

# Acetyl-DL-leucine in Niemann-Pick type C

A case series



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## ABSTRACT

**Objective:** To assess the effects of the modified amino acid acetyl-DL-leucine (AL) on cerebellar ataxia, eye movements, and quality of life of patients with Niemann-Pick type C (NP-C) disease.

**Methods:** Twelve patients with NP-C disease were treated with AL 3 g/d for 1 week and then with 5 g/d for 3 weeks with a subsequent washout period of 1 month. The Scale for the Assessment and Rating of Ataxia (SARA), the Spinocerebellar Ataxia Functional Index (SCAFI), the modified Disability Rating Scale (mDRS), EuroQol 5Q-5D-5L, and the visual analog scale (VAS) were administered. Measurements took place at baseline, after 1 month of therapy, and after 1 month of washout.

**Results:** The SARA score changed from the baseline (median [ $\pm$ SD, interquartile range]) of 10.8 (11.2, 8–24.6) to 7.0 (10.7, 5.6–19.6) on medication (difference: 3.8 points) and 10.5 (11.5, 7.1–23.9) after washout (difference: 3.5 points) ( $p = 0.000412$ ; post hoc  $p = 0.003$  between baseline and on medication, and on medication and washout  $p = 0.005$ ). The SCAFI subscore 9-Hole Peg Test for dominant hand, mDRS score, and VAS score also improved on medication. No side effects except transient dizziness in one patient were reported.

**Conclusions:** Treatment with AL improved ataxic symptoms in patients with NP-C without relevant side effects, thus showing a reasonable risk-benefit profile.

**Classification of evidence:** This study provides Class IV evidence that AL improves cerebellar symptoms and quality of life in patients with NP-C. *Neurology*® 2015;85:1368–1375

## GLOSSARY

**AL** = acetyl-DL-leucine; **IQR** = interquartile range; **mDRS** = modified Disability Rating Scale; **MoCA** = Montreal Cognitive Assessment; **9HPT** = 9-Hole Peg Test; **NP-C** = Niemann-Pick type C; **PSPV** = peak slow-phase velocity; **SARA** = Scale for the Assessment and Rating of Ataxia; **SCAFI** = Spinocerebellar Ataxia Functional Index; **VAS** = visual analog scale.

Niemann-Pick type C (NP-C) is a hereditary lysosomal storage disease characterized by progressive neurologic deterioration and premature death.<sup>1</sup> The disease presents with systemic, psychiatric, and neurologic symptoms, including cerebellar ataxia, most pronounced in juvenile and adult patients.<sup>2–4</sup>

The current disease-specific therapy approved for NP-C is miglustat (Zavesca; Actelion Pharmaceuticals Ltd., Allschwil, Switzerland), which targets sphingolipid synthesis and storage and thus slows the progression of the disease.<sup>5</sup> However, because of the progressive and irreversible nature of the disease, additional symptomatic treatment is needed to improve functioning and quality of life and to alleviate the burden of disease.

The prior study assessing the effect of therapy with the acetylated derivative of a natural amino acid, acetyl-DL-leucine (AL) (Tanganil; Pierre Fabre, Castres, France), in patients with cerebellar ataxia of different etiologies suggested the beneficial effect of this agent.<sup>6</sup> In this study, we evaluated the effect of therapy with AL in patients with genetically and/or biochemically proven NP-C disease.

**METHODS Level of evidence.** The aim of this Class IV evidence study was to evaluate the effect of AL 3 g/d for 1 week (Tanganil 500 mg) and then 5 g/d for the following 3 weeks (in total, 1 month) on cerebellar function, ocular motor function, and subjective satisfaction.

Supplemental data  
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**Standard protocol approvals, registrations, and patient consents.** This case series was an observational study. All patients and/or guardians of patients gave their informed consent for the compassionate use of AL. Signed patient consent-to-disclose forms were also obtained for videos of patients and their family members.

**Patients.** Ten patients with genetically confirmed and 2 patients with biochemically confirmed NP-C disease (5 females, mean age [ $\pm$ SD]  $22.9 \pm 4.9$  years, mean disease duration  $13.7 \pm 4.1$  years, mean age when diagnosis was established  $17.7 \pm 5.3$  years) were included. The clinical characteristics of the patients are given in table 1.

**Evaluations.** To evaluate the overall neurologic status in NP-C disease, the modified Disability Rating Scale (mDRS) by Pineda et al.<sup>7</sup> was applied; the mDRS is a 4-domain scale (ambulation, manipulation, language, and swallowing) in an extended form,<sup>8</sup> which also includes seizures and ocular movements, that assesses the severity of the disease and monitors the effect of treatment. The following cerebellar function evaluations were administered: (1) the Scale for the Assessment and Rating of Ataxia (SARA),<sup>9,10</sup> an 8-item clinical rating scale (gait, stance, sitting, speech, fine-motor function, and taxis; range 0–40, where 0 is the best neurologic status and 40 the worst); and (2) the Spinocerebellar Ataxia Functional Index (SCAFI), comprising 8-m walking time performed by having patients walk twice, as quickly as possible, from one line to another excluding turning, the 9-Hole Peg Test (9HPT), and the number of “PATA” repetitions over 10 seconds (PATA).<sup>11</sup>

Subjective impairment and quality of life were evaluated by using the EuroQol (EQ) 5Q-5D-5L questionnaire<sup>12</sup> and the visual analog scale (VAS). To assess the effect of the therapy on ocular motor function, 3-dimensional video-oculography (Eye-SeeCam)<sup>13</sup> was used to measure the peak velocity of saccades, gain of smooth pursuit, peak slow-phase velocity (PSPV) of gaze-evoked nystagmus (gaze-holding function), PSPV of optokinetic nystagmus, and gain of horizontal vestibuloocular reflex at each visit.<sup>14</sup> To evaluate the potential treatment effect, administration of the SCAFI scale in patients with NP-C was recorded on video (for 9HPT examination, see videos 1 and 2 on the *Neurology*<sup>®</sup> Web site at [Neurology.org](http://Neurology.org)). Measurements and questionnaire administration took place at baseline, after 1 month of therapy with AL (on day  $30 \pm 1$  day), and after a 1-month washout period (on day  $60 \pm 2$  days). To evaluate the cognitive state, the Wechsler Adult Intelligence Scale–Revised (WAIS-R) or Wechsler Intelligence Scale for Children–IV,<sup>15</sup> and Montreal Cognitive Assessment (MoCA),<sup>16</sup> assessing different cognitive domains including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation with a maximum of 30 points and a cutoff score of 26, were administered once at baseline  $\pm 1$  month (see table 1).

Patients and their parents were asked about their subjective improvement on medication; videos of their subjective evaluation of the effect treatment and possible side effects (see video 3) were also recorded. Drug administration and neurologic examination (with one exception: Wechsler Adult Intelligence Scale–Revised/Wechsler Intelligence Scale for Children–IV) were performed by one examiner (T.B.).

**Statistical analysis.** Statistical analysis and figure design were performed using SPSS version 22.0.0 (IBM, Armonk, NY). Differences were considered significant at  $p < 0.05$ . Because data were not normally distributed, related-samples Friedman test with  $\chi^2$  test statistics was run to determine whether there were

differences in measured scores between baseline, on medication, and washout time points. Post hoc analysis with the Wilcoxon signed-rank test was conducted with a Bonferroni correction. Spearman rank correlation coefficient was used to assess the relationships between tested variables. Patients who were not physically capable of performing the particular score tasks were not included in the analysis.

**RESULTS Effects of AL on neurologic status.** The total SARA score was 10.8 (11.2, 8–24.6) at baseline (median [ $\pm$ SD, interquartile range, IQR]), 7.0 (10.7, 5.6–19.6) after 1 month of medication (difference: 3.8 points), and 10.5 (11.5, 7.1–23.9) after 1 month of washout (difference: 3.5 points) (for individual value changes, see table e-1 and figure 1, A and B), indicating an improvement of cerebellar signs on medication ( $\chi^2 = 15.591$ ,  $p = 0.000412$ ). The post hoc testing revealed a statistically significant difference between the baseline and on-medication scores ( $p = 0.003$ ) and between the on-medication and washout scores ( $p = 0.005$ ), but no significant difference between the baseline and the washout scores ( $p = 0.561$ ).

The SCAFI 9HPT of the dominant hand changed significantly ( $\chi^2 = 6.889$ ,  $p = 0.032$ ), yielding significant differences between baseline and on medication ( $p = 0.038$ ) as well as on medication and washout ( $p = 0.033$ ), but not between baseline and washout ( $p = 0.594$ ). There was a general trend for improvement of the 9HPT of the nondominant hand ( $p = 0.121$ ) and 8-m walking time ( $p = 0.178$ ) on medication. The PATA score did not change significantly between measurements ( $p = 0.406$ ) (table e-1; figure 2, A–D).

The total mDRS score (median [ $\pm$ SD, IQR]) was 10.0 (5.35, 7–23) at baseline, 9.0 (5.3, 6–23) on medication (difference: 1 point), and 10.0 (5.4, 6–23) after 1-month washout (difference: 1 point) (table e-1; figure 1, C and D). This change was statistically significant ( $\chi^2 = 13.04$ ,  $p = 0.001$ ). The post hoc testing revealed a statistically significant difference between the baseline and the on-medication scores ( $p = 0.01$ ) and between the on-medication and the washout scores ( $p = 0.024$ ), but no significant difference between the baseline and the washout scores ( $p = 0.083$ ). There was a negative correlation between the neurologic and cognitive status when the baseline mean total SARA score and IQ score was analyzed ( $\rho = -0.756$ ,  $p < 0.05$ ). Correlation analysis also showed a trend for a significant association between MoCA and SARA scores ( $\rho = -0.622$ ,  $p = 0.055$ ) and MoCA and mDRS scores ( $\rho = -0.579$ ,  $p = 0.079$ ).

**Ocular motor function.** The mean peak velocity ( $\pm$ SD, range) of the vertical saccades was 55.0°/s (67.2, 35.8–111.3) at baseline, 71.0°/s (24.3, 44.0–82.0)

**Table 1** Baseline characteristics of the patients included in the study

Patient no./sex/age, y	Age at onset/diagnosis, y	Medication	Genotype	Neurologic and psychiatric findings <sup>a,b</sup>	Internal manifestation/other findings <sup>b</sup>	Ocular motor findings <sup>c</sup>	MRI findings <sup>d</sup>	MoCA <sup>b</sup>	IQ <sup>e</sup>
1/M/13	4.5/10	Levetiracetam 1,750 mg/d, valproate 750 mg/d, miglustat 400 mg/d	NPC1: c.3182T>C, c.3557G>A	a, b, c, d, e, f, g, j, k, o, p, s, t	Medium-grade splenomegaly, PEG	a, b, c, e	b	8	46
2/F/23 <sup>f</sup>	3/19	Levetiracetam 300 mg/d, sertraline 50 mg/d, donepezil 10 mg/d, clonazepam 0.5 mg/d, miglustat 600 mg/d	NPC1: c.2861C>T, c.3557G>A	a, b, c, d, e, f, h, i, j, k, n, o, s, t	Mild splenomegaly, cachectic habitus	a, c, d, e	a, b	NcP	33
3/F/26	7/23	Valproate 600 mg/d, miglustat 500 mg/d	NPC1: c.1935dupT, c.2861C>T	a, b, d, e, f, g, h, j, k, n, o, t, v	PEG, tracheostomy, cachectic habitus	a, b, c, d, e	b	NcP	20
4/F/32	18/28	Sertraline 50 mg/d, vitamin B <sub>1</sub> , B <sub>6</sub> , B <sub>12</sub> 1×/wk	NPC1: c.1028G>A, c.2198C>G	b, c, d, f, h, j, k, s, t	Initial manifestation after birth of her child	a, b, c, e	NP	25	74
5/F/25	6/22	Miglustat 600 mg/d	NPC1: c.3019C>G, c.3592-7_3592-3delCTTTT Polymorphisms c.644A>G, c.1926G>C	b, c, d, f, s, t	Mild splenomegaly	a, b, c, e	b	13	60
6/M/24	10/21	Miglustat 600 mg/d, hearing devices bilaterally	NPC1: c.2474A>G, c.3160G>A	b, c, d, f, h, k, l, m, s, t	Splenomegaly	a, c	n	25	NP
7/M/20	8/18	Risperidone 0.5 mg/d, miglustat 600 mg/d	No mutation in NPC1 and NPC2 genes found <sup>g</sup>	b, c, d, f, k, r, s, t	Mild hepatosplenomegaly	a, c	b	23	NP
8/M/26	13/13	Levetiracetam 200 mg/d, melatonin, miglustat	NPC1: c.1232G>C, c.2861C>T	a, b, c, d, f, k, m, n, s, t	Hepatosplenomegaly	a, c	n	2	46
9/M/20 <sup>f</sup>	5/16	Ramipril 0.125 mg/d, metronidazole, miglustat 600 mg/d, hearing devices	NPC1: c.2861C>T, c.3557G>A	b, c, d, e, l, m, f, t	Hepatosplenomegaly, arterial hypertension, microcytic anemia	a, c, d	NP, CT normal	24	79
10/M/25	12/17	Lamotrigine 350 mg/d, piracetam 3,600 mg/d, ginkgo biloba, miglustat 600 mg/d	NPC1: c.808delG, c.2861C>T	a, b, d, g, i, j, b, s, t, u	Splenomegaly	a, b, c, e	b	14	79
11/M/24	14/15	Miglustat 400 mg/d, ginkgo biloba, vitamin E, piracetam 3,600 mg/d	NPC1: c.1723delG, c.2861C>T	b, c, d, i, r, j, k, l, r, s, t	Mild splenomegaly	b, c, d, f	n	18	81
12/F/17	10/11	Vitamin D 500 I.E./d, miglustat 600 mg/d	No mutation in NPC1 and NPC2 genes found <sup>g</sup>	b, f, i, s, t	Splenomegaly	a, c, e	n	25	NP

Abbreviations: MoCA = Montreal Cognitive Assessment; NcP = not capable of performing the task because of physical limitations; NP = not performed; PEG = percutaneous endoscopic gastrostomy.

<sup>a</sup>Neurologic and psychiatric findings: a = epilepsy; b = ataxic stance and gait; c = dysmetria/tremor upper extremities; d = dystonia; e = contractures of Achilles tendons; f = dysphagia; g = gelastic cataplexy; h = dyskinesias; i = emotional instability; j = clonus lower extremities; k = hyperreflexia; l = stuttering; m = hearing impairment; n = confined to a wheelchair; o = excessive salivation; p = hypomimia; r = organic psychosis; s = dysarthria; t = cognitive impairment; u = logorrhea; v = complete anarthria.

<sup>b</sup>The total possible MoCA score is 30 points; a score of 26 or higher is considered normal. Data at baseline.

<sup>c</sup>Ocular motor findings: a = slow vertical saccades; b = vertical saccade paresis downward; c = impaired vertical smooth pursuit; d = fixation instability, e.g., square wave jerks; e = impaired vertical optokinetic nystagmus; f = strabismus.

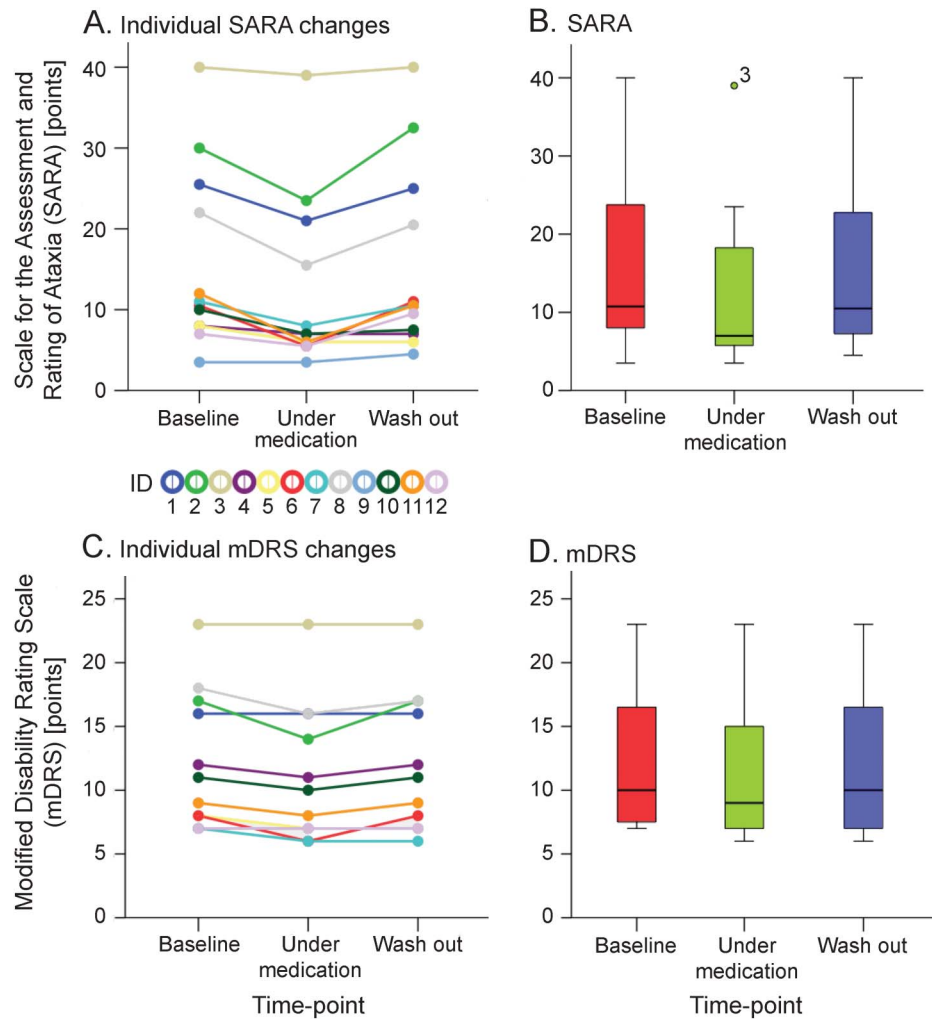
<sup>d</sup>MRI findings: a = supratentorial enlarged liquor spaces; b = generalized atrophy; c = cerebellar atrophy; d = brainstem atrophy; e = leukodystrophy; n = normal findings.

<sup>e</sup>Full Scale IQ as tested by Wechsler Adult Intelligence Scale-Revised or Wechsler Intelligence Scale for Children-IV.

<sup>f</sup>Family relatives (mothers are cousins).

<sup>g</sup>Positive filipin staining (variant type).

**Figure 1** Effect of treatment with acetyl-DL-leucine 5 g/d on neurologic status in patients with Niemann-Pick type C



Individual and value changes on the Scale for the Assessment and Rating of Ataxia (SARA) (A, B) and the modified Disability Rating Scale (mDRS) (C, D). Measurements performed at baseline, after 1 month on medication with acetyl-DL-leucine 5 g/d, and after 1 month of washout. The total SARA score changed significantly from the baseline (median [ $\pm$ SD, interquartile range] of 10.8 (11.2, 8–24.6) to 7.0 (10.7, 5.6–19.6) after 1 month of medication (difference 3.8 points) and 10.5 (11.5, 7.1–23.9) after 1 month of washout (difference 3.5 points), indicating an improvement of cerebellar signs on medication ( $\chi^2_2 = 15.591$ ,  $p = 0.000412$ ). The total mDRS score (median [ $\pm$ SD, interquartile range]) was 10.0 (5.35, 7–23) at baseline, 9.0 (5.3, 6–23) on medication (difference 1 point), and 10.0 (5.4, 6–23) after 1 month of washout (difference 1 point). This change was statistically significant ( $\chi^2_2 = 13.04$ ,  $p = 0.001$ ). The length of the boxes (B, D) indicates the interquartile space (P25–P75), the horizontal line into the box represents the median (P50), and the whiskers indicate the adjacent values. The circle indicates the outlier.

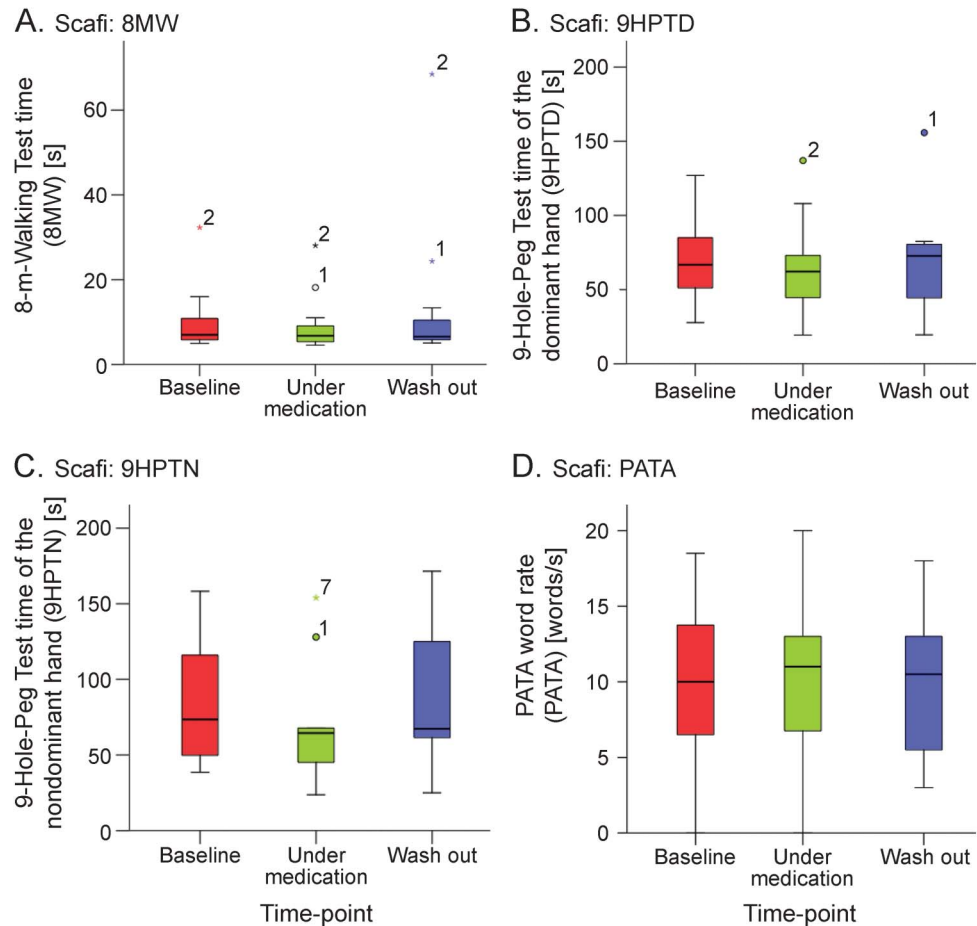
on medication, and 44.0°/s (19.7, 33.0–50.0) after 1 month of washout ( $p = 0.244$ ). The other ocular motor parameters tested also did not significantly change (overall comparisons):  $p$  for peak velocity of horizontal saccades: 0.846, smooth pursuit gain: vertical 0.554, horizontal 0.115;  $p$  for PSPV of gaze-evoked nystagmus: vertical 0.761, horizontal 0.717;  $p$  for horizontal vestibuloocular reflex gain: 0.692; PSPV of optokinetic nystagmus: vertical 0.311, horizontal 0.692.

**Quality of life.** Quality of life, as assessed by the EQ-5D-5L, changed from a baseline score of 0.62 (0.35–0.83)

to 0.72 (0.43–0.83) on medication and 0.52 (0.19–0.85) without medication ( $p = 0.459$ ) (see table e-1 and figure 3A). VAS score changed significantly on medication ( $p = 0.05$ ), increasing from 30 (25–70) at baseline to 45 (35–80) on medication ( $p = 0.02$ ). After 1 month of therapy, VAS score decreased to 30 (20–60) ( $p = 0.776$ ) (see table e-1 and figure 3B).

**Subjective evaluation.** Family and caregivers of 8 of the 12 patients believed there was improvement in one or more areas. Parents of 3 of 12 patients described remarkable behavioral improvement in affect stabilization, cooperation, and ability to act independently

**Figure 2** Effect of treatment with acetyl-DL-leucine 5 g/d on cerebellar status in patients with Niemann-Pick type C, as assessed by the SCAFI



Boxplot representation of cerebellar function, as assessed by the Spinocerebellar Ataxia Functional Index (SCAFI) subscore items 8-m Walk (8MW) test time (A), 9-Hole Peg Test time for dominant (9HPTD) (B) and nondominant (9HPTN) (C) hand, and PATA word count in 10 seconds (D) before, during, and after therapy with acetyl-DL-leucine 5 g/d. The SCAFI 9HPTD item changed significantly ( $\chi^2_2 = 6.889$ ,  $p = 0.032$ ) yielding significant differences between baseline and on medication ( $p = 0.038$ ) as well as on medication and washout ( $p = 0.033$ ), but not between baseline and washout ( $p = 0.594$ ). There was a general trend for improvement of 9HPTN ( $p = 0.121$ ) and 8MW test ( $p = 0.178$ ) times on medication. The PATA score did not change significantly between measurements ( $p = 0.406$ ). The length of the boxes indicates the interquartile space (P25-P75); the horizontal line into the box represents the median (P50), and the whiskers indicate the adjacent values. The circles indicate the outliers and the stars represent an extreme value.

in daily life (e.g., dressing, grooming, drawing). In 3 patients, subjective improvement of dysphagia was also reported (fewer swallowing problems while drinking and eating). In one patient with square wave jerks, subjective improvement of fixation, as reported by the parents, was observed (see table e-1).

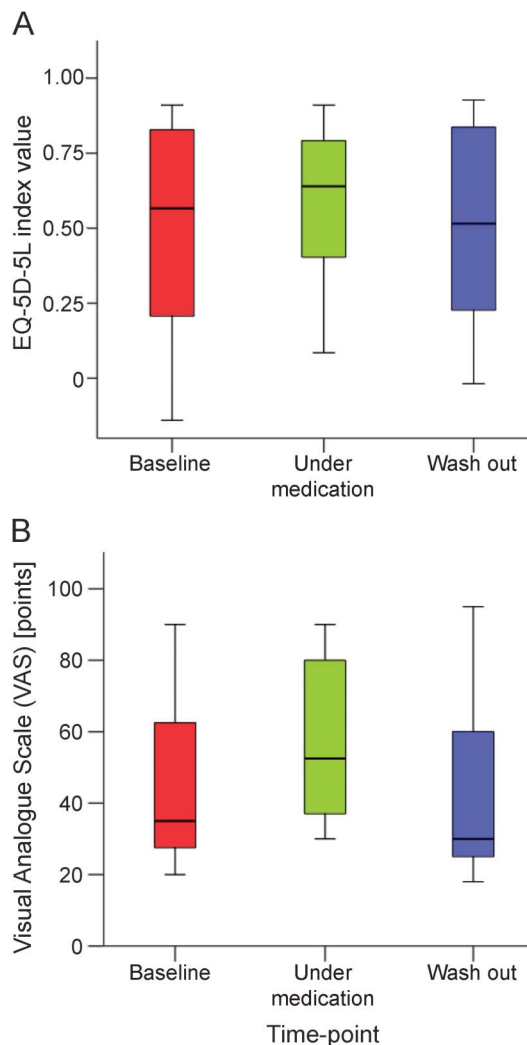
**Side effects.** One patient reported intermittent dizziness on the dosage of 5 g/d, which ceased after the dose was reduced to 3 g/d for 1 week. When the dosage was increased again, the symptoms did not recur.

**DISCUSSION** The major findings of this case series are as follows: first, the modified amino acid AL had a significant effect on cerebellar signs and symptoms in patients with genetically and/or biochemically

proven NP-C disease. Second, the improvement of neurologic status also led to a significant improvement of the quality of life of the patients and their family members. Third, the low frequency (1 of 12) and the temporary nature of the adverse effects suggest a reasonable risk-benefit profile.

AL has been used in France since 1957 to treat acute vertiginous symptoms; however, despite a number of proposed hypotheses, including a stabilization of membrane potential, its pharmacologic and electrophysiologic modes of action have not yet been clarified.<sup>17-19</sup> A fluorodeoxyglucose (FDG)- $\mu$ PET study in a rat model of acute unilateral vestibular lesions demonstrated a significant effect of the *N*-acetyl-L-leucine enantiomer on postural compensation by means of an activation of the vestibulocerebellum

**Figure 3** Effect of treatment with acetyl-DL-leucine 5 g/d on the quality of life of Niemann-Pick type C patients



Boxplot representation of the value changes on the EuroQol 5Q-5D-5L (EQ-5D-5L) questionnaire (A) and the visual analogue scale (VAS) (B). EQ-5D-5L, assessing the quality of life, changed from a baseline of 0.62 (0.35–0.83) to 0.72 (0.43–0.83) on medication and 0.52 (0.19–0.85) without medication ( $p = 0.459$ ). VAS changed significantly on medication ( $p = 0.05$ ), increasing from a baseline of 0.30 (0.25–0.70) to 0.45 (0.35–0.80) on the treatment ( $p = 0.02$ ). After 1 month of therapy, VAS decreased to 0.30 (0.20–0.60) ( $p = 0.776$ ). The length of the boxes indicates the interquartile space (P25–P75), the horizontal line into the box represents the median (P50), and the whiskers indicate the adjacent values.

and a deactivation of the posterolateral thalamus.<sup>20</sup> Clinically, the improvement of cerebellar symptoms in humans in a case series with cerebellar patients of different etiologies indicated the therapeutic efficacy of AL.<sup>6</sup> Furthermore, a PET study in patients with ataxia of different etiologies given AL demonstrated an increased metabolism in the midbrain and lower brainstem in responders.<sup>21</sup> Targeting vestibular together with cerebellar regions is probably one of

the key actions of AL. Impaired central vestibular function in patients with NP-C is very likely in light of the well-known ocular motor<sup>22</sup> and hearing dysfunctions,<sup>23</sup> even though the vestibuloocular reflex, representing peripheral vestibular function, seems to be intact.<sup>24</sup> However, no evidence regarding vestibular function in patients with NP-C has been gained so far, and its improvement might also be responsible for the positive effect of the therapy.

In our cohort of patients with NP-C, AL stabilized stance and gait with a lowered risk of falls and improved dysmetria and intentional tremor, thus improving fine motor function. This had an impact on the daily activities of patients with NP-C, also reflected in increased quality-of-life scores on medication. Improvement of dysarthria and dysphagia was not a consistent finding, probably because of concomitant bulbar syndrome, and considerable impaired cognition, because this leads to absence of communication in some patients. This was also reflected in the fact that neurologically more severely affected patients also had a notably lower IQ with a lowered MoCA score. Because patients with NP-C present with a heterogeneous symptomatology, ranging from palliative cases unable to act independently to a very mild presentation with isolated slow vertical saccades,<sup>25</sup> the test results and reactions to treatment vary considerably. Cognitive impairment and psychiatric comorbidities, such as affective lability with pathologic crying or psychotic presentation with aggressive traits, and the abovementioned frequent generalized dystonia, and—in later stages—spasticity, impeded clinical evaluation of the therapy effect. Of note, a slight stabilization of the affect, increase of drive, social interaction, and improved performance of complex tasks, such as dressing or drawing, on medication was reported by parents and rehabilitation staff (see video 3). This might be a secondary effect of the positive influence on overall neurologic function; nevertheless, a specific but as yet unclear effect on distinct areas responsible for higher cognitive functions and emotions, such as the frontotemporal lobe or the limbic system, should also be taken into consideration.

No remarkable effect of AL therapy on ocular motor function has been noted, especially not on the supranuclear ocular motor centers in the brainstem; however, an improvement of fixation by diminishing the intensity of square wave jerks might suggest a positive effect on cerebellar ocular motor centers. This is in line with the previously shown and abovementioned increase of regional cerebral metabolic rate for glucose in the vestibulocerebellum<sup>20</sup> and brainstem.<sup>21</sup>

The only side effect of the medication was transient, dose-dependent dizziness in one of the 12

patients, thus demonstrating a good risk-benefit profile of the medication.

Our study has several limitations. First, this is an observational study with all its limitations and not a randomized, placebo-controlled trial. Therefore, a placebo effect or a training effect on components of ataxia assessment (e.g., 9HPT) cannot be ruled out. Second, the long-term efficacy of AL was not evaluated. Therefore, a longer-term, placebo-controlled, double-blind, randomized clinical trial of AL in a larger cohort of patients with NP-C is necessary to assess its safety and effects on disease progression. Third, in 2 of the 12 patients, no mutation was found.

This observational study demonstrated that AL had a positive effect on ataxia in patients with NP-C, improved their quality of life, and was well tolerated. Since the mechanism of the AL action is not thought to be NP-C-specific, if AL showed benefit in a placebo-controlled trial in NP-C or any other disease with prominent ataxia, it might be generally useful across all ataxias.

#### AUTHOR CONTRIBUTIONS

T. Bremova: design of the study, conducting experiments, data analysis, data interpretation, drafting/revising the manuscript. V. Malinová: patient recruitment, data interpretation, revising the manuscript for important intellectual content. Y. Amraoui: patient recruitment, revising the manuscript for important intellectual content. E. Mengel: revising the manuscript for important intellectual content. J. Reinke: revising the manuscript for important intellectual content. M. Kolníková: patient recruitment, revising the manuscript for important intellectual content. M. Strupp: study concept, revising the manuscript for important intellectual content.

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#### DISCLOSURE

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