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Children with Bilateral Temporal Arachnoid Cysts may have Glutaric Aciduria Type 1 (GAT1); Operation Without Knowing that may be Harmful

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Summary

Background. Bilateral, temporal arachnoid cysts are common in patients with Glutaric aciduria type 1 (GAT1). The present study investigates whether bitemporal cysts may occur unrelated to GAT1, and it reports our experience with 2 GAT1 patients.

Methods. During the last 11 years, the regional neurosurgical department has seen a total of 147 patients with arachnoid cysts in a population of 890.000. Eight of these patients had bitemporal arachnoid cysts, 4 boys, 3 adult females, and 1 adult male. Urine from 7 of these patients was examined with gas chromatography-mass spectrometry.

Findings. Large amounts of glutaric acid were discovered in the urine of only 2 of these patients, both young boys with severe neurological symptoms of the disease. One of them died 2 years after the clinical start of the disease. The remaining 5 urinary specimens contained low (normal) concentrations of glutaric acid.

Interpretation. For neurosurgeons, it is important to recognise that children with bitemporal arachnoid cysts may have GAT1, and that even simple surgical procedures may be extremely harmful for such patients. All paediatric patients with bitemporal arachnoid cysts should therefore be screened for GAT1 before any surgical procedure takes place, especially if there is also macrocephaly, an acute encephalitis-like illness, or a dystonic, cerebral palsy-like condition. It is concluded that bitemporal arachnoid cysts are extremely rare, and that they may well occur unrelated to GAT1.

Keywords: Arachnoid cyst; metabolic disease; surgery.

Introduction

Glutaric aciduria Type 1 (GAT 1) is an uncommon [12] autosomal recessive inborn error of metabolism, which is due to a deficiency of glutaryl-CoA-dehydrogenase in the metabolism of lysine, hydroxylysine, and tryptophane. Although the disease was recognised already in 1975 [5], many patients were not diagnosed until the clinical course of GAT 1 was described in more detail a decade ago [1, 8, 9, 18]. Still, the condition may represent a diagnostic pitfall [14, 19, 25]. The glutaryl-CoA-dehydrogenase deficiency may lead to neurodegeneration, probably caused by increased amounts of 3-hydroxyglutaric acid [21], and the most typical clinical picture is dramatic, characterised by an acute, encephalitis-like illness, followed by hypotonia, dystonia, choreo-athetosis, and seizures, whereas the picture may be more like cerebral palsy in other cases [16]. Asymptomatic or mild cases have also been reported, however rarely [1, 20]. The disease often has its clinical start around the child's first birthday. It has been claimed that the severe consequences of the condition may be avoided if diagnosed and treated in the presymptomatic stage [7, 17, 21]. GAT1 is diagnosed by demonstration of pathologically high concentrations of glutaric acid in urine from the patient. An enzyme defect may also be demonstrated in fibroblasts [3].

The patients may be macrocephalic, often with a head circumference above the 97.5 percentile already from birth as a presymptomatic finding. MRI or CT scans of the head often reveal intracranial changes that may prompt neurosurgical decompression, such as subdural hygromas or haematomas [13, 19, 25]. However, the surgical management of such conditions, without due regard to the underlying metabolic disorder and the danger of putting the patient into a catabolic state, will almost inevitably cause a devastating neurological worsening [1|0].

Hald and co-workers demonstrated that four out of

five GAT1 patients had bilateral temporal arachnoid cysts, and therefore suggested that patients with bitemporal cysts should be screened for GAT1 [6]. Others have ascribed the widened Sylvian fissures in these patients to an atrophy of the frontal and temporal lobes [1, 14, 19, 26]. To our knowledge, very few of the alleged arachnoid cysts have been confirmed by operation to be a true cyst, and not only a passive accumulation of fluid due to atrophy of the temporal lobes, neither has the prevalence of GAT1 in patients with bitemporal cysts been studied. The aim of the present study is therefore to investigate to what extent bitemporal arachnoid cysts may occur unrelated to GAT1, and to report on the intra-operative findings in one patient with GAT1. An even more important aim is to share our experience with 2 such patients with the neurosurgical community.

Patients and Methods

In Norway, health services are organised within 5 regions, where each region is served by only one neurosurgical department. The region of western Norway has a stable population of 890,000 people, and is served by the department in Bergen. A 26 year-old male was not included in the study because he was not operated on for his bitemporal cysts, and no urinary specimen was obtained. With this exception, the present material of seven patients (see below) probably represents all symptomatic bitemporal cysts that were diagnosed in the health region over a period of 11 years. During the same time span, a total of 147 patients with symptomatic arachnoid cysts were diagnosed in this population and referred to our department. Thus, in this population, bitemporal cysts occurred in 5.4% of patients with arachnoid cysts.

Urinary organic acids were analysed by gas chromatography-mass spectrometry (GC-MS). The samples were acidified, extracted with diethyl ether and methylated before separation in the GC-MS instrument fitted with a fused silica capillary column.

The Patients

For the sake of completeness, all 7 patients with bitemporal cysts are included in the material, however with emphasis on the paediatric patients. Five patients had symmetrical Galassi [4] type II (moderate sized) cysts (Fig. 2), whereas 2 patients had a right-sided type II cyst and a type I (smaller) cyst on the left side (Fig. 1). Table 1 gives a summarised account of the patients' clinical features. The individual case histories are presented in more detail below. The age given for each patient refers to the age of the patient at the first contact with our departments. Except for patient 7, all the patients were operated on to obtain a decompression of the cysts. During these operations, the subdural part of the cyst membrane was opened to allow the insertion of a catheter (2 patients), or removed together with a fenestration of the medial cyst wall to the basal cisterns (4 patients). Thus, the presence of an arachnoid cyst was verified during these operations.

Patient 1. A 73 year old female with a six year history of dizziness and ataxia with slow progression. CT showed bitemporal arachnoid

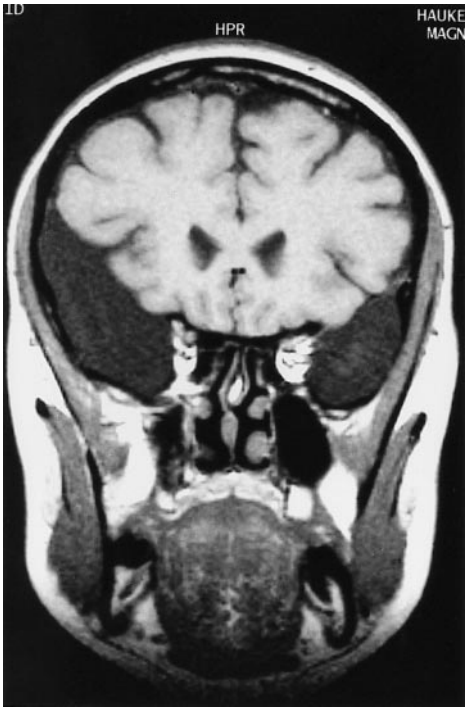

Fig. 1. Patient no. 3. MRI showing a type II [2] cyst on the right side, and a smaller type I cyst on the left side

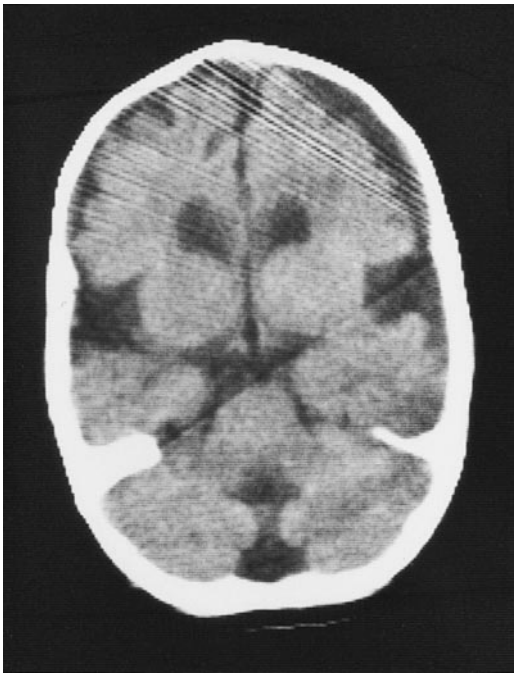

Fig. 2. Patient no. 5. Pre-operative CT scan showing large subdural effusions and bitemporal, symmetrical type II [4] cysts in patient with GAT1. The following operation verified the existence of bitemporal cysts, see text

Table 1. *Summary of Clinical and Radiological Features, Treatment and Clinical Results*

Patient no.	Gender	Age at referral	Symptoms, duration, cyst type*	Treatment and clinical course
1	F	73 years	slowly progressing dizziness for 6 years; right type II, left type I	cysto-subdural shunt [23] from the larger cyst smaller cyst left untreated; no improvement
2	F	40 years	epilepsy since childhood, hydrocephalus; bilateral type II cysts	craniotomy, fenestration of both cysts VP shunt; epilepsy unchanged
3	F	40 years	headache since childhood; severe headache and nausea following minor head injury 3 weeks before referral; right type II, left type I	bilateral craniotomy/fenestration; cured
4	M	8 months	increased head circumference; slight psychomotor retardation; bilateral type II cysts	cysto-peritoneal shunt; symptom free
5	M	1 year	large, and increasing head circumference. Initially a moderately delayed motor development; hospitalised with an acute encephalitis-like condition; bilateral type II cysts	craniotomy, fenestration, VP shunt; GAT1/low protein diet; died at the age of 3
6	M	1 year	lack of well-being; bilateral type II cysts	bilateral craniotomies and fenestration; no symptoms
7	M	6 months	severely ill with encephalitis-like condition; bilateral type II cysts	volume reduction craniectomy. Subduro-peritoneal shunt, later VP shunt; GAT1/low protein diet; still alive, but very sick

* According to Galassi [4].

cysts and some atrophy. She was treated with an internal shunt [23], with no substantial improvement.

Patient 2. A 40 year old female with hydrocephalus and bitemporal arachnoid cysts. She had suffered from absence epilepsy since childhood, and during the last twelve years also generalised tonic/clonic seizures. She was operated on and a ventriculoperitoneal shunt was inserted, and the cysts were fenestrated through a craniotomy. Her main problem, epilepsy, remained unchanged.

Patient 3. A 40 year old female with chronic headache since childhood. After a minor head injury a few weeks before referral, the headache became more intense, with nausea. She was operated on with craniotomy and fenestration, first for the larger (type II) cyst on the right side, 2 years later for the smaller type I cyst on the left side (Fig. 1). The headache disappeared, and she no longer has any symptoms from the cysts.

Patient 4. A boy with normal psychomotor development up to six months of age. Then head circumference increased abnormally and psychomotor development became slightly retarded. When he was eight months old, CT and MRI of the head showed bitemporal and basal arachnoid cysts. He was therefore operated on with cystoperitoneal shunt and a volume reduction craniectomy. After the operations his head circumference and psychomotor development returned to normal.

Patient 5. This boy was born two weeks before term with a head circumference at the 90 percentile. At 2 months of age, the head circumference was over 97.5 percentile, and gross motor development was moderately delayed. He was admitted when he was 1 year-old, with an encephalitis-like clinical picture. CT and MRI of the head showed bitemporal arachnoid cysts (Fig. 2), as well as hydrocephalus and subdural effusions, findings that prompted decompressive neurosurgery in the acute stage, as a metabolic disorder was not suspected at this time. During a right craniotomy, it was verified that the patient had true bitemporal arachnoid cysts, and the ipsilateral as well as the contralateral cyst was fenestrated. The operations caused a marked neurological worsening, and despite diet treatment, he died at 3 years of age during a metabolic crisis with multi-organ failure, four months after the GAT1 diagnosis finally had been established.

Patient 6. This 1 year-old boy was hospitalised because of a general lack of well-being. A CT scan of the head disclosed bitemporal cysts; these were fenestrated through bilateral craniotomies, and his general condition improved.

Patient 7. This boy was 7 months old when he was first referred to hospital for an abnormal increase in head circumference (from the 75 percentile to 1.5 cm above the 97.5 percentile), and a slightly delayed motor development. A CT scan of the head revealed bilateral subdural hygromas/haematomas and what appeared to be bitemporal arachnoid cysts. He was primarily operated on in a hospital outside our health region, with attempted evacuation of the subdural hygromas/haematomas. A few days after this operation, he developed vomiting and diarrhoea, and after another few days, an encephalitis-like condition and seizures. When transferred to our hospital, we suspected a GAT1, but nevertheless decided to operate on him, as he had severe clinical and radiological signs of increased intracranial pressure. Due to large extracerebral haemorrhagic effusions, and a pronounced mismatch between his skull and brain volumes, he was operated on under general anaesthesia, with a subduro-peritoneal shunt and a reduction craniectomy. When the subdural effusions had been drained, the shunt was later transformed into a ventriculoperitoneal shunt under local anaesthesia. Urine samples verified the suspected GAT1 diagnosis. When the metabolic diagnosis was established, we refrained from further surgery, as this would induce a catabolic state in the patient, and thus worsen the metabolic disease. He is now treated with a special GAT1 (low protein) diet, still alive, but severely spastic, and in a poor general condition.

Results

Only two patients (pats. 5 and 7) had abnormal, massive amounts of glutaric acid in the urine (Fig. 3). These patients were the only ones who were severely ill, both with large subdural effusions, and a severe, encephalitis-like condition. The other 5 patients (3 adults, 2 children) had normal, low levels of glutaric acid in the urine. These patients had only symptoms that could be attributed to their arachnoid cysts.

Discussion

The main message of the present report is that children with bitemporal arachnoid cysts may have GAT1, and that even simple surgical procedures may be extremely harmful to such patients. All paediatric patients with bitemporal arachnoid cysts should therefore be screened for GAT1 [6] before any surgical procedure takes place, especially if there is also macrocephaly, an acute encephalitis-like illness, or a dystonic, cerebral palsy-like condition [15]. Even a general anaesthesiological procedure may be harmful to GAT1 patients, as catabolism may increase the production of harmful metabolites, and thus cause a dramatic worsening of the child's condition. The metabolic disorder should be treated with a special low protein diet [10]. The aim of the treatment is primarily to avoid further neurological deterioration, but neurological as well as radiological improvement has also been seen [2]. Recent reports show that neurological deterioration may be arrested or even prevented if the diagnosis is established very early, preferably at a presymptomatic stage [17, 21].

Patients with GAT1 appear to have a high prevalence of bitemporal arachnoid cysts [6]. Although the patient material presented here is small, it can clearly be concluded that the reverse is not necessarily true: bitemporal arachnoid cysts may well exist unrelated to GAT1. The possibility of course exists that the widened Sylvian fissures seen in GAT1 patients are not true cysts, but merely passive accumulations of fluid due to atrophy of the temporal lobes, as suggested by several authors [1, 14, 19, 26]. In the one GAT1 patient operated on by us, however, there was no doubt about the presence of bilateral cysts, with a lateral (subdural) cyst membrane as well as a medial arachnoid membrane closing off the cysts toward the basal cisterns. Also the cases presented by Jamjoom *et al.* [11] most probably had true cysts, as they responded to shunting.

The intracranial arachnoid cyst is in itself an un-

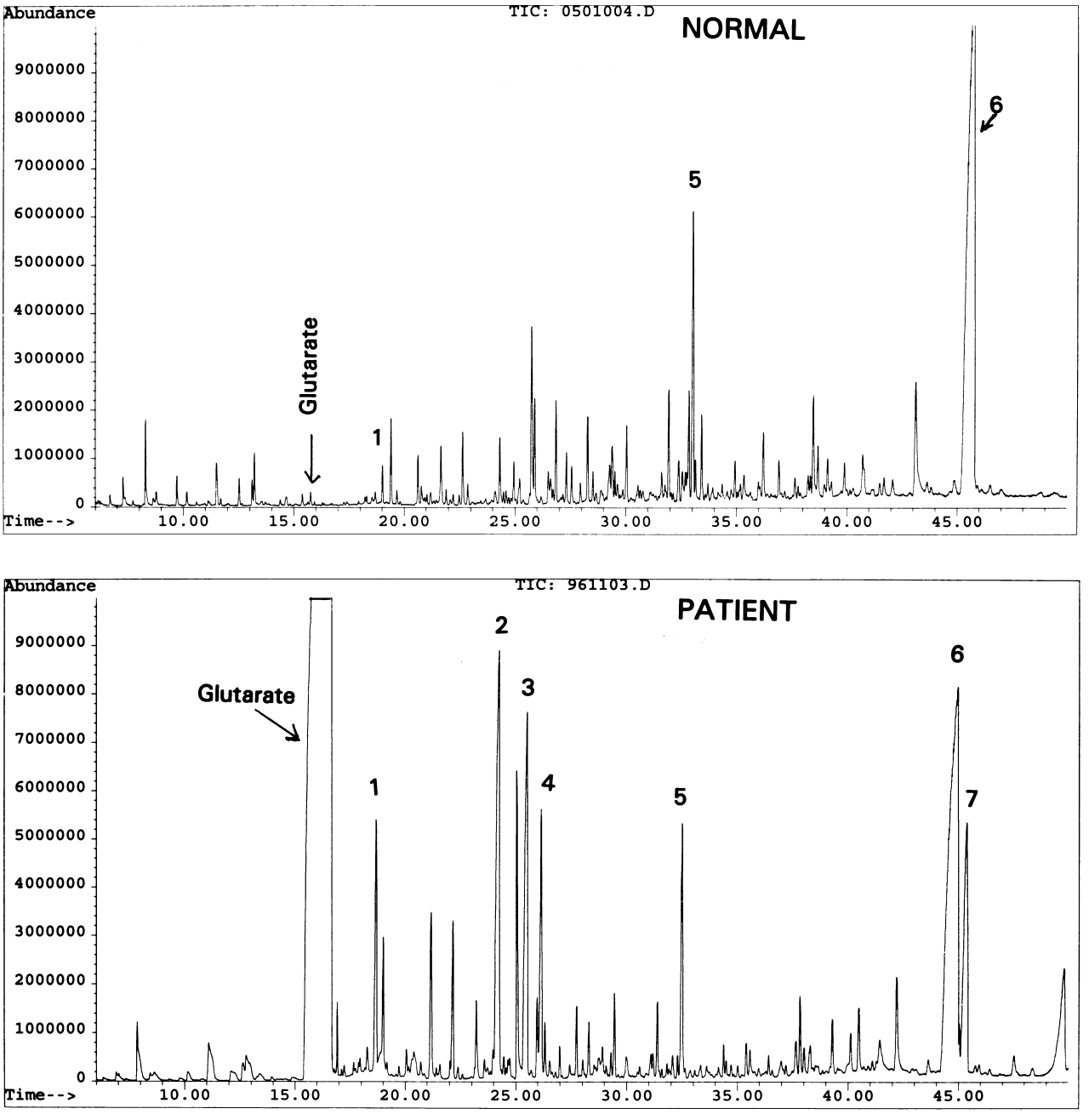

Fig. 3. Organic profile of normal urine (upper) and from patient (no. 5) with glutaric aciduria type 1 (lower). The major (off scale) peak in the patient is glutaric acid. The other peaks are: *1* adipic acid, *2* phenoxyacetic acid (drug metabolite), *3* 2-ketoglutaric acid, *4* 3-hydroxyglutaric acid, *5* citric acid, *6* hippuric acid, and *7* Thiopental (drug metabolite)

common condition, possibly caused by a duplication of the arachnoid [24]. The temporal fossa is a predilection site, and temporal cysts have a distinct, but hitherto not understood, preponderance for the left side and the male gender [24]. Bitemporal cysts are rare; in our population of patients with arachnoid cysts, only about 5% had bitemporal lesions. The observation that GAT1 often is associated with such a rare condition [6] is intriguing, and suggests a causal relationship. It is possible that the metabolic disorder exerts its effect not only on the formation and maturation of the central nervous system, but also on the mesodermal, meningeal anlage in early embryonic life.

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Comment

The authors present here the connection of a reasonably rare inborn error of metabolism; Glutaric aciduria type I (GAT1) with bilateral temporal arachnoid cysts. They found 7 patients with bilateral arachnoid cysts out of a total of 147 during eleven referral years in their area; four children and three adults. The adults, all over 40 at the time had no GAT1 in their urine analyses. Two out of the 4 infants, all below 1 year at the time of referral had GAT1. Both of these patients deteriorated immediately after the planned decompressive surgery with a metabolic crisis. The diagnosis of GAT1 was confirmed later; one died at the age of three, the other one is treated with low protein specific diet but is severely neurologically ill.

The infants with GAT1 are at the beginning often neurologically normal, they may have early macrocephalia and bilateral sylvian cysts on neuroradiology. They may easily develop acute encephalitic type of reactions that may turn to truncal ataxia, hypotonia or even dystonia later [1]. If the main cause (glutaryl-CoA-dehydrogenase deficiency) can be diagnosed before neurological deterioration, treatment with adequate diet and avoidance of stress and catabolism may prevent the neurological complications [2]. Here both infants with the syndrome had a catastrophic postoperative deterioration certainly connected with the extra stress.

This message is very important for general neurosurgeous.

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