although his hearing appeared normal. He had a marked startle response to sound.

His sister had died in 1971, aged 13 months, having presented two months earlier with generalised convulsions followed by coma. She had previously been well, with normal development. No cause was found for her illness. Permission for postmortem was not granted. This illness occurred two weeks after her third whooping cough immunization.

In view of the acidosis and recurrent fits, the suggestion of a defect in pyruvate metabolism, and the possibility of a similarly affected sibling, a tentative diagnosis of Leigh's encephalopathy was made. This remained the diagnosis over the following three years.

At 11 months he had a further acidotic episode (lowest bicarbonate 12·6mmol/l). He was not dehydrated and there was no obvious pecipitating factor. He had not achieved new developmental milestones. He was noted to have variable muscle tone of his limbs and choreiform movements. Over the following year, while on regular diazepam, he had five further convulsions. Control improved with sodium valproate.

During his third year he developed marked athetoid movements and dystonia. He did not reach out for objects. His head control was less than that of a six-month-old infant. He was not vocalising. More detailed investigation at this stage included skin fibroblast pyruvate carboxylase activity, red-cell transketolase activity with and without added thiamine and urinary inhibition of ATP-thiamine pyrophosphate phosphototransferase. These investigations were all normal and failed to provide additional evidence for the diagnosis of Leigh's encephalopathy. In view of the lack of deterioration of neurological state and a CT scan showing cerebral

atrophy, it seemed more likely that he had athetoid cerebral palsy with mental retardation. However, this did not explain the two episodes of acidosis.

Now, at nine years, he is still unable to sit. He has very poor head control with dystonia and athetosis, which becomes particularly marked when he is agitated. As a result it is difficult to elicit his reflexes but his knee jerks are present and normal. Plantar reflexes are flexor. His left arm is usually held extended and internally rotated. He does not reach for objects with his right hand. He is aware of his surroundings and shows the social response of an 18-month-old-child. From eight months he has had breath-holding attacks which usually have an emotional precipitant. He screams, holds his breath, becomes cyanosed and may lose consciousness. He also has a tendency to sweat profusely and has intermittent episodes of unexplained fever.

At present his weight is 12kg, length 92cm, both well below the 3rd centile. His head circumference is 50cm, on the 3rd centile. During his first year his weight and height increased appropriately; he then failed to thrive. There is no evidence of chronic infection or malabsorption. His calorie intake has been variable, ranging from 800 to 1800kcal/day, with protein intake 3 to 5g/kg/24 hours.

As a result of the recent establishment of the techniques used to diagnose organic acidurias at our Regional Metabolic Unit, it was decided that this further selective investigation should be undertaken.

Results of investigations at nine years of age

Urinary organic acids were analysed by gas chromatography with mass spectrometry (Goodman and Markey 1981). Interpretation was complicated by the presence of valproic acid and its metabolites. The major abnormal peak was glutaric acid (4·9mmol/mmol creatinine) with a smaller but abnormal amount of 3-hydroxyglutaric acid.

The capacity of cultured fibroblasts to oxidise various radiolabelled substrates was measured by the methods of Bennett *et al.* (1984*a*). The oxidation of DL(6-C14) lysine was grossly deficient (<7 per cent of control mean) whilst that of (1-C14) oleate, (1-C14) octanoate and (1-C14) butyrate was normal. Plasma carnitine concentration was grossly decreased—total carnitine 10·1μmol/l (normal range 23·6 to 59·3μmol/l); free carnitine 9·5μmol/l (normal range 19·8 to 45·1μmol/l) and acyl carnitines 0·6μmol/l (normal range 0·8 to 19·0μmol/l.

Discussion

Glutaric aciduria type I results from failure to metabolise the amino acids lysine, hydroxylysine and tryptophan. It was first described by Goodman *et al.* (1975) and is inherited as an autosomal recessive condition. The presenting symptoms and clinical course of the eight reported cases, together with our patient, are shown in Table I.

The mean age at onset of illness was seven months and in all cases occurred before 14 months; the presenting features were hypotonia with delayed development or an encephalitic-type illness. All showed motor inco-ordination with hypotonia in infancy leading to dystonia with choreo-athetoid movements. The majority were severely incapacitated by this. A stepwise deterioration was seen in two patients following acidotic/encephalitic-like illnesses. The clinical course of the others was variable but some, like our patient, later entered a stable phase. Convulsions occurred in four of the nine and episodes of acidosis were recorded in only five. The degree of mental retardation is variable; two children at school, aged seven and nine, were reported to have normal intelligence, possibly suggesting that these cases have a milder form of the disease. However, it is interesting to note that in neither of these two cases were acidotic episodes or fits reported, possibly suggesting that these may have affected mental development in the others.

The diagnosis is suggested by the history and clinical findings and is confirmed by the presence of excess glutaric acid and 3-hydroxyglutaric acid in the urine. The metabolic abnormalities result from a deficiency of glutaryl CoA dehydrogenase, which has been demonstrated in various body tissues including fibroblasts (Goodman *et al.* 1975). Antenatal diagnosis is possible as the deficiency has been shown in the cultured amniotic fluid cells of an affected fetus. (Goodman *et al.* 1980).

Our patient had a urinary organic acid profile consistent with the diagnosis, although interpretation was complicated by the presence of sodium valproate and metabolites (Bennett *et al.* 1984*b*). Fibroblast oxidation studies confirmed the diagnosis by showing a gross defect in lysine oxidation with normal fatty acid oxidation.

The low plasma carnitine level is probably secondary to the basic metabolic defect and has been described in a variety of organic acid disorders (Chalmers *et al.* 1983). It may have important implications for treatment.

The pathogenesis of the disease has been investigated. Postmortem studies (Goodman *et al.* 1977, Leibel *et al.* 1980) have shown severe neuronal loss in the caudate nucleus and putamen with a marked decrease in gamma-aminobutyric acid (GABA) content and GABA synthetase

TABLE I

Cases of glutaric aciduria

Reference	*Sex*	*Age onset (mths)*	*Presentation*	*Convulsions*	*Acidosis*	*Estimated mental ability*	*Development and clinical course*
Goodman *et al.* 1975	F	3	Irritable, neurological deterioration following mild gastroenteritis	—	—	?	1 yr—generalised spasticity, scissoring —tonic neck posturing
Goodman *et al.* 1975	M	7½	Poor head control, unable to sit	—	+ Chronic acidosis	Retarded	2 yrs—generalised spasticity 7½ yrs—dystonia athetosis, opisthotonus —numerous admissions, high fever, vomiting and diarrhoea 10 yrs—died, 24 hr illness diarrhoea and vomiting, acidotic
Gregerson *et al.* 1977	M	?	2 yrs—difficulty walking, mild cerebellar ataxia	—	—	Normal at 8 yrs. Doing well at school	6 yrs—walking—mild ataxia—speech dysarthric 9 yrs—involuntary movements increased—choreiform hyperkinetic movements, dystonic extensor and flexor spasms
Gregerson *et al.* 1977	M	14	Convulsions, encephalic-like illness	+	—	Retarded	14 mths—walking 18 mths—unable to walk or sit—multiple choreiform movements hypotonic 4 yrs—intermittent dystonic extensor and flexor spasms
Kyllerman and Steen 1977	F	4–7	3 episodes crying, apnoea, cyanosis	+	+ +	Normal at 2 yrs	12 mths—walking, says a few words—following illness poor head control—hypotonic athetosis
		12	Fever, vomiting, convulsions, encephalic-like illness, acidotic				2 yrs—improvement—sitting—dyskinesis—further episode diarrhoea, convulsion, acidosis, further deterioration—loss motor function—dystonia
Brandt *et al.* 1978	F	6	Hypotonic	—	—	Normal at 10 yrs	2 yrs—walking with support—athetoid movements—talking short sentences 5 yrs—rides tricycle—able to swim—hyperkinesis—intellectual development normal 10 yrs—severely handicapped—needs support walking—wheelchair—speech dysarthric
Whelan *et al.* 1979	M	5	Semi-comatose, gen. jerking movements, reflexes normal, EEG—metabolic encephalopathy	—	+	Severely retarded, vision +, hearing + 0–3 mths at 1 yr	12 mths—no head control
Leibel *et al.* 1980	M	6	Hypotonic	+	+ + +	Severely retarded, 3 mths level at 2½ yrs	18 mths—unable to roll or sit 20 mths—choreoathetosis 23 mths—acidosis 28 mths—quadriperetic myoclonic jerks + bilateral tonic neck reflexes
		10	Diarrhoea, vomiting, focal tonic-clonic seizure				2½ yrs—choreoathetosis scissoring 3½ yrs—died
Present report	M	7	Acidosis, encephalic-like illness, convulsions	+	+ +	Severely retarded—social response 18 mths old	7 mths—unable to sit, central hypotonia, poor head control 11 mths—dystonia and choreiform movements 2-3 yrs—marked athetoid movements, with dystonia, breath-holding episodes 9 yrs—as above—unable to sit

activity in the basal ganglia and substantia nigra. GABA is a major inhibitory neurotransmitter in the central nervous system, with the highest concentrations found in this area of the brain (Roberts 1976). It is known that GABA synthetase is inhibited by glutaric acid (Stokke *et al.* 1976).

Attempts have been made to reduce the level of glutaric acid production by restricting the dietary intake of lysine and tryptophan, using amino-acid mixtures. The resulting diet was not tolerated well because of unpalatability. Limiting the protein intake to 1·5g/kg/24 hours has been shown to reduce the urinary excretion of glutaric acid with some improvement in motor ability and decrease in hyperkinesia. (Brandt *et al.* 1979). However, no changes in neurological signs were seen, possibly because irreversible neuronal damage had already taken place.

Riboflavin is a co-enzyme for glutaryl CoA dehydrogenase and large doses have been shown to decrease the excretion of glutaric acid, presumably by increasing its metabolism (Brandt *et al.* 1979). It is possible that treatment with riboflavin and a low-protein diet during infancy (before neuronal damage occurs) may considerably improve the prognosis of these patients.

Sodium valproate inhibits GABA transaminase (Pinder *et al.* 1977) and may prove of benefit in controlling symptoms. In view of the inhibition of GABA synthetase by glutaric acid, treatment with a GABA analogue 4 amino 3(4-chlorophenyl) butyric acid (baclofen) is logical and has produced symptomatic improvement, with decrease in dystonia, in the three patients reported (Brandt *et al.* 1979).

Our patient has had his fits controlled with sodium valproate since the age of two years. Since diagnosis he has been on a reduced protein/high-calorie diet (2g protein/kg/day and 100kcals/kg/day) and, for the last six months, riboflavin supplements (100mg bd). There has been no improvement in his clinical state since these dietary changes.

Our patient was initially diagnosed as having Leigh's encephalopathy on the basis of the clinical findings and the minimally elevated blood lactate and pyruvate concentrations. This disorder runs a variable course and the clinical picture may be similar to glutaric aciduria. The diagnosis of Leigh's encephalopathy can only be made with certainty on the postmortem findings of necrotising lesions in a characteristic distribution within the nervous system (Pincus 1972). Leigh's encephalopathy should not be diagnosed on clinical grounds without having first investigated urinary organic acids.

Organic acidurias are characteristically associated with metabolic acidosis, especially when presenting in the acute neonatal form. However, acidosis may not occur in all cases and was found in only five of the nine cases reviewed here. Dystonia, poor head control and athetoid movements were present in all the reported cases of glutaric aciduria.

We would suggest that any child with chronic neurological handicap of undetermined aetiology with these features should have appropriate investigations for urinary organic acids.

Authors' Appointments
Peter Stutchfield, Senior Registrar in Paediatrics, Alder Hey Hospital, Liverpool.
Mary Anne Edwards, Senior Biochemist, Department of Clinical Chemistry, Birmingham Children's Hospital.
R. G. F. Gray, Senior Biochemist, Department of Clinical Chemistry, Birmingham Children's Hospital.
P. Crawley, Consultant Paediatrician, Lea Castle Hospital, Kidderminster.
*Anne Green, Top Grade Biochemist, Department of Clinical Chemistry, Birmingham Children's Hospital, Ladywood, Birmingham B16 8ET.

**Correspondence to last author.*

SUMMARY
The late diagnosis of glutaric aciduria type I was made for a nine-year-old boy with previous diagnoses of Leigh's encephalopathy and of athetoid cerebral palsy. Techniques for the diagnosis of glutaric aciduria were not widely available when this boy was first investigated. The eight previously reported cases of this disease are reviewed. The clinical findings are very similar to those of Leigh's encephalopathy, and the latter diagnosis can only be made at postmortem examination. Diagnosis of a genetic disorder has important implications, and the authors suggest that patients labelled as Leigh's encephalopathy should be reviewed and selectively investigated for biochemical disorders, particularly those of organic acid metabolism.

RÉSUMÉ
Acidurie glutarique de type I prise pour une encéphalopathie de Leigh avec infirmité motrice cérébrale
Un diagnostic tardif d'acidurie glutarique de type I a été porté chez un garçon de 9 ans après un diagnostic

antérieur d'encéphalopathie de Leigh et d'infirmité motrice cérébrale de type athétosique. Les techniques de diagnostic de l'acidurie glutarique n'étaient pas aisément disponibles lors des premiers examens de ce garçon. Les 8 cas antérieurement rapportés de la maladie sont revus. Les données cliniques sont très comparables à celles de l'encephalopathie de Leigh et ce dernier diagnostic ne peut être fait qu'à l'examen post-mortem. Le diagnostic d'un trouble génétique a d'importantes implications et les auteurs suggèrent que les malades étiquetés encéphalopathie de Leigh soient revus, que des désordres biochimiques soient sélectivement recherchés chez eux, particulièrement ceux qui concernent le métabolisme des acides organiques.

ZUSAMMENFASSUNG

Glutaracidurie Typ I fehldiagnostiziert als Leigh's Enzephalopathie und Cerebralparese

Bei einem neunjährigen Jungen wurde die Spätdiagnose Glutaracidurie Typ I gestellt, bei dem zuvor die Diagnosen Leigh's Enzephalopathie und athetoide Cerebralparese gestellt worden waren. Als dieser Junge zuerst untersucht wurde, waren die Techniken zur Bestimmung einer Glutaracidurie noch nicht überall verfügbar. Es wird ein Überblick über die acht zuvor beschriebenen Fälle dieser Erkrankung gegeben. Die klinischen Befunde ähneln sehr denen der Leigh's Enzephalopathie, die letztere Diagnose kann nur durch eine postmortem Untersuchung bestätigt werden. Die Diagnose einer genetischen Erkrankung hat wichtige Folgeentscheidungen. Die Autoren regen an, daß Patienten, die als Leigh's Enzephalopathie diagnostiziert wurden, nochmals kontrolliert und selektiv auf biochemische Erkrankungen, unter besonderer Berücksichtigung der des organischen Säurestoffwechsels, untersucht werden sollten.

RESUMEN

Aciduria glutarica del tipo i diagnosticada equivocadamenate como una encefalopatia de Leigh y parálisis cerebral

El diagnóstico posterior de aciduria glutamaica tipo I se hizo en un niño de nueve años de edad, que previamente se habia diagnosticado de encefalopatía de Leigh y de parálisis cerebral atetósica. Cuando el niño fue primeramente diagnosticado las técnicas de diagnóstico de la aciduria glutárica no eran fácilmente asequibles. Se revisan los ocho casos previamente publicados. Los hallazgos clínicos son muy semejantes a los de la encefalopatía de Leigh y el diagnóstico posterior sólo puede hacerse por el examen posmortem. El diagnóstico de una alteración genética tiene importantes implicaciones y los autores sugieren que los casos etiquetados de encefalopatía de Leigh deberian ser revisados e investigados selectivamente en busca de alteraciones metabólicas, sobre todo las del metabolismo de los ácidos orgánicos.

References

Bennett, M. J., Curnock, D. A., Engel, P. C., Gray, R. G. F., Hull, D., Patrick, A. D., Pollitt, R. J. (1984*a*) 'Glutaric aciduria type II: biochemical investigation and treatment of a child diagnosed prenatally.' *Journal of Inherited Metabolic Disorders,* **7,** 57–61.

— Green, A., Pollitt, R. J., Worthy, E. (1984*b*) 'The routine investigation of urinary organic acids in selected paediatric patients: results over a 2½ year period.' *Annals of Clinical Biochemistry,* **21,** 45–50.

Brandt, N. J., Brandt, S., Christensen, E., Gregersen, N., Rasmussen, K. (1978) 'Glutaric aciduria in progressive choreoathetosis.' *Clinical Genetics,* **13,** 77–80.

— Gregersen, N., Christensen, E., Rasmussen, K. (1979) 'Treatment of glutaryl CoA dehydrogenase deficiency (glutaric aciduria)—experience with diet, riboflavin and GABA analogues.' *Journal of Pediatrics,* **94,** 669–673.

Chalmers, R. A., Roe, C. R., Tracey, B. M., Stacey, T. E., Hoppel, C. L., Millington, D. S. (1983) 'Secondary carnitine insufficiency in disorders of organic acid metabolism: modulation of acyl CoA/CoAsH ratios by L-carnitine *in vivo*.' *Biochemical Society Transactions,* **11,** 724–725.

Goodman, S. I., Gallegos, D. A., Pullin, C. J., Halpern, B., Truscott, R. J. M., Wise, G., Wilcken, B., Ryan, E. D., Whelan, D. T. (1980) 'Antenatal diagnosis of glutaric acidemia.' *American Journal of Human Genetics,* **32,** 659–699.

— Markey, A. P. (1981) *Diagnosis of Organic Acidemias by Gas Chromotography-Mass Spectrometry.* New York: Alan R. Liss.

— — Moe, P. G., Miles, B. S., Teng, C. C. (1975) 'Glutaric aciduria; A 'new' disorder of amino acid metabolism.' *Biochemical Medicine,* **19,** 12–21.

— Morenberg, M. D., Shikes, R. H., Breslich, D. J., Moe, P. G. (1977) 'Glutaric aciduria: biochemical and morphologic considerations.' *Journal of Pediatrics,* **90,** 746–750.

Gregersen, N., Brandt, N. J., Christensen, E., Grøn, I., Rasmussen, K., Brandt, S. (1977) 'Glutaric aciduria: clinical and laboratory findings in two brothers.' *Journal of Pediatrics,* **90,** 740–745.

Kyllerman, M., Steen, G. (1977) 'Intermittently progressive dyskinetic syndrome in glutaric aciduria.' *Neuropëdiatrie,* **8,** 397–404.

Leibel. R. L., Shih, V. E., Goodman, S. I., Bauman, M. L., McCabe, E. R. B., Zwerdling, R. G., Bergman, I., Costello, C. (1980) 'Glutaric acidemia: A metabolic disorder causing progressive choreoathetosis.' *Neurology,* **30,** 1163–1168.

Pincus, J. H. (1972) 'Subacute necrotising encephalomyelopathy (Leigh's disease): a consideration of clinical features and etiology.' *Developmental Medicine and Child Neurology,* **14,** 87–101.

Pinder, R. M., Bragden, R. N., Speight, T. M. (1977) 'Sodium valproate, a review of its pharmacological properties and therapeutic efficacy in epilepsy.' *Drugs,* **13,** 81–123.

Roberts, E. (1976) 'Disinhibition as an organizing principle in the nervous system—the role of the GABA system. Application to neurologic and psychiatric disorders.' *In* Roberts, E., Chaze, T. M., Tower, D. B. *GABA in Nervous System Function.* New York: Raven Press.

Stokke, O., Goodman, S. I., Moe, P. G. (1976) 'Inhibition of brain glutamate decarboxylase by glutarate, glutaconate and beta-hydroxyglutarate: explanation of the symptoms in glutaric aciduria?' *Clinica Chimica Acta,* **66,** 411–415.

Whelan, D. T., Hill, R., Ryan, E. D., Spate, M. (1979) 'L-Glutaric acidemia: investigation of a patient and his family.' *Pediatrics,* **63,** 88–93.