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LETTER TO THE EDITORS

Prophylactic treatment of migraine with and without aura with acetyl-DL-leucine: a case series

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Dear Sirs,

The prophylactic treatment of migraine is still challenging, not only because of the effectiveness of drugs given but also because of their side effects which result in a low therapy adherence [4]. Therefore, there is still a need for new, well-tolerated, and effective drugs.

In animal studies, it was shown that the modified amino acid acetyl-DL-leucine (already approved for the treatment of vertigo in 1957) normalizes neuronal membrane potential [7]. Since spreading depression and fluctuations of membrane potential are discussed as one of the crucial mechanisms of migraine [3], we hypothesized that this acetyl-DL-leucine may be effective for the prophylactic treatment of migraine. Therefore, we evaluated its effects on the frequency of attacks of migraine with and without aura.

In a prospective observational case series, ten patients (six females, age range 18–70 years, Table 1) were treated on an individual basis with acetyl-DL-leucine during a period from 01/2017 to 09/2018. All fulfilled the diagnostic criteria for migraine with or without aura [1], two also for additional vestibular migraine [5]. They gave their written informed consent. Patients took 1 g tid for 5 days orally as tablets each containing 500 mg, then 2 g in the morning and 1.5 g at noon and night, i.e., a total of 5 g/day (similar to previous studies for other diseases [2, 6]). None of the patients were taking other prophylactic treatment during this period. In the longer term, one patient reduced the dosage to 4 g/day. Patients received a diary to note the number of attacks of migraine, aura and days with headache (including migraine) per month. These outcomes were paired for each patient, before vs. during treatment using the Wilcoxon signed rank test.

Before treatment, the median number of attacks of migraine per month was 6.5 (range 2–30, $n = 10$). When patients were treated for at least 3 months, the median number of migraine attacks per month was 1 (range 0–5, $n = 10$; $p = 0.002$). Before treatment, the median number of days with headache per month was 10.5 (range 4–25, $n = 10$), while during treatment it was 1.7 (range 0–8, $n = 10$; $p = 0.006$; Table 1). Three out of ten patients (no. 1, 6, 9) with migraine with visual aura reported that not only the number of days of migraine but also the number of auras per month was lower; two patients (no. 5, 10) had migraine in combination with vestibular migraine, in both of them the number of vertigo attacks also decreased (Table 1).

In terms of side effects, the drug was well-tolerated: except for one patient who reported transient problems with night sleep after the dosage was increased to 5 g/day, no further adverse events were reported by the patients. Currently, on 09/2018, eight out of ten patients (two patients stopped medication because they were free of symptoms for more than 3 months) are still on treatment (treatment duration 4–17 months), demonstrating a good compliance and adherence.

Based on the mode of action [7], this simple molecule reduced the number of attacks of migraine and days of headache per month. It is important to note that acetyl-DL-leucine also had an impact on the aura. Finally, it has a very good safety profile.

This case series has some methodological limitations: small number of individuals; not placebo-controlled

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Table 1 Clinical characteristics (sex, age at the time of initiation of the treatment) of the ten patients, number of attacks of migraine and days with headache per month before and during the treatment with acetyl-DL-leucine, dosage, side effects, duration of treatment, comments and current situation

Pat.	Age, sex	Type of migraine	Attacks of migraine per month before treatment	Days with headache per month before treatment	Attacks of migraine per month during treatment[a]	Days with headache per month during treatment[a]	Duration (months) of treatment	Comments	Status September 2018
1	56, male	Migraine with and without visual aura	4 attacks of headache 5 attacks of visual aura	4	0.5	0.5	16	Significant improvement of not only headache but also isolated aura from 4 per month to 0.5; dosage of 3 g/day was not sufficient, had to be increased to 5/g	Stopped medication on June 1st, follow-up
2	48, female	Migraine without aura	4	4	1	1	10	Significant improvement of duration of migraine, quality of life, much less anxiety, emotional relief	On treatment with 5 g/day
3	54, male	Migraine, rarely (1–2/a) visual aura	4	5	2	2	13	The patient continued treatment for 6 months, then discontinued for 3 months. In the 5 weeks following termination, the frequency of migraine attacks was 4/month; then he resumed treatment and after 3 months, the number of migraine attacks was 2/month	On treatment with 5 g/day
4	38, female	Migraine without aura	2	6	1	1.3	4	Stable	On treatment with 5 g/day

Table 1 (continued)

Pat.	Age, sex	Type of migraine	Attacks of migraine per month before treatment	Days with headache per month before treatment	Attacks of migraine per month during treatment[a]	Days with headache per month during treatment[a]	Duration (months) of treatment	Comments	Status September 2018
5	70, female	Migraine and vestibular migraine, without aura	3.3	5	1.2	2	11	Attacks were shorter and had a lower intensity during treatment; attacks of vestibular migraine also decreased from 2 to 1 per month	On treatment with 4 g/day
6	65, male	Migraine with and without visual aura	20	25	5	8	6	Before treatment he was taking painkillers (incl. Triptans) almost daily; under treatment only 5 day/month; reduction of attacks of visual aura from 10 to 2; QoL also considerably improved	Stopped treatment on June 1st, follow-up
7	27, female	Migraine without aura	12	20	4	4	5	Under treatment, QoL considerably improved	On treatment with 5 g/day
8	18, female	Migraine with visual aura	Around 30	24	1	1	14	Not only the headache improved but also the attacks of vertigo. QoL improved a lot. Reduced the dosage to 3 g/day, migraine attacks re-occurred, now back to 5 g/day and stable	On treatment with 5 g/day

Table 1 (continued)

Pat.	Age, sex	Type of migraine	Attacks of migraine per month before treatment	Days with headache per month before treatment	Attacks of migraine per month during treatment[a]	Days with headache per month during treatment[a]	Duration (months) of treatment	Comments	Status September 2018
9	32, female fem	Migraine with visual aura	4	20	0	2	5	During treatment dramatic improvement already after 4 weeks and no attacks of visual aura; no more days of sick leave, highly satisfied with the therapy. QoL significantly improved	On treatment with 5 g/day
10	56, male	Migraine and vestibular migraine, without aura	15 migraine attacks 12 attacks of vertigo	15	0	0	17	No more attacks of vestibular migraine. Stopped medication after 6 months; attacks re-occurred. Started treatment again	On treatment with 5 g/day

QoL quality of life

[a]Patients were treated for at least 3 months. Mean number of migraine attacks per month and mean number of days with headache per month given by the patients were used when they were treated for at least 1 month

(taking into account the strong placebo effect in patients with migraine); no dose finding; and statistical comparisons were performed without weighting for length of observation (however, all patients were treated and observed for at least 5 months).

In conclusion, this small observational study suggests that acetyl-DL-leucine can be effective in the prophylactic treatment of migraine as well as of aura. These findings could be the basis for a randomized controlled trial in patients with different types of migraine.

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Author contributions MS: conception of the study, acquisition and interpretation of the data, drafting the manuscript. OB: statistical analysis, interpretation of the data, and revising the manuscript for content. KF: conception of the study and recruitment of patients. AS: acquisition and interpretation of the data, as well as drafting the manuscript.

Compliance with ethical standards

Conflicts of interest M. Strupp is Joint Chief Editor of the Journal of Neurology, Editor in Chief of Frontiers of Neuro-otology and Section Editor of F1000. He has received speaker's honoraria from Abbott, Actelion, Auris Medical, Bayer, Biogen, Eisai, Grünenthal, GSK, Henning Pharma, Interacoustics, Merck, MSD, Otometrics, Pierre-Fabre, TEVA, and UCB. He is a shareholder of IntraBio. He acts as a consultant for Abbott, Actelion, AurisMedical, Heel, IntraBio and Sensorion. O. Bayer and K. Feil report no relevant conflicts of interest/financial disclosures. A. Straube has received speaker's honoraria from Allergan, Novartis, TEVA and Recordati. He received honoraria for adboard participation from Allergan, Novartis, TEVA, Eli Lilly, electroCore.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent All patients gave their informed consent for the compassionate use of acetyl-DL-leucine.

References

1. Headache Classification Committee of the International Headache Society (2013) The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33:629–808
2. Bremova T, Malinova V, Amraoui Y, Mengel E, Reinke J, Kolnikova M, Strupp M (2015) Acetyl-DL-leucine in Niemann-Pick type C: a case series. Neurology 85:1368–1375
3. Brennan KC, Pietrobon D (2018) A systems neuroscience approach to migraine. Neuron 97:1004–1021
4. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB (2015) Adherence to oral migraine-preventive medications among patients with chronic migraine. Cephalalgia 35:478–488
5. Lempert T, Olesen J, Furman J, Waterston J, Seemungal B, Carey J, Bisdorff A, Versino M, Evers S, Newman-Toker D (2012) Vestibular migraine: diagnostic criteria. J Vestib Res 22:167–172
6. Strupp M, Teufel J, Habs M, Feuerecker R, Muth C, van de Warrenburg B, Klopstock T, Feil K (2013) Effects of acetyl-DL-leucine in patients with cerebellar ataxia: a case series. J Neurol 260:2556–2561
7. Vibert N, Vidal PP (2001) In vitro effects of acetyl-DL-leucine (tanganil) on central vestibular neurons and vestibulo-ocular networks of the guinea-pig. Eur J Neurosci 13:735–748