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ORIGINAL ARTICLE

Subdural hematoma in glutaric aciduria type 1: High excreters are prone to incidental SDH despite newborn screening

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Abstract

Subdural hematoma (SDH) was initially reported in 20% to 30% of patients with glutaric aciduria type 1 (GA1). A recent retrospective study found SDH in 4% of patients, but not in patients identified by newborn screening (NBS). 168 MRIs of 69 patients with GA1 (age at MRI 9 days – 73.8 years, median 3.2 years) were systematically reviewed for presence of SDH, additional MR and clinical findings in order to investigate the frequency of SDH and potential risk factors.

SDH was observed in eight high-excreting patients imaged between 5.8 and 24.4 months, namely space-occupying SDH in two patients after minor accidental trauma and SDH as an incidental finding in six patients without trauma. In patients without trauma imaged at 3 to 30 months (n = 36, 25 NBS, 27/9 high/low excreters), incidence of SDH was 16.7% (16% in NBS). SDH was more common after acute (33.3%) than insidious onset of dystonia (14.3%) or in asymptomatic patients (5.9%). It was only seen in patients with wide frontoparietal CSF spaces and frontotemporal hypoplasia. High excreters were over-represented among patients with SDH (6/27 vs 0/9 low excreters), acute onset (10/12), and wide frontoparietal CSF spaces (16/19).

Incidental SDH occurs despite NBS and early treatment in approximately one in six patients with GA1 imaged during late infancy and early childhood. Greater risk of high excreters is morphologically associated with more frequent enlargement of external CSF spaces including frontotemporal hypoplasia, and may be furthered aggravated by more pronounced alterations of cerebral blood volume and venous pressure.

KEYWORDS

atrophy, glutaric aciduria type 1, MRI, newborn screening, subdural hematoma

1 | INTRODUCTION

Glutaric aciduria type 1 (GA1, OMIM#231670) is a rare inherited metabolic disorder of L-lysine, L-hydroxylysine, and L-tryptophan metabolism caused by deficiency of glutaryl-CoA dehydrogenase which results in the accumulation of the putatively toxic metabolites glutaryl-CoA and glutaric and 3-hydroxyglutaric acid (GA, 3-OH-GA), particularly within the brain.

Without treatment, about 90% of patients identified after onset of symptoms develop bilateral striatal injury during the first 6 years of life. Striatal injury results in a complex, predominantly dystonic, movement disorder superimposed on axial muscular hypotonia. This manifests either as acute-onset dystonia following an acute encephalopathic crisis (AEC) precipitated by catabolic states (eg, febrile illness, vomiting/diarrhoea, perioperative fasting periods) or insidiously without an apparent acute event. In contrast, patients with pre-symptomatic diagnosis by newborn screening (NBS) and adherence to guideline-recommended maintenance and emergency treatment rarely develop dystonia.[1-4]

Based on urinary GA concentrations two biochemical phenotypes have been defined, namely low excreters with up to 30% residual enzyme activity and high excreters with loss of GCDH activity. While high and low excreters have the same a priori risk of developing movement disorder,[5] either acutely or insidiously, recent reports highlight a higher frequency of progressive extrastriatal MRI changes, increased intracerebral concentrations of GA and 3-OH-GA detected by in vivo ^{1}H-MR spectroscopy, as well as larger head circumference in high excreters.[6-8]

Subdural hematoma (SDH) in children frequently results in diagnostic investigation for GA1, but systematic data on prevalence of SDH in GA1 are scarce. SDH has initially been reported in 20% to 30% of patients identified after onset of symptoms[9] and may occur after minor accidental head trauma or even spontaneously.[10,11] A more recent retrospective analysis found a much lower incidence of 4% in 25 patients with no SDH among patients identified by NBS.[12] In order to investigate the frequency, age distribution, and potential risk factors of SDH in GA1, we systematically analysed MRI for presence of SDH in a cohort of 69 patients with GA1, namely 38 prospectively followed patients identified by NBS and 31 patients diagnosed by targeted metabolic work-up or high-risk family screening.

2 | PATIENTS AND METHODS

As part of the ongoing prospective study on long-term outcome of GA1 patients since 1999 (approval by the Institutional Ethics Committee of the University of Heidelberg, #314/2002, S-49/2010), patients with MR imaging were identified for retrospective evaluation for SDH. 168 MRI scans from 69 patients with GA1 (age at MRI 9 days – 73.8 years, median 3.2 years, 39 patients with 1-8 follow-up MRIs) were systematically reviewed for SDH. Presence of frontotemporal hypoplasia and/or widening of frontoparietal CSF spaces was qualitatively assessed by two experienced paediatric neuroradiologists (IH, AM).

Diagnosis had been confirmed by molecular genetic analysis of the *GCDH* gene and/or analysis of residual GCDH activity. Thirty-eight patients were diagnosed by NBS, 27 were diagnosed by metabolic work-up after the onset of symptoms and four by high-risk family screening including prenatal diagnosis in one younger sibling. Biochemical phenotype (high/low excreter) was classified according to a previous definition[13]; 54 patients were high and 15 low excreters.

Fourteen patients had AEC, defined as acute onset of a dystonic movement disorder after an episode likely to precipitate catabolism (eg, febrile illness) during infancy or childhood. Fifteen patients had insidious onset of motor symptoms, defined as dystonia manifesting without an apparent AEC event, and associated with a characteristic MRI pattern,[14] and two patients had acute-on-insidious onset of motor symptoms. Of 38 patients without motor symptoms, 10 patients were diagnosed after the age of 6 years ("late diagnosis"). Metabolic *maintenance treatment* was assessed as "according to guideline recommendations" if it consisted of (1) a neonatally initiated low lysine diet adapted for age with supplementation of a lysine-free, tryptophan-reduced, arginine-fortified amino acid supplement for patients aged 0-6 years, (2) a protein-controlled nutrition for patients beyond age 6 years, and (3) oral carnitine supplementation, and *emergency treatment* if it consisted of a temporary carbohydrate-enriched, low- to no-protein protocol and was initiated within 24 hours of onset of potentially catabolic episodes.[15,16] For assessment of macrocephaly, head circumference in patients up to age 17 years was transformed into a SD score (SDS) using the LMS method and age-dependent standard values.[17,18] Statistical analysis was computed with R language for statistical analysis (version 4.1.0). Two-way contingency tables were analysed with Boschloo's exact test (R package "Exact"). No a priori hypotheses were specified and due to small sample sizes, all *P*-values should be regarded as descriptive measures.

3 | RESULTS

3.1 | GA1 patients with SDH

SDH was observed in eight patients imaged between 5.8 and 24.4 months. All eight were high excreters; six had been identified by NBS and two by targeted metabolic work-up (Table 1). Two patients identified by NBS developed SDH with

TABLE 1 Clinical and MRI findings of GA1 patients with SDH

Pat.	Biochemical phenotype	Sex	Diagn. mode	Age at diagn (mo)	Age at MRI with SDH (mo)	Adeq. maint. Tx	Adeq. ermerg. Tx	Motor sympt.	Trauma	SDH	SDH width (mm)	SDH: uni/bilat.	SDH on FU (age at FU)	Front. par. CSF spaces	Front. temp. hypo-plasia	Macrocephaly	GA[b]	3OH-GA[b]	Age at GA/3OH-GA (mo)
p1	High	f	NBS	0.3	13.8	Yes	Yes	asympt.	No	Yes	6	unilat.	Resolution (5.2 years)	Wide	Yes	Yes	4817.3	235.6	13.8
p2	High	m	NBS	0.2	12.2	Yes	No	insid.	No	Yes	5	unilat.	Resolution (26.1 months)	Wide	Yes	No	4176	129	148.8
p3	High	m	NBS	0.3	5.8	Yes	No	Acute-on-insid. (5 months AEC)	No	Yes	7	unilat.	No FU	Wide	Yes	No	1097.3	356.2	8.6
p4	High	m	NBS	0.2	24.4	Yes	No	AEC (12 months)	No	Yes	4	bilat.	No FU	Wide	Yes	No	803.6	171.8	24.3
p5	High	m	targ.	5	6.3	No	No	AEC (5 months)	No	Yes	6	unilat.	Resolution (22.2 months)	Wide	Yes	No	3261	164.6	11.6
p6	High	f	targ.	21	21.8	No	No	AEC (21 months)	No	Yes	2	unilat.	Resolution (23.0, 32.9 months)	Wide	Yes	Unknown, "hydrocephalic"	1037.9	100	32.8
p7	High	m	NBS	0.25	11.6	No	Yes	insid.	Yes	Yes	12	unilat.	Surgical drainage	No prior imaging	Yes	No	2313.9	97.9	40.3
p8[a]	High	f	NBS	0.1	23.1	Yes	Yes	asympt.	Yes	Yes	26	unilat.	Surgical drainage	Wide at 12.6 months	Yes	No	1763.7	183.6	15.8

Note: Patients are sorted according to associated trauma, mode of diagnosis, onset, and age at MRI with SDH.

Abbreviations: adeq. maint./emerg. Tx, adequate maintenance/emergency treatment; AEC, acute encephalopathic crisis; asympt., asymptomatic; diagn., diagnosis; front.par., frontoparietal; front.temp., frontotemporal; FU, follow up; insid., insidious; sympt., symptoms; mo, months; NBS, newborn screening; targ., targeted metabolic testing; uni/bilat., uni/bilateral.

[a]Prev. reported in Reference 10.

[b]GA/3OH-GA as mmol/molCrea.

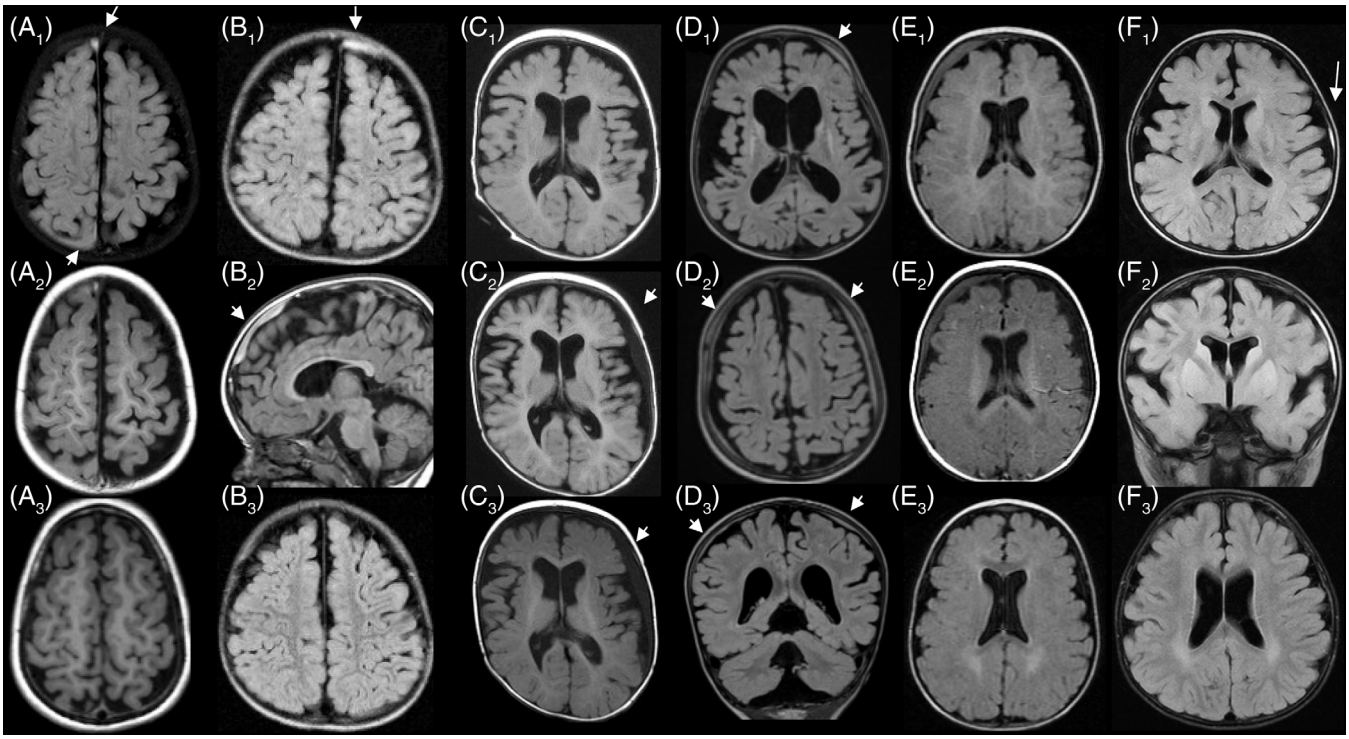

FIGURE 1 Incidental SDH in patients without trauma. A, Patient 1 with right frontal and parietal SDH and wide frontoparietal sulci at 13.8 months ($A_{1,2}$, arrows in A_1). On follow-up at 5.2 years SDH has resolved, sulci are less wide (A_3). B, Left frontopolar SDH in patient 2 aged 12.2 months ($B_{1,2}$, arrows), resolution and less wide frontoparietal CSF spaces at follow-up at 26 months (B_3). C, Predominantly left sided widening of frontoparietal CSF spaces in patient 3 at 3.0 months (C_1) and subsequent left frontoparietal SDH at follow-up 1 month after AEC aged 5.8 months ($C_{2,3}$, arrows). D, Thin, bilateral lamellae (arrows) in the single MRI of patient 4 aged 24.4 months, 12 months after AEC. E, Right frontoparietal CSF in patient 5 at 6.3 months ($E_{1,2}$) with resolution and less wide frontoparietal CSF spaces at 22 months (E_3). F, In patient 6, thin SDH at 21.8 months is best appreciated on coronal FLAIR images (F_2, NB FLAIR-hyperintense striatum in subacute phase of AEC), which has resolved on follow-up at 32.9 months (F_3). (FLAIR: A_1, $B_{1,3}$, $C_{1,2}$, $D_{1\text{-}3}$, $E_{1,3}$, $F_{1\text{-}3}$; T1: $A_{2,3}$, B_2, C_3, E_2)

significant mass effect following minor head trauma and underwent surgery, namely a twin sibling without prior MRI examination and one previously reported patient.[10]

In the six patients without trauma, SDH was observed as an incidental finding. SDH was unilateral in five and bilateral in one patient, with a maximal width of 2 to 7 mm (Figure 1), and resolved spontaneously in the four patients with follow-up. All six patients had widening of frontoparietal CSF spaces and frontotemporal hypoplasia at time of SDH. Two of the six patients had been diagnosed by targeted metabolic work-up after AEC. All four patients identified by NBS had received adequate maintenance treatment, one was asymptomatic and one each developed insidious, acute-on-insidious, and acute onset of motor symptoms after delayed emergency treatment.

3.2 | Age at imaging and frequency of incidental SDH

Similar to previously reported patients, SDH in our patients was only observed in late infancy and early childhood. Incidence will therefore vary with patients' ages at imaging, as patients not imaged during this phase will be unlikely to have SDH while their inclusion will decrease incidence as an estimate of frequency.

We therefore estimated the frequency of SDH not associated with trauma ("incidental SDH") and identified potential risk factors in a subgroup of patients imaged between 3 and 30 months. This age range was derived by intuitively widening the age span during which SDH was observed to cover a presumably vulnerable age range. Incidental SDH occurred in six of 36 patients (16.7%) imaged during this time.

3.3 | Incidental SDH: mode of diagnosis, biochemical phenotype, and motor symptoms

Among the 36 patients without trauma imaged between three and 30 months, SDH was not more common in patients identified by NBS (16%) compared to high-risk family screening and metabolic work-up of symptomatic patients (18.2%, $P = .999$, Boschloo's test; Table 2).

TABLE 2 Summary of clinical and MRI findings for GA1 patients imaged between three and 30 months

Age at MRI 3-30 months			Trauma	No trauma			
			SDH	SDH	No SDH	Total	SDH %/total no trauma
Patients	n=		2	6	30	36	16.7%
Sex	Female		1	2	21	23	8.7%
	Male		1	4	9	13	30.8%
						1.8 f/m	
Diagnosis	NBS		2	4	21	25	16.0%
	targ&high-risk		0	2	9	11	18.2%
Excreter	HE		2	6	21	27	22.2%
	LE		0	0	9	9	0.0%
						3.0 HE/LE	
Motor symptoms	AEC		0	4	8	12	33.3%
	asympt.		1	1	16	17	5.9%
	insid.		1	1	6	7	14.3%
	AEC	HE	0	4	6	10	40.0%
		LE	0	0	2	2	0.0%
						5.0 HE/LE	
	asympt.	HE	1	1	11	12	8.3%
		LE	0	0	5	5	0.0%
						2.4 HE/LE	
	insid.	HE	1	1	4	5	20.0%
		LE	0	0	2	2	0.0%
						2.5 HE/LE	
Macrocephaly	Yes		0	1	4	5	20.0%
(known in 23 HE, 9 LE)				1 HE/0 LE	3 HE/1 LE	4 HE/1 LE	
	No		2	4	23	27	14.8%
	Unknown		0	1	3	4	25.0%
Frontoparietal CSF spaces[a]	Wide		n.a.	6	13	19	31.6%
	Normal		n.a.	0	17	17	0.0%
						1.1 wide/normal	
	Wide	HE	n.a.	6	10	16	37.5%
		LE	0	0	3	3	0.0%
						5.3 HE/LE	
	Normal	HE	n.a.	0	11	11	0.0%
		LE	0	0	6	6	0.0%
Frontotemp. hypoplasia[a]	Yes		2	6	27	33	18.2%
	No		0	0	3	3	0.0%
	Yes	HE	2	6	21	27	22.2%
		LE	0	0	6	6	0.0%
						4.5 HE/LE	
	No	HE	0	0	0	0	0.0%
		LE	0	0	3	3	0.0%

Abbreviations: AEC, acute encephalopathic crisis; asympt, asymptomatic; HE, high excreter; insid., insidious; LE, low excreter; NBS, newborn screening; targ. &high-risk, targeted metabolic testing and high-risk screening.

[a]Rated as wide/present if wide/present in ≥1 MRI and as normal/absent if normal/absent in all MR examinations of a patient.

The ratio of high to low excreters of 3 to 1 was consistent with that recently reported for a national cohort.[1] High excreters were overrepresented among patients with SDH (6/27 high vs 0/9 low excreters, $P = .129$, Boschloo's test). Urinary GA and 3-OH-GA concentration in patients with SDH were within the range observed for other high-excreting patients and in patients with multiple measurements values nearest to the MRI with SDH were not necessarily the highest.

Incidental SDH was more common in patients with AEC (33.3%, 4/12 pts., $P = .108$, Boschloo's test) than in insidious onset and asymptomatic patients (14.3%, 1/7 pts. and 5.9%, 1/17 pts., respectively). More frequent detection of incidental SDH in high excreters and after AEC was not due to different "sampling rates" of subgroups, since the number of MRIs per patient was similar for subgroups, namely 1.5 and 1.6 for high and low excreters and 1.4, 1.3, and 1.5 for patients with AEC, insidious onset, and without motor symptoms.

3.4 | Incidental SDH: macrocephaly, frontoparietal CSF spaces, and frontotemporal hypoplasia

SDH was not more common in patients with macrocephaly: Five of 32 patients with documented head circumference and imaging between 3 and 30 months were macrocephalic, including patient #1 with incidental SDH. Patient #6 with initial suspicion of hydrocephalus and diagnosis after AEC, but without documented head circumference at the time of SDH, was also likely macrocephalic. Four patients with incidental SDH were normocephalic as were both patients with trauma-associated SDH.

Widening of frontoparietal CSF spaces was present in 19 of 36 patients (31.6%), including all patients with incidental SDH. It was significantly more common in patients with SDH ($P = .014$, Boschloo's test) and nearly twice as common in high compared to low excreters (59% vs 33%, respectively) with a tendency for overrepresentation of high excreters (16/3 high/low excreters, $P = .064$, Boschloo's test).

Frontotemporal hypoplasia was present in all high excreting patients, including all patients with incidental SDH, and significantly more common than in low excreters ($P = .005$, Boschloo's test).

4 | DISCUSSION

Initially thought to suggest non-accidental head trauma, in particular in combination with retinal haemorrhages, SDH has become a recognised complication in patients with GA1, occurring after minor accidental head trauma or spontaneously.[9,19-22] Although specific metabolic testing for GA1 is frequently performed for work-up of SDH in children irrespective of the presence of suggestive imaging changes,[23] SDH in GA1 is usually combined with further, disease-specific imaging findings[22] which is confirmed by the present study.

The results of the present, long-term observational study of 69 GA1patients with 168 MRI scans demonstrate that *incidental SDH* (1) occurs in approximately one in six patients during a vulnerable period of late infancy and early childhood despite early identification by NBS and treatment, remaining self-limited with spontaneous resolution, (2) was exclusively found in patients with a high excreting phenotype and associated with wide external CSF spaces rather than macrocephaly, and that (3) *traumatic SDH* with mass effect may occur after minor head trauma. Due to the observational nature and small sample size of our study, we statistically analysed two-way contingency tables without an appropriate type 1 error adjustment and without preceding power and sample size analysis. Therefore, all reported *P*-values should be regarded as descriptive measures. While this descriptive analysis is able to substantiate our conclusions from the data, further studies need to evaluate these results.

4.1 | SDH in GA1: Incidence and age at imaging

Since patients with SDH may remain asymptomatic and regular MRI follow-up of GA1 patients in the absence of new symptoms is not recommended by current guidelines,[15] the frequency of SDH in GA1 is unknown. SDH was initially reported in 20% to 30% of GA1 patients diagnosed after the manifestation of neurologic symptoms.[9] A recent retrospective study found an incidence of only 4% in 25 patients imaged with MRI and/or CT and predicted an even further decreasing incidence due to early treatment after NBS[12] while another recent study found SDH in 34% of symptomatic GA1 patients diagnosed following specific metabolic work-up.[24]

As SDH in GA1 apparently occurs during a relatively limited age range, age at imaging will affect the incidence observed and very likely explains some of the discrepancy. SDH in our patients was only observed during a limited age range of five to 24 months, which is consistent with a peak incidence of SDH in previously reported patients during late infancy with median and mean ages of 9 and 13.5 months and a maximum age of 24 months.[10-12,19-21,25-45] Also consistent with previous reports, incidental, asymptomatic SDH without associated trauma spontaneously resolved in our patients with follow-up.[11,25,43,46]

Consequently the overall incidence of SDH in our patients of 11.6% very likely underestimates the frequency

of SDH since 31 of 69 patients were first imaged after the age of 3 years or only before the age of 3 months and thus outside a presumed period of vulnerability. The effect of age at imaging on observed frequency is even more pronounced for patients not identified by NBS: With 20 of 31 patients first imaged after the age of 3 years, the overall incidence of SDH was 6.5% (2/31) compared to 18.2% for the subgroup imaged between 3 and 30 months. Interestingly, the overall incidence of SDH patients not identified by NBS is similar to results of a national cohort study (5.9%),[12] for which age at imaging was not reported.

Taking into account the limited age range during which SDH occurs in GA1, the incidence of 22.2% for both, traumatic and incidental SDH in our patients imaged between three and 30 months and of 16.7% for incidental, non-trauma-associated SDH provides a more realistic estimate of the frequency of SDH in GA1. This notion is supported by an incidence of SDH of 34% in previously reported group of 29 patients imaged between two and 56 months,[24] while age at imaging was not reported for two other groups with an incidence of 13% and 15%.[46,47]

4.2 | Risk factors for SDH in GA1 patients

SDH results from tearing of bridging veins as they cross the subdural space to enter a venous sinus. SDH is most common in infants and elderly, with larger shearing stress in infants due to greater distortion of the softer, unmyelinated brain.[48] Consistent with the concept of wide external CSF spaces as a risk factor for SDH, these were wide in all patients with SDH and SDH was significantly more common in patients with widening of frontoparietal CSF spaces, but not more frequent in patients with macrocephaly. This underlines the importance of the proportion between skull and brain, namely, the width of external CSF space, irrespective of head circumference.

Higher frequency of SDH in GA1 compared to 2.3% in patients with benign enlargement of the subarachnoid spaces,[49] however, suggests additional predisposing factors inherent to GA1. Morphologically, frontotemporal hypoplasia in GA1 with greater overall enlargement of subarachnoid spaces is a likely contributing factor, which was present in all GA1 patients with SDH.

Metabolically, the biochemical phenotype appears to be an important risk factor for the development of SDH in GA1: Among our patients SDH occurred exclusively in high excreters. Reviewing the literature for reported findings consistent with a high or low-excreting phenotype, we identified 11 reports consistent with[20,21,25,26,28-31,34,35,42] and five likely consistent with a high-excreting phenotype,[11,19,33,36,37] but none (likely) consistent with a low-excreting phenotype. While high and low excreters have the same a priori risk of developing movement disorder of acute or insidious onset,[4,5] high excreters more frequently have extrastriatal MRI changes including progressive subependymal nodules in late diagnosed patients and malignant brain tumours in three high-excreting patients.[6,8,42] Mean head circumference in high excreters is larger though not necessarily resulting in macrocephaly.[7] Intracerebral accumulation of GA and 3-OH-GA detected by vivo MR spectroscopy is greater in high excreters[6] which is in line with the loss of GCDH activity compared to up to 30% residual enzyme activity in low excreters.[50] Factors potentially contributing to more pronounced changes in high excreters include increased neurotoxicity due to greater accumulation of GA and 3-OH-GA, more severe impairment of energy metabolism of neurons and astrocytes,[51] disturbance of neurotransmission,[52] possibly augmented by selective glutarylation of mitochondrial proteins.[53] In addition, endogenous intoxication of the brain compartment due to GCDH deficiency has been reported to induce arteriolar dilation with elevated cerebral blood volume and cerebral venous hypertension which will not only increase the risk of subdural and retinal haemorrhage but also increases interstitial fluid and CSF volume.[54] Thus high excreters not only had significantly more frequent frontotemporal hypoplasia and widening of frontotemporal CSF spaces as a morphological predisposing factor for SDH. In addition, high excreters can be expected to experience a greater extent of arteriolar dilatation und venous hypertension, even more pronounced in the wake of acute metabolic decompensation. This might explain the more frequent SDH in high excreters after AEC than in asymptomatic and insidious-onset patients.

To conclude, incidental, asymptomatic SDH occurs despite NBS and early treatment in approximately one of six patients with GA1 imaged during late infancy and early childhood. Greater risk of individuals with the high-excreting phenotype is morphologically associated with more frequent enlargement of external CSF spaces including frontotemporal hypoplasia, and may be furthered aggravated by more pronounced alterations of cerebral blood volume and venous pressure due to greater accumulation of toxic metabolites.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Stefan Kölker designed and initiated the long-term outcome study. Inga Harting, Nikolas Boy, and Stefan Kölker designed the MRI study, Inga Harting and Alexander Mohr reviewed MRIs, Inga Harting and Nikolas Boy analysed and interpreted the data; all authors examined patients and/or collected data. All authors revised the manuscript and approved the submission.

ETHICS APPROVAL

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The study was approved by the Institutional Ethics Committee of the University of Heidelberg (#314/2002, S-49/2010).

INFORMED CONSENT

Informed consent was obtained from all patients or their legal guardians prior to being included in the study. No study patient has withdrawn informed consent.

DATA AVAILABILITY STATEMENT

The MRI images are not publicly available under data protection laws.

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