

Bilateral arachnoid cysts of the sylvian region in female siblings with glutaric aciduria type I

Report of two cases

ZAIN ALABEEDEN B. JAMJOOM, M.D., EMI OKAMOTO, M.D.,
ABDUL-HAKIM B. JAMJOOM, F.R.C.S. ED. (SN), OSAMA AL-HAJERY, M.D.,
AND ABDULLAH ABU-MELHA, M.D.

Division of Neurosurgery and Departments of Pediatrics and Radiology, Security Forces Hospital, Riyadh, Saudi Arabia

Two sisters, aged 6 and 2 1/2 years, presented with macrocephaly and delayed motor development and were found on computerized tomography to have bilateral arachnoid cysts of the sylvian region. Cystoperitoneal shunting of the larger cysts resulted in considerable neurological improvement in both children. Subsequent screening of the patients' urine for organic acids showed that the two sisters were suffering from glutaric aciduria type I (GA-I). To the best of the authors' knowledge, this is the first report to provide clear radiological and surgical evidence of the association between GA-I and bilateral arachnoid cysts of the sylvian region. The role of the shunting procedure used in these cases is discussed.

KEY WORDS • arachnoid cyst • glutaric aciduria type I • cystoperitoneal shunt • computerized tomography

ARACHNOID cysts are nontumorous intracranial fluid collections that may develop throughout the cerebrospinal axis with a predilection for the sylvian region.²⁴ Most arachnoid cysts are solitary lesions that occur sporadically. Multiple or bilateral arachnoid cysts are uncommon,^{5-7,20,26,28} and a familial occurrence has been reported in only a few cases.^{13,16,22} In recent years, an association between bilateral arachnoid cysts and glutaric aciduria type I (GA-I) has been suggested, but clear radiological, surgical, or autopsy evidence of such an association has been lacking.¹² In this report, we describe the first cases of surgically confirmed bilateral arachnoid cysts of the sylvian region in two sisters who suffered from GA-I.

Case Reports

Case 1

This 6-year-old girl was evaluated in our pediatric clinic because of delayed developmental milestones and difficulty in walking. She was born by induction of delivery. At birth, she was noticed to have a large head but was discharged from the hospital 3 days after a normal skull x-ray film was obtained. The patient had no history of exposure to infections, drugs, or trauma either *in utero* or after birth.

She sat at 1 year and walked at 3 years. Although she was later able to walk up stairs and run, she continued to fall easily. According to her parents, the child's language development had been normal except for stuttering. She was doing fairly well in kindergarten.

Examination. On examination, the patient was alert and obeyed simple commands. She appeared to be mentally slow and blunted. She weighed 18.2 kg and was 106 cm tall. Her head circumference (54 cm) was large with frontal bossing and a flat nasal bridge. Her muscle tone was generally decreased with lax and hypermobile joints. The results of routine laboratory tests were within normal limits.

Computerized tomography (CT) revealed a large (13 × 10 × 6 cm), sharply demarcated, nonenhancing cystic mass in the left sylvian region, causing a marked compression of the ventricular system and a shift of the midline structures. Another similar, but considerably smaller (5 × 2 × 2 cm) lesion with no mass effect was also present in the right sylvian area. The attenuation values of both lesions were similar to that of the cerebrospinal fluid (CSF), suggesting bilateral arachnoid cysts (Fig. 1A).

Operation. The patient underwent placement of a left-sided cystoperitoneal shunt with a low-pressure Pudenz valve. Cerebrospinal fluid analysis revealed normal cell

Arachnoid cysts and glutaric aciduria

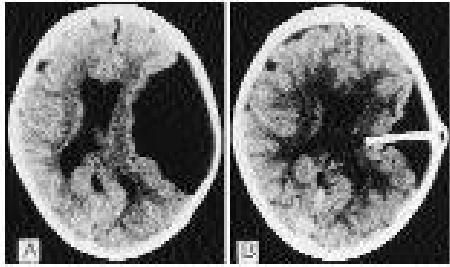


FIG. 1. Computerized tomography scans in the patient in Case 1. A: Preoperative scan showing cystic lesions with cerebrospinal fluid-like densities in both sylvian regions. The right cyst exhibits signs of chronic pressure, including compression of the ipsilateral ventricle and bulging of the overlying bone. B: Postoperative scan demonstrating marked reduction in the size of the shunted cyst.

count, protein, and sugar, and microbiological tests were negative. Her postoperative course was uneventful, and she was discharged from the hospital on the 3rd day after surgery.

Follow-Up Examinations. On follow-up examinations at 3-month intervals, the girl appeared much improved, as confirmed by her parents. Her gait was steadier, and she was more active than prior to the operation. These improvements were also noticed by the teachers in her kindergarten. A control CT scan obtained 9 months after the shunting procedure showed a marked reduction in the size of the left cyst and disappearance of the midline shift (Fig. 1B). Screening of the patient's urine for organic acids revealed elevated glutaric acid and 3-OH glutaric acid levels, characteristic of GA-I. The venous ammonia level was $172 \mu\text{mol/L}$ (normal $11\text{--}48 \mu\text{mol/L}$) and the lactate level was $9.6 \mu\text{mol/L}$ (normal $< 2.4 \mu\text{mol/L}$). The patient's capillary blood gases were normal as was her chromosomal analysis.

Case 2

This 2 1/2-year-old girl was the younger sister of the patient described in Case 1. She also presented at the same time with delayed motor development. Her prenatal medical history was unremarkable. She was delivered at our hospital by induction of labor for overcarriage. The girl's Apgar scores at 1 and 5 minutes had been 9 and 10, respectively. Her birth weight was 3200 g, length 47.5 cm, and head circumference 36 cm.

Examination. On examination, the child was alert and followed visual cues purposefully. Her head circumference (51 cm) was slightly above normal, whereas her weight (11.9 kg) was within and her height (85 cm) slightly below the expected range for her age. Her cranial nerves were intact. She had full muscle power but the muscle tone was decreased. She was able to sit and stand with support, but unable to walk. Occasional choreo-athetotic movements were seen.

Computerized tomography of the child's head showed CSF-containing cysts in both sylvian regions measuring $10 \times 4 \times 3 \text{ cm}$ on the left side and $5 \times 2 \times 1 \text{ cm}$ on the right (Fig. 2A).

In view of the absence of a midline shift and focal neu-

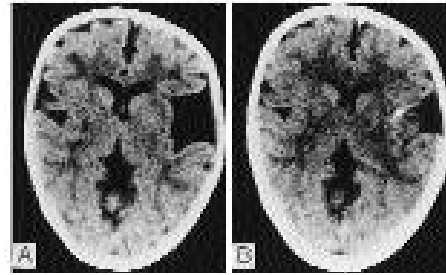


FIG. 2. Computerized tomography scans in the patient in Case 2. A: Preoperative scan showing bilateral cerebrospinal fluid-containing cysts of the sylvian regions. Note the straight medial border of the lesion on the left side. B: Postoperative scan confirming considerable shrinkage of the shunted cyst.

rological signs, we initially elected to observe the patient. A follow-up CT scan 6 months later showed no change in size or shape of the cysts. Nevertheless, the parents, being impressed by the remarkable postoperative improvement of her sister, insisted that an operation be performed on this child as well.

Operation. At operation a left temporal, low-pressure cystoperitoneal shunt was inserted. The child had a smooth postoperative recovery.

Follow-Up Examination. On follow-up examination 6 weeks later, the parents reported that the child was making attempts to walk independently. A control CT scan showed a considerable reduction in the size of the arachnoid cyst on the left side (Fig. 2B).

Urine analysis for organic acids showed elevated glutaric acid and 5-OH glutaric acid excretion. The child's venous ammonia and lactate levels were within normal range, as were her blood gases. Her chromosomal analysis was normal.

Family History

In addition to themselves, the patients' immediate family consisted of their parents (mother 34 years and father 37 years of age) who are first-degree cousins, and two additional sisters, aged 9 years and 6 months. Both of these siblings as well as the parents were healthy and their heads were normal in shape and size. They all underwent cranial CT scans and urine organic acid screening, which revealed no abnormalities. The family lost a female child (their first child) who was delivered prematurely in the 8th month of gestation and died at the age of 12 days. The cause of death was unknown. Moreover, between the births of patients described here the mother had two spontaneous abortions that occurred during the 3rd and 4th months of gestation. Nothing is known about the sex of the fetuses. The children's paternal uncle had 9 children, most of whom experienced delayed walking.

Discussion

Glutaric aciduria type I is an autosomal recessively inherited metabolic disorder caused by a deficiency of glutaryl-coenzyme A dehydrogenase activity.^{9,10} This mitochondrial enzyme is responsible for the oxidation and

carboxylation of glutaryl-coenzyme A, an intermediate step in the catabolism of lysine and tryptophan. The condition was first recognized by Goodman, *et al.*,⁹ in 1975; since that time it has been reported with increasing frequency from various parts of the world.^{2,4,14,20} The disease is characterized by intermittent or chronic metabolic acidemia, extrapyramidal movement disorders (predominantly dystonia and choreoathetosis), and the presence of large amounts of glutaric and β -hydroxyglutaric acids in the urine,^{1,2,10,11,14,15,17-19} although some patients may not exhibit acidosis during the course of illness.⁴ Other clinical manifestations include psychomotor retardation,^{1,2,4,10,11,14,17} macrocephaly,^{1,2,4,14,15,17,19} seizures,^{1,11,17,18} and hypotonia.^{1,4,11,14,18,19} The symptoms usually start early in childhood, either insidiously or acutely, and may be associated with fever, vomiting, and diarrhea.^{10,17,18} The subsequent course of the disease varies considerably, ranging from a mild and rather static to a rapidly progressive course, often with a fatal outcome.^{2,4,10,14,17} Interestingly, this marked clinical variability may exist even among homozygous individuals within a family who exhibit identical biochemical profiles. This suggests that some epigenetic factors or environmental influences play a role in the manifestation of symptoms.^{2,14}

Postmortem studies reveal bilateral shrinkage and gray discoloration of the putamen as the main structural abnormality in patients with GA-I. Microscopically, there is extensive neuronal loss and astrocytic gliosis in the putamen and lateral part of the caudate nucleus, together with spongiform changes in the white matter.^{4,10,17} This neuronal loss is probably responsible for the decreased levels of γ -aminobutyric acid in the brain and CSF of patients with GA-I and may account for the extrapyramidal symptoms.^{17,18} The exact mechanism of the neuronal degeneration is still obscure. Based on the structural similarity between glutaric and glutamic acids, it has been suggested that accumulation of glutaric acid may exert excitotoxic effects on neurons that normally respond to glutamic acid.¹⁷

The diagnosis of GA-I is based on the detection of a high concentration of glutaric acid in the urine and a low plasma carnitine level. Modern neuroimaging techniques, including CT scanning and magnetic resonance (MR) imaging, are indispensable in detecting associated intracranial changes.²¹ An early radiological finding that may precede clinical symptoms consists of the widening of external CSF spaces in the frontotemporal regions, presumably resulting from frontal and temporal lobe atrophy.^{1,2,4,14,19} Alternatively, some patients show bilateral subdural effusions.^{2,12,17} More characteristic abnormalities, however, include diffuse symmetrical lucencies on CT scans and increased signal intensities on T_2 -weighted MR images involving white matter and basal ganglia. These changes are best seen during phases of acute illness and probably indicate demyelination and edema.^{1,14,18,19} In more chronic cases, there is shrinkage of the putamen and the lateral aspect of the caudate with "straightening" of the internal capsule.¹⁴

Many patients with GA-I display bilateral fluid collections in the sylvian regions that may take a peculiar configuration of "bat-wings."¹⁹ The exact nature of these fluid collections is not clear. In most radiological reports, they have been interpreted as representing dilated sylvian cis-

terns as a result of poor operculization or advanced frontotemporal atrophy.^{2,4,20} This view has been supported by the absence of pressure effects exerted by these collections on their surroundings, and the occasional concomitant enlargement of other basal cisterns and the ventricles.

In contrast, Hald and colleagues¹² have recently suggested that the sylvian fluid collections probably represent arachnoid cysts. These authors based their assumption purely on radiographic considerations, primarily the absence of CT findings suggestive of temporal lobe hypogenesis, such as undulations of the temporal lobe margins adjacent to the cistern,²⁵ and the common association with subdural hematomas.²⁶ To the best of our knowledge, no surgical or autopsy proof has thus far been provided to substantiate this assumption.

The two cases presented here resemble previously reported cases of GA-I in all clinical aspects, and their biochemical findings leave no doubt about the diagnosis of GA-I. In addition, both patients displayed bilateral fluid collections in the sylvian regions, but unlike the cases described thus far in the literature, one lesion (on the left side in Case 1) was clearly space-occupying and caused compression of the ipsilateral ventricle, shift of the midline, and bulging of the overlying temporal bone. These features preclude the possibility that an atrophic process was the only cause of the fluid collection and favor, instead, the diagnosis of an arachnoid cyst. The diagnosis of an arachnoid cyst was also justifiable in the second patient because, despite the absence of clear space-occupying properties, the CT scan showed that the left temporal fluid collection had a straight medial border, a finding often considered to be characteristic of an arachnoid cyst.³ In both patients, other diagnoses of cystic intracranial space-occupying lesions, such as porencephalic, neoplastic, or hydatid cysts, seem to be sufficiently excluded by the typical location and characteristics of the lesions on CT, and the normal biochemical and cytological examination of the CSF-like fluid content of the cysts. The remarkable reduction in the size of both cysts following cystoperitoneal shunting provides for the first time surgical confirmation of the diagnosis of arachnoid cysts. It is debatable whether a histopathological examination of the cyst wall is mandatory for the diagnosis of an arachnoid cyst.^{22,23}

Bilateral arachnoid cysts in siblings have been reported previously in only three families, but none of these cases was surveyed for metabolic disorders.^{13,16,22} Based on our present observations, we believe that all cases of familial or bilateral arachnoid cysts should be screened for metabolic and genetic diseases.

Patients with GA-I have thus far been treated with low protein diets, special formulas low in lysine and tryptophan, and supplementation of riboflavin and L-carnitine. These therapeutic measures have had limited effects in symptomatic individuals, whereas their value as a prophylaxis in asymptomatic carriers remains to be determined.^{2,18} The postoperative improvement in both the motor and mental functions of our first patient shows that neurological deterioration in patients with GA-I is not always caused by the underlying metabolic derangement; at the same time, it emphasizes that early recognition and treatment of associated lesions, such as arachnoid cysts or subdural hygromas, should be an integral part of the management of GA-I. Because the clinical symptoms and

Arachnoid cysts and glutaric aciduria

signs caused by these additional pathologies are often indistinguishable from those resulting from the primary metabolic disorder, repeated cranial CT scans or MR imaging are indispensable for a timely diagnosis of any evolving lesion, especially during episodes of deterioration. Furthermore, in view of the frequent incidence of severe neurological disability in individuals with GA-I, family members of affected persons should be screened to detect the carriers among them. Parents who have one affected child should be offered genetic counseling and prenatal diagnosis by determining the glutaric acid concentration in amniotic fluid or glutaryl-coenzyme dehydrogenase activity in cultured amniotic cells.²

Many questions remain to be answered concerning the relationship between GA-I and the formation of arachnoid cysts. It is widely accepted that arachnoid cysts represent developmental anomalies arising from splitting or duplication of the primitive arachnoid membrane during early embryonal life.^{5,8,24,27,29} However, nothing is known about factors that can invoke such erroneous development. With regard to GA-I, the location of the arachnoid cysts coincides very well with the predilection areas of brain atrophy, namely the frontotemporal regions. It is, therefore, possible that splitting or duplication of the developing arachnoid membrane would be indirectly induced by early atrophy or hypoplasia of the adjacent brain rather than being a direct sequela of the enzyme deficiency *per se*.

Acknowledgment

The authors would like to thank Hilda A. Sumandar for her excellent secretarial assistance.

References

- Altman NR, Rovira MJ, Bauer M: Glutaric aciduria type I: MR findings in two cases. **AJNR** **12**:966-968, 1991
- Amir N, Elpeleg ON, Shalev RS, et al: Glutaric aciduria type I: enzymatic and neuroradiologic investigations of two kindreds. **J Pediatr** **114**:983-989, 1989
- Banna M: Arachnoid cysts on computed tomography. **AJR** **127**:979-982, 1976
- Bergman I, Finegold D, Gartner JC, et al: Acute profound dystonia in infants with glutaric acidemia. **Pediatrics** **83**:228-234, 1989
- Choux M, Raybaud C, Pinsard N, et al: Intracranial supratentorial cysts in children excluding tumor and parasitic cysts. **Childs Brain** **4**:15-32, 1978
- Ciricillo SF, Cogen PH, Harsh GR, et al: Intracranial arachnoid cysts in children. A comparison of the effects of fenestration and shunting. **J Neurosurg** **74**:230-235, 1991
- Dei-Anang K, Voith D: Cerebral arachnoid cysts: a lesion of the child's brain. **Neurosurg Rev** **12**:59-62, 1989
- Go KG, Houthoff HF, Blaauw EH, et al: Morphology and origin of arachnoid cysts. Scanning and transmission electron microscopy of three cases. **Acta Neuropathol** **44**:57-62, 1978
- Goodman SI, Kohlhoff JG: Glutaric aciduria: inherited deficiency of glutaryl-CoA dehydrogenase activity. **Biochem Med** **13**:138-140, 1975
- Goodman SI, Norenberg MD, Shikes RH, et al: Glutaric aciduria: biochemical and morphologic considerations. **J Pediatr** **90**:746-750, 1977
- Gregersen N, Brandt NJ, Christensen E, et al: Glutaric aciduria: clinical and laboratory findings in two brothers. **J Pediatr** **90**:740-745, 1977
- Hald JK, Nakstad PH, Skjeldal OL, et al: Bilateral arachnoid cysts of the temporal fossa in four children with glutaric aciduria type I. **AJNR** **12**:407-409, 1991
- Handa J, Okamoto K, Sato M: Arachnoid cyst of the middle cranial fossa: report of bilateral cysts in siblings. **Surg Neurol** **16**:127-130, 1981
- Haworth JC, Booth FA, Chudley AE, et al: Phenotypic variability in glutaric aciduria type I: report of fourteen cases in five Canadian Indian kindreds. **J Pediatr** **118**:52-58, 1991
- Iafolla AK, Kahler SG: Megalencephaly in the neonatal period as the initial manifestation of glutaric aciduria type I. **J Pediatr** **114**:1004-1006, 1989
- Kuzuhara M, Shimora T, Yojima K, et al: Two cases of arachnoid cyst in siblings. **No To Hattatsu** **2**:309, 1980
- Leibel RL, Shih VE, Goodman SI, et al: Glutaric acidemia: a metabolic disorder causing progressive choreoathetosis. **Neurology** **30**:1163-1168, 1980
- Lipkin PH, Roe CR, Goodman SI, et al: A case of glutaric acidemia type I: effect of riboflavin and carnitine. **J Pediatr** **112**:62-65, 1988
- Mandel H, Braun J, El-Peleg O, et al: Glutaric aciduria type I. Brain CT features and a diagnostic pitfall. **Neuroradiology** **33**:75-78, 1991
- Nagasawa H, Yamaguchi S, Suzuki Y, et al: Neuroradiological findings in glutaric aciduria type I: report of four Japanese patients. **Acta Paediatr Jpn** **34**:409-415, 1992
- Naidu SB, Moser HW: Value of neuroimaging in metabolic diseases affecting the CNS. **AJNR** **12**:413-416, 1991
- Pomeranz S, Wald U, Amir N, et al: Arachnoid cysts: unusual aspects and management. **Neurochirurgia** **31**:25-28, 1988
- Rengachary SS: Comment on a paper by McCullough DC, Harbert JC, Manz HJ: Large arachnoid cysts at the cranial base. **Neurosurgery** **6**:81, 1980
- Rengachary SS, Watanabe I, Brackett CE: Pathogenesis of intracranial arachnoid cysts. **Surg Neurol** **9**:139-144, 1978
- Robertson SJ, Wolpert SM, Runge VM: MR imaging of middle cranial fossa arachnoid cysts: temporal lobe agenesis syndrome revisited. **AJNR** **10**:1007-1010, 1989
- Rogers MA, Klug GL, Siu KH: Middle fossa arachnoid cysts in association with subdural haematomas. A review and recommendations for management. **Br J Neurosurg** **4**:497-502, 1990
- Sato K, Shimoji T, Yaguchi K, et al: Middle fossa arachnoid cyst: clinical, neuroradiological, and surgical features. **Childs Brain** **10**:301-316, 1983
- Shirane R, Tanaka T, Andoh A, et al: Bilateral symmetrical middle cranial fossa arachnoid cysts in a neonate. **Surg Neurol** **26**:395-398, 1986
- Starkman SP, Brown TC, Linell EA: Cerebral arachnoid cysts. **J Neuropathol Exp Neurol** **17**:484-500, 1958

Manuscript received July 6, 1994.

Accepted in final form September 27, 1994.

Address reprint requests to: Zain Alabedeen B. Jamjoom, M.D., Division of Neurosurgery, Security Forces Hospital, P.O. Box 3643, Riyadh 11481, Saudi Arabia.