J Neurol (2015) 262:1373–1375
DOI 10.1007/s00415-015-7734-3

LETTER TO THE EDITORS

Failure to confirm benefit of acetyl-DL-leucine in degenerative cerebellar ataxia: a case series

Johann Otto Pelz[1] · Christopher Fricke[1] · Dorothee Saur[1] · Joseph Classen[1]

Received: 12 February 2015 / Revised: 30 March 2015 / Accepted: 31 March 2015 / Published online: 11 April 2015
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Dear editors,

Recently, Strupp and co-workers [1] demonstrated that acetyl-DL-leucine (Tanganil®; Pierre Fabre Médicament, Boulogne, France) may lead to substantial symptomatic improvement in various forms of degenerative cerebellar ataxia (DCA) differing widely in symptom duration, severity and etiology. Medication was given for about 7 days, and 12 of their 13 patients benefited, while no side effects were reported [1]. However, endpoints were assessed unblinded, rendering objective evaluation of treatment response difficult.

Here, we report our observations in a series of patients suffering from DCA who were treated with acetyl-DL-leucine. Pharmacological treatment was combined with physio- and occupational therapy as both are important non-pharmaceutical components of the treatment of DCA [2, 3].

The study was conducted as a series of individual treatment efforts and confirms to the 1964 Declaration of Helsinki and its later amendments. After they had given informed consent for the off-label use of acetyl-DL-leucine, 10 patients with DCA (Table 1) were treated in-hospital with 5 g acetyl-DL-leucine once daily for a total duration of 7 days. Furthermore, each patient received altogether five sessions of physiotherapy at 45 min and five sessions of occupational therapy at 30 min, individually matched to the patient's symptoms and including dedicated gait and balance training.

✉ Joseph Classen
joseph.classen@medizin.uni-leipzig.de

[1] Department of Neurology, University of Leipzig, Liebigstraße 20, 04103 Leipzig, Germany

Video-recorded measurements at baseline (off-drug) and on day 7 of active treatment (on-drug) were based on the Scale for the Assessment and Rating of Ataxia (SARA) [5, 6]. SARA scores were assessed from the video recordings by three investigators who were blinded with regard to the time point of video recording. Additionally, patients were asked about their subjective improvement on medication, and possible side effects during treatment were evaluated.

Statistical analyses were performed with SPSS version 20.0 (IBM Corporation; New York, NY, USA). A p value <0.05 was considered as statistically significant.

There was excellent interrater agreement for assessment of SARA scores from video recordings with an intraclass correlation (absolute mode) between investigators of ≥ 0.97 ($p < 0.001$). Mean and median SARA scores were similar between baseline and at day 7 of treatment with acetyl-DL-leucine (Wilcoxon signed-rank test; $p = 0.17$, respectively, $p = 0.38$; Table 2). During in-hospital treatment, no side effects were observed.

Although 7 of 10 patients reported subjective amelioration of cerebellar symptoms, we failed to detect any significant improvement as measured by SARA in assessments blinded to treatment status to reduce rater bias [7]. As physiotherapy was shown to be beneficial for individuals with DCA [2, 3], it is unlikely to have obscured any positive effect of acetyl-DL-leucine. Notably, (pre-)clinical trials studied acetyl-DL-leucine only in vestibular diseases [8, 9], so its potential mode of action in DCA remains speculative.

One limitation of our case series is that, in contrast to Strupp and co-workers [1], patients in our case series received the liquid formulation of acetyl-DL-leucine orally, because Tanganil® tablets were no longer available in Germany. Since both, the solid and liquid formulation contain neither stabilizers nor any active pharmaceutical

Table 1 Patients characteristics

Patient no.	Sex	Age	Type	Age at onset	Duration (in years)	Brain MRI findings	Neurological findings other than cerebellar ataxia	Physiotherapy in before
1	Male	46	ADCA	42	4	Atrophy of vermis and pons	1, 4	Yes
2	Male	53	Possible MSA-C*	49	4	Atrophy of vermis and pons	2, 4, 5	Yes
3	Female	43	SCA 2	20	23	No MRI performed	1, 4	Yes
4	Female	52	SEOA#	19	33	No signs of cerebellar atrophy	1, 4, Flexor-predominant paresis of lower limbs	Yes
5	Female	65	SCA 6	62	3	Atrophy of cerebellum and "hot cross bun sign"	2	Yes
6	Female	68	Probable MSA-C*	67	1	Atrophy of cerebellum and pons and "hot cross bun sign"	3	No
7	Female	80	ADCA	69	11	Atrophy of cerebellum	2, 5	Yes
8	Male	54	Probable MSA-C*	51	3	"Hot cross bun sign" and T2-hyperintensities in the MCP	2, 5	Yes
9	Male	46	SCA 8	24	22	No MRI performed	3	Yes
10	Female	64	Probable MSA-C*	61	3	Atrophy of cerebellum and pons and "hot cross bun sign"	3, 4, 5	Yes

ADCA autosomal dominant cerebellar ataxia, *MSA-C* multiple system atrophy with predominance of cerebellar ataxia, *SCA* spinocerebellar ataxia, *SEOA* sporadic early onset ataxia, *MRI* magnetic resonance imaging, *MCP* middle cerebellar peduncle, *1* polyneuropathy (PNP) without involvement of the autonomic nervous system (ANS), *2* PNP with involvement of the ANS, *3* only autonomic PNP, *4* pyramidal signs, *5* extrapyramidal signs

* Diagnosis of multiple system atrophy according to consensus guidelines [4]

No relatives with cerebellar ataxia. Genetic testing was negative for Friedreich ataxia and also negative for spinocerebellar ataxia type 1, 2, 3, 6, 8, 10, 12, 17

Table 2 Assessment of endpoints: SARA scores at baseline and after 7 days of treatment with acetyl-DL-leucine (mean and median values of blinded assessment from video recordings by 3 raters), side effects during treatment and subjective improvement as reported by patients

Patient no.	SARA at baseline (mean/median)	SARA after 7 days of treatment (mean/median)	Side effects	Subjective improvement	Self-medication*
1	9.0/10.0	10.2/10.0	No	No	No
2	10.3/10.0	9.5/10.5	No	Yes	Yes self-stopped (no effect)
3	31.3/30.5	30.5/30.0	No	No	Yes advised to stop (new diarrhea and no effect)
4	29.5/29.5	30.2/30.0	No	Yes	No
5	15.8/16.0	15.5/16.0	No	Yes	Yes self-stopped (no effect)
6	6.8/6.0	4.7/5.0	No	No	No
7	26.2/26.0	26.0/26.0	No	Yes	No
8	11.7/11.5	12.0/12.0	No	Yes	Yes self-stopped (no effect)
9	13.8/13.5	12.7/13.0	No	Yes	No
10	18.5/18.0	15.7/15.5	No	Yes	Yes continued (positive effect)
Mean	17.3/17.1	16.7/16.8	0/10	7/10	

SARA Scale for the Assessment and Rating of Ataxia

* Since acetyl-DL-leucine is an over-the-counter drug in France altogether 5 of 10 patients ordered it via online pharmacy and continued self-medication after discharge from hospital. They gave reports about further effects during their follow-up visit in our outpatient clinic for movement disorders 2–5 months later

ingredients other than acetyl-DL-leucine, we consider it unlikely that the lack of any beneficial clinical effect is attributable to different formulations.

Because the decision to treat was solely based clinically on the presence of DCA, our series contains cases of heterogeneous aetiologies and heterogeneous patterns of cerebellar signs. Therefore, failure of this syndrome-oriented approach to demonstrate beneficial effects does not exclude potential efficacy in a future symptom-oriented trial, or one that is based on nosology.

In summary, we failed to confirm a beneficial effect of acetyl-DL-leucine in combination with an intensive short-term physio- and occupational therapy in patients with DCA. At the present time, acetyl-DL-leucine cannot be recommended for treatment of patients with cerebellar ataxia.

Acknowledgments No funding was received for this work.

Conflicts of interest The authors declare that there are no conflicts of interest relevant to this work.

Ethical standard The authors declare that the research documented has been carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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