DOI: 10.1002/jimd.12033

ORIGINAL ARTICLE

WILEY JIMD SSIEM

Patterns, evolution, and severity of striatal injury in insidious- vs acute-onset glutaric aciduria type 1

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Communicated by: Jerry Vockley

Abstract

Background: Striatal injury in patients with glutaric aciduria type 1 (GA1) results in a complex, predominantly dystonic, movement disorder. Onset may be acute following acute encephalopathic crisis (AEC) or insidious without apparent acute event.

Methods: We analyzed clinical and striatal magnetic resonance imaging (MRI) findings in 21 symptomatic GA1 patients to investigate if insidious- and acute-onset patients differed in timing, pattern of striatal injury, and outcome.

Results: Eleven patients had acute and ten had insidious onset, two with later AEC (acute-on-insidious). The median onset of dystonia was 10 months in both groups, and severity was greater in patients after AEC ($n = 8$ severe, $n = 5$ moderate) than in insidious onset ($n = 4$ mild, $n = 3$ moderate, $n = 1$ severe). Deviations from guideline-recommended basic metabolic treatment were identified in six insidious-onset patients. Striatal lesions were extensive in all acute-onset patients and restricted to the dorsolateral putamen in eight of ten insidious-onset patients. After AEC, the two acute-on-insidious patients had extensive striatal changes superimposed on pre-existing dorsolateral putaminal lesions. Two insidious-onset patients with progressive dystonia without overt AEC also had extensive striatal changes, one with sequential striatal injury revealed by diffusion-weighted imaging. Insidious-onset patients had a latency phase of 3.5 months to 6.5 years between detection and clinical manifestation of dorsolateral putaminal lesions.

Conclusions: Insidious-onset type GA1 is characterized by dorsolateral putaminal lesions, less severe dystonia, and an asymptomatic latency phase, despite already existing lesions. Initially normal MRI during the first months and deviations from guideline-recommended treatment in a large proportion of insidious-onset patients substantiate the protective effect of neonatally initiated treatment.

1 | INTRODUCTION

In glutaric aciduria type 1 (GA1, OMIM#231670), a rare inherited metabolic disorder of L-lysine, L-hydroxylysine, and L-tryptophan metabolism, the putatively neurotoxic metabolites glutaryl-CoA and glutaric and 3-hydroxyglutaric acid (GA, 3-OH-GA) accumulate in body tissues, particularly within the brain, due to a deficiency of glutaryl-CoA dehydrogenase. Without treatment, about 90% of patients develop striatal injury during the first six years of life, mostly between the ages of 3 and 36 months, resulting in a complex, predominantly dystonic, movement disorder

superimposed on axial muscular hypotonia.[1] Patients may develop acute onset of dystonia following an acute encephalopathic crisis (AEC) precipitated by catabolic states (e.g., febrile illness, vomiting/diarrhea, perioperative fasting periods) or insidious onset of movement disorder without an apparent acute event.[2–5] Two biochemical phenotypes, low and high excretors, have been defined based on the urinary excretion of GA,[6] both sharing the same disease course with a similar risk for neurologic disease.[1] However, this assessment has been challenged by recent observations revealing a high frequency of white matter abnormalities progressing with age and increased intracerebral concentrations of GA and 3-OH-GA detected in vivo by proton magnetic resonance spectroscopy [^{1}H-MRS] in high excretors.[7] Moreover, patients with late diagnosis of GA1 ("late onset") show exclusively high excreting phenotype.[8]

It has been speculated that acute and insidious presentation of movement disorder might differ only in the timing of injury, insidious onset resulting from perinatal events.[4] However, this hypothesis was not supported by a prospective follow-up study of patients diagnosed by newborn screening (NBS), demonstrating that deviations from metabolic maintenance treatment, in particular deviations from low lysine diet, are the major risk factor for dystonia of insidious onset.[3] In that study, the four insidious-onset patients with imaging had striatal lesions restricted to the dorsolateral putamen, contrasting with the generally extensive lesions observed after acute onset of dystonia. We, therefore, analyzed clinical presentation and striatal magnetic resonance imaging (MRI) changes in order to better understand pattern, time course, and clinical correlates of striatal changes in patients with symptomatic GA1.

2 | PATIENTS AND METHODS

As part of our ongoing prospective study on the long-term outcome of GA1 patients since 1999,[3,9] the MRI scans of the 60 patients with GA1 currently followed were systematically reviewed for the presence of striatal changes by an experienced pediatric neuroradiologist. A total of 23 patients with striatal changes on at least one MRI scan were identified. One late-onset patient with a history of stroke-like episodes since the age of 61 years and unilateral gliosis, defect, and susceptibility artifact of the right anterior caudate and lenticular nucleus consistent with postischemic residuum[8] was excluded from further analysis.

The clinical, biochemical, genetic, and MRI characteristics of the resulting group of 22 patients are summarized in Table 1. Twelve patients had been identified by NBS and ten had been diagnosed by targeted screening, five before implementation of the German national NBS panel in 2005, four coming from countries without NBS programs at time of birth, and one low excreting patient having been missed by NBS. Diagnosis had been confirmed by mutation analysis of the *GCDH* gene on chromosome 19p13.13 in 17 patients and by the analysis of residual enzyme activity in five patients. Biochemical phenotype (high/low excretor) was classified according to a previous definition.[6]

The pattern of striatal changes (localized/extensive signal changes, atrophy on visual inspection, new/increasing changes on follow-up) was assessed on axial T2-weighted images on 52 MRI scans of these 22 patients. If available, diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) maps (30 MRIs from 14 patients) was reviewed for altered diffusion, namely restricted, elevated, or pseudonormalized diffusion (normal ADC in combination with T2-hyperintensity).

Patients were clinically assessed as (1) asymptomatic or suffering from (2) acute onset of dystonia precipitated by AEC or (3) insidious onset of movement disorder without an acute precipitating event. Although dystonia is the most prominent movement disorder in GA1, motor function is also significantly impaired by truncal hypotonia, in particular in infants and children. The severity of movement disorder was assessed as previously described,[3] namely as "mild" if children showed no significant disability in daily life, as "moderate" if motor dysfunction caused disability but some motor functions were preserved, and as "severe" if movement disorder caused significant disability with few motor skills left.

The treatment of insidious-onset patients was reviewed for deviations from recommended baseline and/or emergency metabolic treatment. Treatment according to guideline recommendations should consist of low lysine diet with supplementation of a lysine-free, tryptophan-reduced, arginine-containing amino acid supplement in children up to 6 years of age and of protein-controlled nutrition for patients above 6 years in combination with oral carnitine supplementation. Intermittent emergency treatment should be initiated without delay during potentially catabolic episodes (e.g., fever, vomiting, feeding problems) and consists of a carbohydrate-enriched, low- to no-protein protocol.[9,10]

3 | RESULTS

3.1 | Clinical presentation

Of the 22 patients with striatal changes on MRI, one low-excreting patient diagnosed by NBS remained asymptomatic and his discrete MRI changes at the lateral border of the putamen resolved on follow-up (patient 1). The other 21 patients were symptomatic, 11 with acute and ten with insidious onset of movement disorder.

TABLE 1 Biochemical, genetic, and magnetic resonance imaging (MRI) findings of patients (sorted by clinical manifestation and age at first MRI)

Patient	Excretor	M/F	Mutation (protein code)	Diagnosis (age)	Treatment	Movement disorder			Age at MRI	Striatum	Putamen		Diffusion putamen (ADC maps)
						Insid./acute	Age at onset	Severity			Y/N	Local.	
1[a]	Low	M	p.Gln160Arg, p.Lys170Asn	NBS (5 days)	Full tx	Asympt.	Asympt.	None	7.5 months	Y	Y	Lateral	Facilitated
									15 months	Y	Y	Lateral	Facilitated
									6.5 years	N	N	Normalized	Normalized
2	High	F	p.Tyr197fs, p.Tyr197fs	NBS (10 days)	Full tx and mult. emerg. adm.	Insid.	6 months	Severe	1.4 months	N	N	Normal	–
									7.6 months	Y	Y	Extensive	–
									16.6 months	Y	Y	Extensive	Facilitated
									7.2 years	Y	Y	Extensive	Facilitated
3[b]	Low	F	p.Arg161Gln, p.Cys228Arg	NBS (11 days)	Delayed basic tx	Insid.	2 years	Mild	1.5 months	Y	Y	Dorsolat.	–
									25 months	Y	Y	Dorsolat.	–
4[b,c]	High	F	p.Tyr413X, p.Tyr413X	NBS (7 days)	Full tx	Insid.	5 months	Mild	1.6 months	Y	Y	Dorsolat.	–
5[a,c]	High	M	p.Glu365Lys, p.Glu365Lys	NBS (7 days)	tx discontinued	Insid.	6.5 years	Moderate	5.4 months	N	N	Normal	–
									12 months	Y	Y (left)	Dorsolat.	–
									2.2 years	Y	Y (left)	Dorsolat.	–
									6.5 years	Y	Y (left)	Dorsolat.	Facilitated
									8.8 years	Y	Y (left)	Dorsolat.	Facilitated
									13.1 years	Y	Y (left)	Dorsolat.	Facilitated
									14.2 years	Y	Y (left)	Dorsolat.	Facilitated
									14.9 years	Y	Y (left)	Dorsolat.	Facilitated
6[b,c]	High	F	p.Arg128Gln, p.Ala421Val	NBS (7 months)	Delayed basic tx	Insid.	4.6 years	Mild	7.3 months	Y	Y	Dorsolat.	–
7[c]	Low	M	n.d.	Targ. (12 months)	Delayed basic tx	Insid.	10 months	Mild	2.3 years	Y	Y	Dorsolat.	–
8	High	F	p.Arg294Gln, p.Arg386[a]	NBS (8 days)	↓diet. Lys, several mo→ severe malnutrition	Insid.	9 months	Mild (15 months) - moderate (3 years)	2.6 years	Y	Y	Extensive	Facilitated dorsolat. putamen > remaining striatum
9[a]	High	M	p.Ala421Val, p.Arg76X	Targ. (60 months)	Delayed basic tx	Insid.	≤ 60 months (first formal clin. assessment at 5.5 years)	Moderate	13.0 years	Y	Y	Dorsolat.	–
									15.8 years	Y	Y	Dorsolat.	–
									20.0 years	Y	Y	Dorsolat.	Facilitated
									25.1 years	Y	Y	Dorsolat.	Facilitated

TABLE 1 (Continued)

Patient	Excretor	M/F	Mutation (protein code)	Diagnosis (age)	Treatment	Movement disorder			Age at MRI	Striatum	Putamen		Diffusion putamen (ADC maps)
						Insid./acute	Age at onset	Severity			Y/N	Local.	
									27.0 years	Y	Y	Dorsolat.	Facilitated
10	High	M	p.Arg402Gln, p.Arg402Gln	NBS (9 days)	Full tx and mult. emerg. adm. delayed emergency tx	Insid. + later AEC (5 months)	2 months → AEC at 5 months	Truncal hypotonia and hypertonia of extremities → AEC → moderate	0.8 months	N	N	Normal	normal
									3.0 months	Y	Y	Dorsolat.	Facilitated dorsolat.
									5.8 months	Y	Y	Extensive	Facilitated dorsolat. putamen > remaining striatum
11[b]	High	M	p.Gly171Trp, p.Val400Met	NBS (7 days)	Full tx → delayed emergency tx	Insid. + later AEC (19 months)	15 months → AEC at 19 months	Persistent truncal hypotonia, motor retardation → AEC → severe	17 months	Y	Y	Dorsolat.	–
									19 months	Y	Y	Extensive	–
									24 months	Y	Y	Extensive	Facilitated dorsolat. putamen > remaining striatum
12[b]	High	F	p.Lys174Pro, p.Lys174Pro	NBS (7 days)	Delayed emergency tx	Acute	5 months	Severe	1.2 months	N	N	Normal	Normal
									7.5 months	Y	Y	Extensive	Facilitated
13[c]	High	F	n.d.	Targ. (4 months)	Diagn. and tx after AEC	Acute	4 months	Moderate	5.4 months	Y	Y	Extensive	–
14	High	M	n.d.	Targ. (5 months)	Diagn. and tx after AEC	Acute	5 months	Moderate	6.3 months	Y	Y	Extensive	–
									1.9 years	Y	Y	Dorsolat.	–
15[c]	Low	F	p.Met263Val, p.Met263Val	Targ. (11 months)	Diagn. and tx after AEC	Acute	10 months	Severe	10 months	Y	Y	Extensive	Pseudonormalized
									1.7 years	Y	Y	Extensive	–
16	Low	F	n.d.	Targ. (20 months)	Diagn. and tx after AEC	Acute	20 months	Severe	20 months	Y	Y	Extensive	Restricted
									21 months	Y	Y	Extensive	Pseudonormalized
									31 months	Y	Y	Extensive	Facilitated
17	High	F	n.d.	Targ. (21 months)	Diagn. and tx after AEC	Acute	21 months	Moderate	22 months	Y	Y	Extensive	Pseudonormalized
									23 months	Y	Y	Extensive	Facilitated
									33 months	Y	Y	Extensive	Facilitated
18	High	M	p.Ala378Val, p.Ala378Val	NBS (6 days)	Delayed emergency tx	Acute	12 months	Severe	2.0 years	Y	Y	Extensive	Facilitated

TABLE 1 (Continued)

Patient	Excretor	M/F	Mutation (protein code)	Diagnosis (age)	Treatment	Movement disorder		Severity	Age at MRI	Striatum	Putamen		Diffusion putamen (ADC maps)
						Insid./acute	Age at onset				Y/N	Local.	
19[b,c]	High	F	p.Glu365Lys, p.Glu365Lys	NBS (7 days)	Delayed emergency tx	Acute	9 months	Moderate	2.1 years	Y	Y	Extensive	–
20[c]	High	M	p.Glu365Lys, p.Glu365Lys	Targ. (5 months)	Diagn. and tx after AEC	Acute	5 months	Severe	5.6 years	Y	Y	Extensive	–
21	High	F	p.Arg402Trp, p.Arg402Trp	Targ. (15 months)	Diagn. and tx after AEC	Acute	15 months	Severe	11.6 years	Y	Y	Extensive	–
									13.6 years	Y	Y	Extensive	–
									15.7 years	Y	Y	Extensive	Facilitated
22[c]	High	F	p.Ala421Val, p.Ala421Val	Targ. (37 months)	Diagn. and tx after AEC	Acute	37 months	Severe	21.5 years	Y	Y	Extensive	Facilitated

asympt.: asymptomatic; diet.: dietary; dorsolat.: dorsolateral; F: female, insid.: insidious onset; M: male; mult. Emerg. adm.: multiple emergency admissions; NBS: newborn screening; targ.: targeted screening.

[a]MRIs from patients 1 and 5 (8.8 years) were also included in Harting et al.[7]

[b]Patients 3 (case 2), 4, 6, 11 (case 4), 12, and 19 (case 3) were also included in Heringer et al.[3]

[c]Patients 4, 6, 7, 13, 15, 20, 21, and initial three MRIs from 5 were also included in Harting et al.[28]

Deviations from the recommended metabolic maintenance treatment were identified in six of ten insidious-onset patients. Two further insidious-onset patients required multiple admissions for emergency treatment during the first year of life despite adequate maintenance treatment, and the remaining two became symptomatic despite the absence of obvious treatment deviations. Two insidious-onset patients subsequently suffered AEC following delayed emergency treatment (acute-on-insidious; patients 10 and 11), while dystonia worsened without unequivocal AEC in patient 2 with multiple admissions for emergency treatment and in patient 8 with severe malnutrition due to inadequately low daily lysine intake for several months.

The median onset of movement disorder was similar for acute-onset (median age at onset: 10 months, range 4-37) and insidious-onset patients (median age at onset: 10 months, range 5-78, unknown in one patient with first formal assessment at 5.5 years). Dystonia was more severe in acute ($n = 7$ severe, $n = 4$ moderate dystonia) or acute-on-insidious patients ($n = 1$ each moderate and severe dystonia) compared to insidious-onset patients without later AEC ($n = 4$ mild, $n = 3$ moderate, $n = 1$ severe dystonia).

Pathogenic variations in the *GCDH* gene were different in 14 of 17 patients with mutation analysis and identical in one insidious-onset patient and two siblings with acute-onset GA1 (p5,p19/20), thus not correlating with the type of onset. The proportion of low and high excretors was similar for insidious- and acute-onset patients (2/10 and 2/11, respectively). The clinical, biochemical, genetic, and MRI findings are summarized in Table 1.

3.2 | Patterns of striatal injury

All 21 symptomatic patients had persisting striatal changes consistent with lesions. Different patterns of striatal lesions were observed in insidious- versus acute-onset patients (Figure 1). Acute-onset patients had extensive T2-hyperintensity, involving putamen and caudate, and resulting in atrophy in the chronic stage in ten patients. Only one patient had not developed atrophy by follow-up 14 months later, when the striatum had a mottled appearance with mild, extensive T2-hyperintensity and more accentuated hyperintensity of the dorsolateral and the left anteromedial putamen (patient 14, Figure 2M). Diffusion in acute-onset patients was restricted in the patient imaged during AEC, pseudonormalized in the three patients imaged during the subacute phase, and was facilitated in the six patients examined at least two months after AEC.

In contrast to extensive striatal T2-hyperintensity in acute-onset patients, T2-hyperintensity was restricted to the dorsolateral putamen in eight of ten insidious-onset patients, occurring bilaterally in seven and unilaterally in one patient.

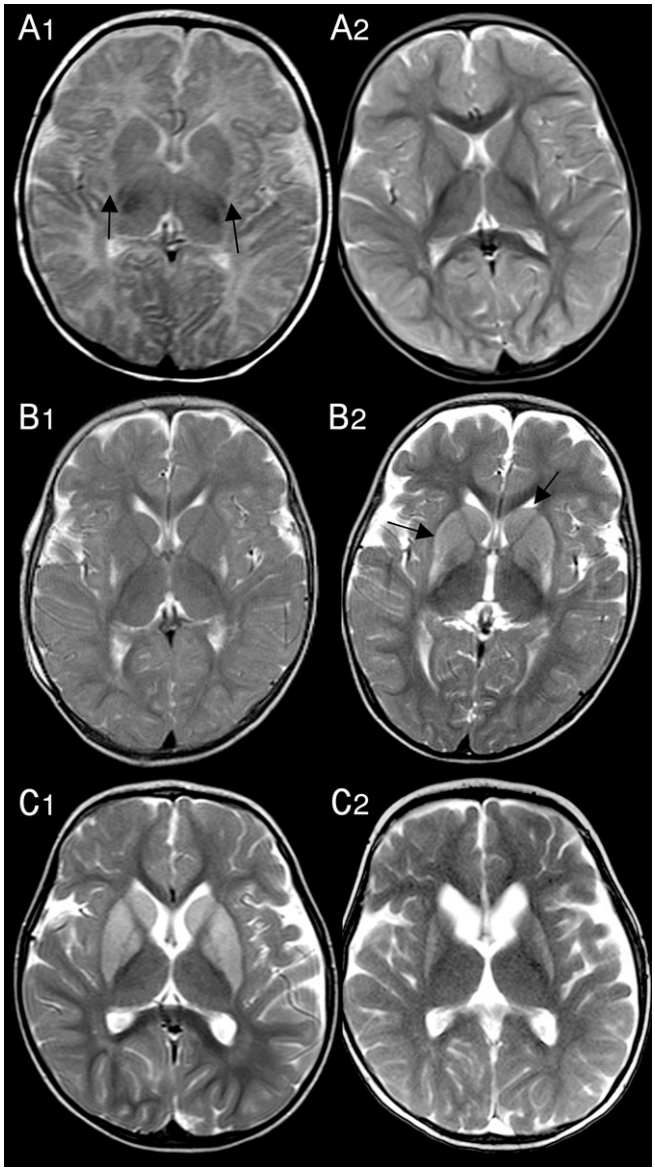

FIGURE 1 Examples of the characteristic pattern of striatal lesions in insidious-, acute-on-insidious-, and acute-onset type glutaric aciduria type 1 (GA1). $A_{1,2}$: Insidious-onset patient (p3) with T2-hyperintense dorsolateral putamen at 1.5 and 25 months, more easily appreciated after myelination. $B_{1,2}$: Acute-on-insidious-onset patient (p11) with hyperintense dorsolateral putamen at 17 months and superimposed, diffuse striatal T2-hyperintensity at 19 months with acute encephalopathic crisis (AEC). $C_{1,2}$: Acute-onset patient (p16) with diffuse striatal T2-hyperintensity at 22 and 33 months, with atrophy on follow-up

The two acute-on-insidious-onset patients had additional extensive striatal T2-hyperintensity with involvement of the caudate following AEC. The initially involved dorsolateral putamen remained more T2-hyperintense and conspicuous compared to the secondary, extensive striatal changes and diffusion was, correspondingly, more strongly elevated in the dorsolateral putamen, reflecting the sequential injury (patients 10 and 11; Figures 2G,H and 3A,B).

Striatal T2-hyperintensity not limited to the dorsolateral putamen was also observed in the two insidious-onset patients with worsening of dystonia but without overt AEC (patients 2 and 8; Figure 2I,J). In patient 2, extensive, mild T2-hyperintensity of the striatum was observed during one of the already multiple admissions for emergency treatment at 7.6 months. Following further stepwise deterioration of dystonia, the atrophic, strongly hyperintense striatum was indistinguishable from that of acute-onset patients. In patient 8, imaged after a long period of malnourishment and deterioration of dystonia, diffusion was clearly facilitated in the dorsolateral putamen but only mildly facilitated in the remaining putamen (Figure 3C), consistent with older, pre-existing injury of the dorsolateral and more recent injury of the remaining putamen, identical to the pattern in acute-on-insidious patients. Striatal T2-hyperintensity not limited to the dorsolateral putamen was also observed in the two insidious-onset patients with worsening of dystonia but without overt AEC (patients 2 and 8; Figure 2I,J). In patient 2, extensive, mild T2-hyperintensity of the striatum was observed during one of the already multiple admissions for emergency treatment at 7.6 months. Following further stepwise deterioration of dystonia, the atrophic, strongly hyperintense striatum was indistinguishable from that of acute-onset patients. In patient 8, imaged after a long period of malnourishment and deterioration of dystonia, diffusion was clearly facilitated in the dorsolateral putamen but only mildly facilitated in the remaining putamen (Figure 3C), consistent with older, pre-existing injury of the dorsolateral and more recent injury of the remaining putamen, identical to the pattern in acute-on-insidious patients.

3.3 | Time course of striatal injury in insidious-onset patients

Six insidious-onset patients were imaged during the first year of life. In three of these patients, the striatum was normal at initial MRI between 0.8 and 5.4 months (patients 2, 5, and 10, including normal DWI in patient 10) and striatal T2-hyperintensity had only developed by follow-up at 3 to 12 months, in patient 10 with corresponding facilitated diffusion. In the other three patients, the dorsolateral putamen was already T2-hyperintense on initial scans acquired between 1.5 and 7.3 months (patients 3, 4, and 6; no DWI).

The remaining four insidious-onset patients were first imaged beyond the age of one year and in those with DWI, diffusion was facilitated, as well as in follow-up scans of patient 5.

4 | DISCUSSION

Symptomatic patients with GA1 have a complex movement disorder with predominant dystonia superimposed on axial

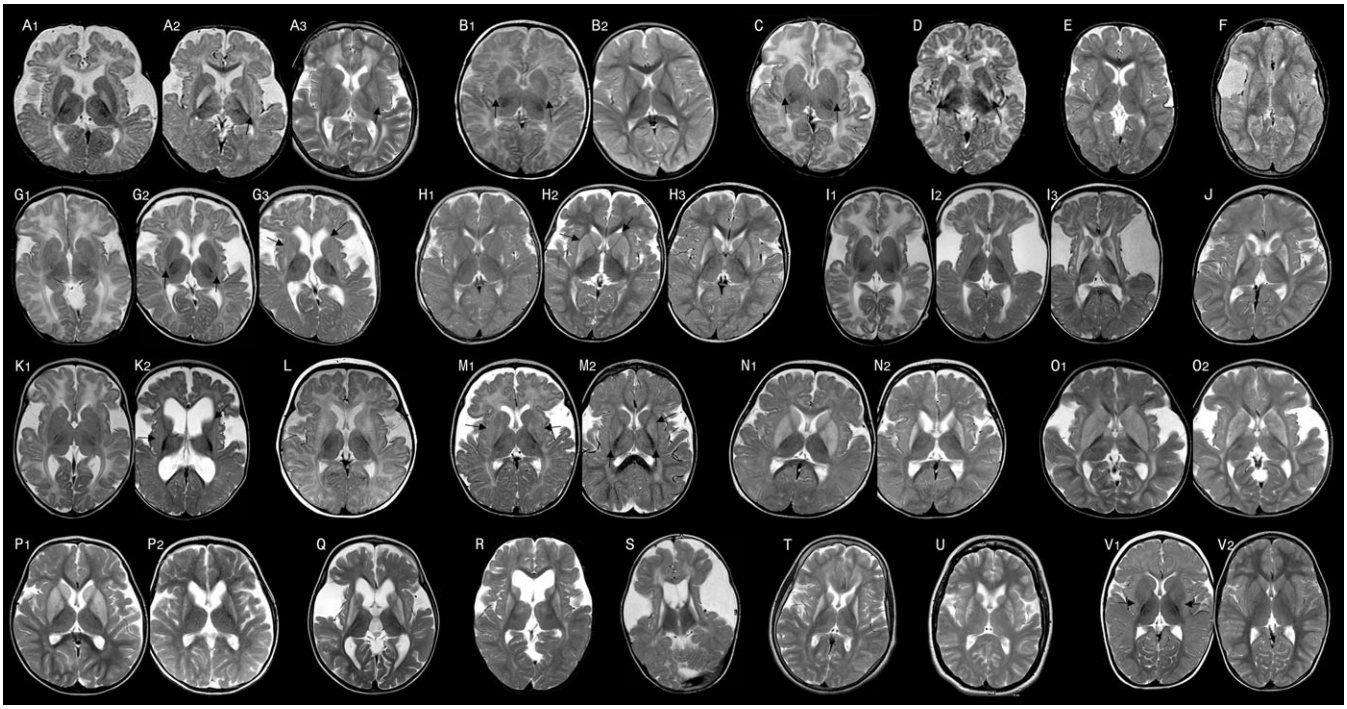

FIGURE 2 Striatal changes on T2-weighted images in the ten insidious-onset (**A-J**), 11 acute-onset patients (**K,U**), and single asymptomatic patient (**V**). **A-F** T2-hyperintense dorsolateral putamen in insidious-onset patients without subsequent deterioration of motor disability [**A** patient 5 at 5.4 months (A_1, normal) and 14.9 years (A_2); **B** patient 3 at 1.5 (B_1) and 25 (B_2) months; **C** patient 4 at 1.6 months; **D** patient 6 at 7.3 months; **E** patient 7 at 2.3 years; **F** patient 9 at 25.1 years].**G**, **H** Composite pattern in acute-on insidious-onset patients [**G** patient 10 at 0.8 months (G_1, normal), 3 months (G_2, dorsolateral putamen), and 5.8 months (G_3, add. diffuse striatal hyperintensity); **H** patient 11 at 17 months (H_1, dorsolateral putamen), 19 months (H_2, add. diffuse striatal hyperintensity, swelling), and 24 months (H_3, beginning atrophy)]. **I**, **J** Insidious-onset patients with deterioration but without AEC (**I** patient 2 at 1.4 months (I_1, normal) and 7.6 months (I_2); **J** patient 8 at 2.6 years). **K–U** Extensive striatal T2-hyperintensity in acute-onset patients [**K** patient 12 at 1.2 months (K_1, normal) and 7.5 months (K_2); **L** patient 13 at 6.3 months; **M** patient 14 at 6.3 months (M_1) and at 1.9 years without atrophy and with mottled appearance of striate (M_2); **N** patient 15 at 10 months (N_1) and 1.7 years (N_2); **O** patient 17 at 22 (O_1) and 33 (O_2) months; **P** patient 16 at 20 (P_1) and 31 (P_2) months; **Q** patient 18 at 2 years; **R** patient 19 at 2.1 years; **S** patient 20 at 5.6 years; **T** patient 21 at 15.7 years; **U** patient 22 at 21.5 years. **V** Transient T2-hyperintensity at the lateral border of the putamen, sparing the dorsal most portion in patient 1 at 7.5 months (arrows in V_1) and normal striatum at 6.5 years (V_2)

muscular hypotonia. The term "insidious onset" is used if movement disorder develops without apparent acute event, in distinction to patients with acute onset following AEC. It is, as yet, not clear if the two modes of onset of movement disorder are associated with different timing and pattern of striatal injury and outcome. It was initially speculated that insidious and acute presentation of movement disorder differed only in the timing of injury, insidious onset resulting from perinatal events and before any opportunity of therapeutical intervention.[4] A subsequent follow-up study of patients diagnosed by NBS did not support this hypothesis but demonstrated that deviations from metabolic maintenance treatment, in particular deviations from low lysine diet, are the major risk factor for insidious-onset dystonia.[3] Moreover, findings in the six patients of that study with MRI, namely three insidious-, two acute-onset, and one acute-on-insidious-onset patient, suggested different patterns. We, therefore, analyzed clinical and striatal MRI changes in a total of 21 symptomatic patients with GA1 including these six patients previously reported by our group[3] in order to better understand and characterize the different disease variants in symptomatic GA1.

4.1 | Striatal lesions differ in insidious- versus acute-onset patients

In distinction to extensive striatal T2-hyperintensity and subsequent atrophy in acute-onset patients, insidious-onset patients had a typical pattern of circumscribed T2 -hyperintensity of the dorsolateral putamen without atrophy on follow-up. This pattern has previously been described in an 8-month-old infant and two adult sisters with insidious onset[4,11] and appears to be characteristic of this disease variant.

Patients with acute-on-insidious presentation had a corresponding, composite pattern of sequential striatal injury in which extensive, mild striatal T2-hyperintensity was superimposed on initial, characteristic T2-hyperintensity of the dorsolateral putamen after AEC. This pattern has previously

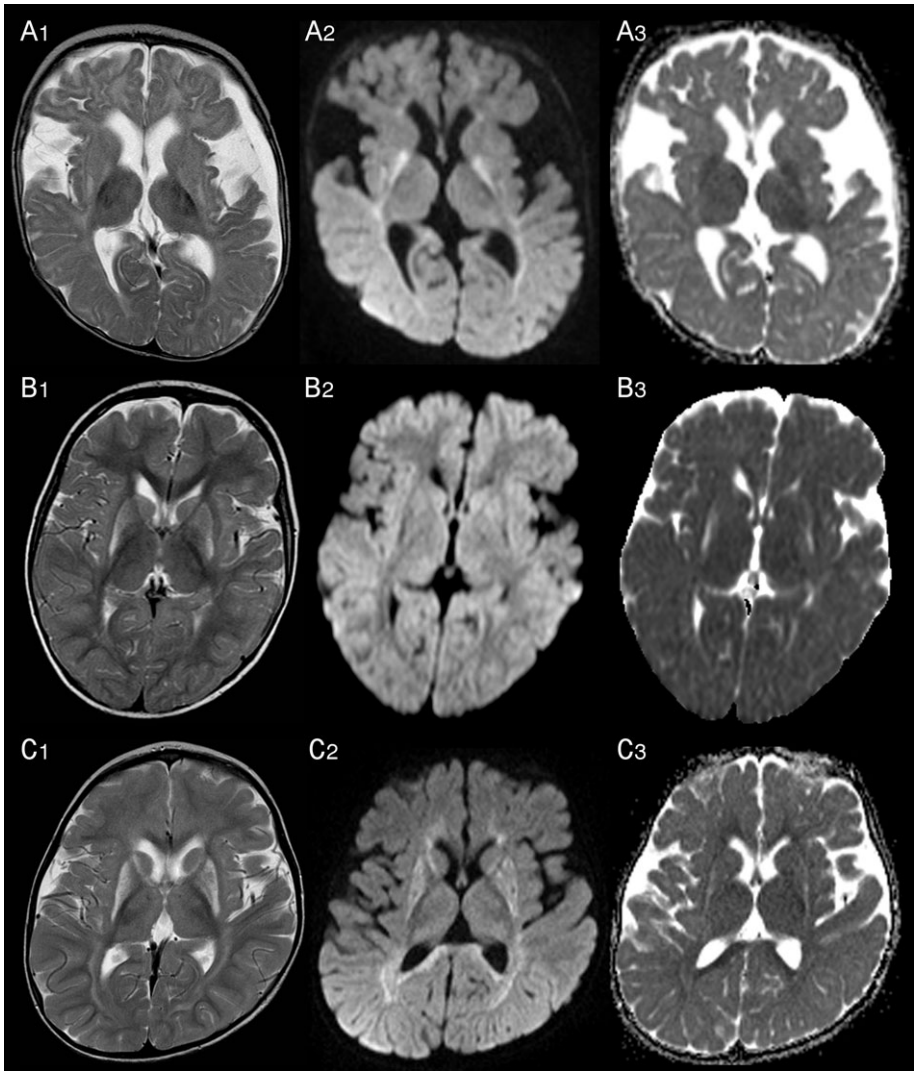

FIGURE 3 Pattern of sequential striatal injury in insidious-onset patients with progressive dystonia [each row displays from left to right T2-, corresponding diffusion-weighted image (DWI) and apparent diffusion coefficient (ADC) map annotated with 1,2,3, respectively]. **A**, **B** Following AEC, the pre-existing lesions of the dorsolateral putamen in patients 10 (**A**) and 11 (**B**; see also Figure $2G_2$, H_1) are more T2-hyperintense and diffusion is more highly elevated than in the remaining, newly affected striatum with its mild T2-hyperintensity and mildly elevated diffusion. **C** Extensively T2-hyperintense striatum in the single MRI of patient 8 imaged after deterioration; DWI reveals sequential injury with clearly elevated diffusion of older, pre-existing lesions of the dorsolateral putamen and mildly elevated diffusion of the more recently injured, remaining striatum

been observed in an 8-month-old patient with acute motor regression [patient 2 in Strauss et al.[4]] and is depicted in another published patient.[12,13] Sequential injury in our acute-on-insidious patients was documented by follow-up MRI, but was also evident from differing diffusion properties, namely clearly facilitated diffusion of the pre-existing lesions of the dorsolateral putamen and only mildly facilitated diffusion of the remaining striatum. Interestingly, this diffusion pattern of sequential injury was also present in an insidious-onset patient who was only imaged after dystonia had worsened without overt AEC, revealing pre-existing lesions of the dorsolateral putamen characteristic of insidious-onset disease and subsequent extensive striatal involvement not evident on T2-weighted images.

4.2 | Severity, timing of striatal injury, and associated events in insidious-onset type GA1

It has previously been described that striatal injury begins in the dorsolateral putamen and that the severity of the resulting dystonia is related to the extension of injury anteriorly and medially.[13] Consistent with smaller extent of striatal injury in insidious-onset patients, dystonia was, overall, less severe in insidious- compared to acute-onset patients.

Interestingly, the extent to which the putamen is involved apparently also affects the temporal evolution of dystonia. In contrast to tight temporal coupling between extensive striatal injury and manifestation of dystonia in acute onset, insidious-onset patients experience a phase of latency between the detection of lesions and clinical manifestation of dystonia. Notably, four of our six insidious-onset patients with lesions of the dorsolateral putamen on MRI during the first 2 years of life were asymptomatic; one had non-specific motor retardation due to persistent muscular hypotonia and only one had truncal hypotonia combined with muscular hypertonia of the extremities, suggestive of evolving dystonia. The absence of movement disorder despite lesions of the dorsolateral putamen has previously been noted in two neonates and a temporal pattern of insidious-onset movement disorder, namely development of truncal hypotonia at

age 2 to 3 months followed by delayed motor development and emergence of movement disorder at age 4 to 6 months, was described in six Amish patients.[4] In our insidious-onset patients, the median onset of dystonia at 10 months was somewhat later and the latency phase was more variable. Latency may be quite long, as evidenced by patient 11, who was noted for motor retardation due to persistent axial hypotonia and feeding problems, which may indicate onset of dystonia. However, dystonia did not become clinically apparent before the first MRI at 17 months, which demonstrated lesions of the dorsolateral putamen, and was further aggravated after AEC at age 19 months. This case underlines the difficulty of prospective clinical appraisal of insidious-onset movement disorder, since truncal hypotonia and motor retardation are non-specific findings and occur in approximately 50% of neonates and infants with GA1, often transiently and without development of dystonia.[10] However, significant muscular hypotonia persisting or deteriorating beyond the age of 6 months should prompt neurologic re-evaluation, since it may indicate onset of dystonia.

As clinical findings are, thus, not conclusive for the timing of injury in insidious-onset GA1 and since there is no peripheral biochemical marker, MRI is currently the only method not only to detect but also to estimate age of striatal lesions using DWI in analogy to hypoxic ischemic injury and ischemic stroke. In neonates with hypoxic-ischemic encephalopathy (HIE), restricted diffusion of basal ganglia and thalami pseudonormalizes at the end of the first week[14–16] and, somewhat later, between days 8 and 14, in adults with ischemic stroke.[17,18] This sequence of acutely restricted diffusion, followed by pseudonormalization and swelling in the subacute phase and facilitated diffusion in the chronic atrophic phase, is also seen in striatal lesions of patients with acute-onset GA1 [e.g., patient 16 in Strauss et al.[4]] and in other neurometabolic disorders with so-called metabolic stroke, e.g., methylmalonic academia.[19] Acutely restricted diffusion reflects cytotoxic edema, narrowing the extracellular space and, thereby, decreasing the magnetic resonance-visible diffusion of water within the extracellular space. Experimental data for GA1 implicate, among others, disrupted mitochondrial energy homeostasis and excitotoxicity as factors of striatal injury,[20,21] with mitochondrial dysfunction as the shared final pathway of ischemic and "metabolic stroke". Restricted striatal diffusion in patients with GA1 imaged in the setting of AEC,[4,22–24] moreover, fits well with early ischemic neuronal damage of the putamen observed on histopathology in a 10-year-old patient who died during AEC.[25] The onset of vasogenic edema progressively counteracts the effect of cytotoxic edema with pseudonormalization during the subacute phase, while facilitated diffusion of chronic striatal lesions in patients imaged several months after AEC [e.g., patients 12, 16–18; Figure 2A-C in Strauss et al.[4]] is consistent with severe neuronal loss and fibrous gliosis in chronic degeneration.[25–27]

But while restricted diffusion, as an indicator of acute injury, is well documented for acute-onset patients, it has, as yet, been neither reported nor did we observe it in our patients. This is not a question of resolution, as dorsolateral putaminal lesions are much larger than the punctate ischemia routinely detected in adults with stroke, but of MRI being fortuitously acquired during a few days of restricted diffusion in an asymptomatic patient.

Thus, the time frame of striatal injury in insidious-onset GA1 can currently only be extrapolated from normal initial MRIs (0.8 to 5.4 months; patients 2, 5, and 10) and from the manifestation of striatal injury either as MRI lesions in asymptomatic patients [0.2 to 17 months, patients 3–6 and 11, case 3 and second imaged neonate in Strauss et al.[4]] or onset of dystonia in patients without prior imaging (9 to ≤60 months, patients 8 and 9). This time frame is consistent with the age-limited vulnerability of the striatum known from acute-onset patients, in whom dystonia occurs almost exclusively during the first 6 years of life and, most commonly, between the age of 3 and 36 months.[1] White matter changes, in contrast, increase with increasing age, consistent with chronic intracerebral accumulation of neurotoxic metabolites, and not correlated to AEC.[7,8,28]

The initial assumption that striatal injury in insidious-onset patients occurs during a period of early postnatal catabolism and before the opportunity of therapeutical intervention[4] is not supported by normal initial MRI in a neonate and two infants including normal DWI as the most sensitive indicator of striatal injury in the neonate. Together with the observation that insidious onset of movement disorder in a genetic cohort vanished following improvement of dietary management[29] and the large proportion of patients with deviations from recommended dietary treatment, this is consistent with a protective effect of neonatally initiated dietary treatment preventing insidious onset of movement disorder in GA1.

5 | CONCLUSION

Lesions of the dorsolateral putamen are characteristic of insidious-onset glutaric aciduria type 1 (GA1). Insidious-onset patients differ from acute-onset patients not only in the smaller extent of striatal lesions and corresponding less severe dystonia, but also a latency phase when lesions are already present but patients are asymptomatic or have non-specific truncal hypotonia and/or delay of motor development.

While lesions in insidious-onset patients may be detected as early as the perinatal and early infant period, our findings do not support the notion of perinatal injury occurring before

the opportunity of therapeutic intervention. Instead, initially normal MRI scans in a neonate and two young infants, together with deviations from baseline metabolic treatment identified in six insidious-onset patients, substantiate the protective effect of neonatally initiated guideline-recommended treatment.

ACKNOWLEDGEMENTS

We thank the patients and their parents for their support and participation in this study. S. Kölker received funding from the European Union via Chafea, in the framework of the Health Programme, for the project "European registry and network for intoxication type metabolic diseases" (E-IMD; grant no. December 1, 2010). The author confirms independence from the sponsors; the content of the article has not been influenced by the sponsors.

COMPLIANCE WITH ETHICAL STANDARDS

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. Patients were pseudonymized and data only included if written informed consent was obtained from patients and/or parents. The study was approved by the Institutional Ethics Committee of the University of Heidelberg (#314/2002, S-49/2010). No study patient has withdrawn informed consent.

CONFLICT OF INTEREST

N. Boy, S. F. Garbade, J. Heringer, A. Seitz, and I. Harting declare that they have no conflict of interest.

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How to cite this article: Boy N, Garbade SF, Heringer J, Seitz A, Kölker S, Harting I. Patterns, evolution, and severity of striatal injury in insidious- vs acute-onset glutaric aciduria type 1. *J Inherit Metab Dis*. 2019;42:117–127. https://doi.org/10.1002/jimd.12033