Received: 28 April 2019 | Accepted: 1 May 2019

DOI: 10.1111/epi.16070

Epilepsia®

Letter

Is adrenocorticotropic hormone (ACTH) therapy loaded with severe side effects? Do not use synthetic ACTH at the same dosages as "natural" ACTH

To the Editors:

I read with great interest the recent paper by Dressler et al on the efficacy and tolerability of the ketogenic diet versus high-dose adrenocorticotropic hormone (ACTH) for infantile spasms.[1]

The conclusions are the following: "KD [ketogenic diet] is as effective as ACTH in the long term but is better tolerated. Adverse effects needing acute medical intervention occurred more often with ACTH (30% with KD, 94% with ACTH, respectively; $P < .001$)." There was one death during ACTH therapy.

High-dose synthetic ACTH was used at the same dosage, 150 IU/m^2 given in two divided doses daily, as recommended by the US consensus report,[2] then tapered gradually. The total treatment duration was 28 days.

However, it is to be noticed that the ACTH drugs used in both studies are different in the USA and Europe. "Natural" ACTH (corticotropin gel) is used in the USA, whereas the synthetic derivate zinc tetracosactide (Synacthen Depot) is used in Europe. The duration of stimulation of adrenals (measured by serial plasma and urinary 11-hydroxysteroids assays) by depot tetracosactide is twice as long as that of corticotropin gel (24-48 and 12-18 hours, respectively).[3] Impaired hypothalamic-pituitary-adrenal function might be a reason that children treated with zinc tetracosactide have an increased incidence of relatively serious adverse effects.[4,5] This is due to the unnecessary prolonged action. Likewise, increasing the dose of natural ACTH will cause a cumulative effect and induce adverse effects (mostly hypertension). Consequently, it is now recommended to use synthetic ACTH every other day due to its prolonged action, which has been the practice in the UK.[6,7]

Keeping this in mind, in the trial of Dressler et al, extremely high daily doses were used, leading to an incorrect conclusion**.** It is not surprising in my opinion that the high incidence of adverse effects of ACTH was a significant negative outcome in the study, leading to the conclusion favoring the ketogenic diet. High doses and synthetic derivates are known to be associated with significantly more side effects (eg, hypertension infections and hypertrophic cardiomyopathy).[8,9] By using minimal effective doses and minimal effective time, ACTH is a safe and well-tolerated drug for infantile spasms.

DISCLOSURE

I have no conflict of interest to disclose. I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Raili Riikonen

University of Eastern Finland, Kuopio, Finland
Email: raili.riikonen@kolumbus.fi

ORCID

Raili Riikonen https://orcid.org/0000-0003-3311-9940

REFERENCES

1. Dressler A, Benninger F, Trimmel-Schwahofer P. Efficacy and tolerability of the ketogenic diet versus high-dose adrenocorticotropic hormone for infantile spasms: a single-center parallel-cohort randomized controlled trial. Epilepsia. 2019;60:441–51.
2. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. Epilepsia. 2010;51:2175–89.
3. Treadwell B, Dennis P. Comparison of depot tetracosactrin and corticotrophin gel. Br Med J. 1969;4:720–3.
4. Sorel L. Apropos of 196 cases of infantile myoclonic encephalopathy with hypsarrythmia. Treatment with purified ACTH. Hazards of synthetic ACTH [in French]. Rev Electroencephalogr Neurophysiol Clin. 1971;1:112–3.
5. Cret L, David M, Macabéo V, Frédérich A, et al. Spastic flexion disorders: clinical and metabolic problems observed during treatment with zinc tetracosactide [in French]. Pediatrie. 1976;31:33–48.
6. Lux AL, Edwards SW, Hancock E, et al. The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. Lancet. 2004;364:1773–8.
7. O'Callaghan FJ, Edwards SW, Alber FD, et al. Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomized, multicentre, open-label trial. Lancet Neurol. 2017;16:33–42.
8. Riikonen R, Donner M. ACTH therapy in infantile spasms: side effects. Arch Dis Child. 1980;55:664–72.
9. Riikonen R. ACTH therapy of West syndrome. Finnish views. Brain Dev. 2001;23:642–6.

Received: 21 May 2019 | Accepted: 22 May 2019

DOI: 10.1111/epi.16075

GRAY MATTERS

Epilepsia®

Letter

Response to "Is ACTH therapy loaded with severe side-effects? Do not use synthetic ACTH with the same dosages as 'natural' ACTH"

To the Editor-in-Chief of *Epilepsia*

We thank Professor Riikonen for her interest in our study[1] and appreciate the opportunity to respond to her remarks:

Management of infantile spasms (IS) remains challenging, and new therapeutic options are urgently needed. Clinical outcome depends primarily on the achievement of complete electroclinical remission, rapid/immediate treatment-response, and low relapse-rates. In addition, safety issues are of special concern in infants.

Adrenocorticotropic hormone (ACTH) is thought to be the best single treatment currently available for IS.[2] In our study, we therefore used ACTH as comparator to evaluate the ketogenic diet (KD).

At study initiation in June 2008, commonly accepted treatment protocols for ACTH were not available. The protocol used at our institution at that time was in line with the German Guidelines, based on the recommendations of the "Königsteiner Arbeitskreis"[3]: Synacthen Depot, i.m.,15-45 (maximum 60) IU/m^2/d for 1 month, followed by gradual taper (ie, every other day for 1 month, every third day for 1 month, and so on); treatment duration: 6 months.

Because of unsatisfactory results with respect to both efficacy and side effects (primarily Cushing syndrome and infections), the high-dose–short-duration protocol described in our article was initiated[1,4]: Synacthen Depot, i.m., 150 IU/m^2/d, divided b.i.d. for 2 weeks, followed by taper (30 IU/m^2/d for 3 days, 15 IU/m^2/d for 3 days, 10 IU/m^2/d for 3 days, and finally 10 IU/m^2 every other morning for 6 days). High-dose synthetic ACTH administered on a daily basis (120-160 IU/m^2/d) had also been used by others.[5–7] In addition, there were no comparative studies of synthetic and natural ACTH high-dose protocols.[4]

When comparing the two protocols used in our patients, long-term electroclinical remission was better with high-dose ACTH (30% high-dose vs 18% low-dose) and relapses occurred less often (39% vs 60%). With respect to side effects, acute medical interventions were necessary more often in the initial phase of the high-dose compared with the low-dose protocol (treatment of arterial hypertonia necessary in 92% vs 64%; intravenous potassium needed in 54% vs 9%), whereas Cushing syndrome (27% vs 46%) and infections (18% vs 27%) occurred less frequently (data not published). All side effects were transient. So far, no long-term consequences have occurred. Mortality (one child died) was lower than reported by others.[6]

In line with our results, recently published data also suggest that high-dose ACTH does not seem to be significantly more effective than low-dose ACTH but is associated with more acute side effects. Consequently, treatment protocols have been adapted in many centers and also by us.[8]

We therefore agree with the concerns of Professor Riikonen and we cannot recommend the high-dose protocol used in our study. However, it remains still unclear which low dose is to be used.

We also agree that our design may have biased results in favor of the KD with respect to safety. However, there might have also been some bias in favor of ACTH with respect to efficacy. Consequently, the results obtained can only be interpreted in the context of the treatment protocol used.

DISCLOSURE

Neither of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Martha Feucht[1]
Anastasia Dressler[1]
Franz Benninger[2]
Petra Trimmel-Schwahofer[1]
Gudrun Gröppel[1]
Barbara Porsche[1]
Klaus Abraham[1]
Angelika Mühlebner[1]
Sharon Samueli[1]
Christoph Male[1]

[1]*Department of Pediatrics and Adolescent Medicine, Medical University Vienna, Vienna, Austria*
Email: martha.feucht@meduniwien.ac.at

[2]*Department of Child and Adolescent Psychiatry, Medical University Vienna, Vienna, Austria*

ORCID

Martha Feucht https://orcid.org/0000-0001-7691-8158
Anastasia Dressler https://orcid.org/0000-0002-1518-8646

REFERENCES

1. Dressler A, Benninger F, Trimmel-Schwahofer P, et al. Efficacy and tolerability of the ketogenic diet versus high-dose ACTH for infantile spasms: a single center parallel-cohort randomized controlled trial. Epilepsia. 2019;60:441–51.
2. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. Cochrane Database Syst Rev. 2013;6:CD001770.
3. Königsteiner-Arbeitskreis-für-Epileptologie. Standardtherapien der, Epilepsien im Kindes- und Jugendalter. II. West-Syndrom (BNS-Krämpfe, infantile spasms). Epilepsie-Blätter. 1991;4:20–1.
4. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. Epilepsia. 2010;51:2175–89.
5. Riikonen R. Long-term otucome of West syndrome: a study of adults with a history of infantile spasms. Epilepsia. 1996;37:367–72.
6. Riikonen R. Long-term outcome of patients with West syndrome. Brain Dev. 2001;23:683–7.
7. Riikonen R. A long-term follow-up study of 214 children with the syndrome of infantile spasms. Neuropediatrics. 1982;13:14–23.
8. Tibussek D, Klepper J, Korinthenberg R, et al. Treatment of infantile spasms: report of the interdisciplinary guideline committee coordinated by the German-speaking society for neuropediatrics. Neuropediatrics. 2016;47:139–50.

Received: 21 May 2019 | Revised: 21 May 2019 | Accepted: 22 May 2019

DOI: 10.1111/epi.16074

Epilepsia®

GRAY MATTERS

Letter

Linnaeus was not an evolutionary biologist: The importance of motivations in classification systems

To the Editors:

In their excellent "Critique of the 2017 epileptic seizure and epilepsy classifications," Lüders et al argue that a system of classification should be organized according to the most important characteristics of that which is to be classified.[1] By way of example, they write that Linnaeus (1707-1778) based his classification of plants and animals on information pertaining to evolution. This is not the case—the first edition of his *Systema Naturae* was published in 1735, >70 years before the birth of Charles Darwin (1809-1882)—and unfortunately misrepresents Linnaeus' motivations. Although this error likely reflects only a minor oversight, understanding the motivations behind any classification system is important and can go a long way toward understanding its ultimate form.

Carl Linnaeus formalized a system for classifying plants and animals according to a hierarchical arrangement into the familiar categories of kingdom, phylum, class, order, family, genus, and species. The definitive revised edition of his *Systema Naturae* was the 10th edition, published in 1758-1759, some 23 years after the first edition (perhaps suggesting that it is the nature of classification systems to change over time…). The basis of the original Linnaean system rests not on evolutionary relationships—Linnaeus felt that species themselves were immutable creations of God [2]—but rather on a careful evaluation and comparison of species traits. The more two species appeared to share in common, the more closely together they were classified.[3] His task in classifying species is presented as a purely descriptive one, intended to highlight the glory of divine creation:

> If therefore the Maker of all things, who has done nothing without design, has furnished this earthly globe, like a museum, with the most admirable proofs of his wisdom and power; […] it follows, that man is made for the purpose of studying the Creator's works, that he may observe in them the evident marks of divine wisdom." (Linnaeus, 1798, p 20)[2]

The hierarchical arrangement of plants and animals provided a framework for understanding the relationships between species, but it was not until several decades later that Darwin would dispense with the idea of immutability, and substitute the idea that similar species "descended with modifications" from common ancestors—the modern idea of evolution.[3]

One might fairly argue that this is an inconsequential or pedantic point to raise. But historical accuracy is imperative; in 50 or perhaps 100 years, both the 2017 International League Against Epilepsy (ILAE) classifications and the semiological seizure classification may well be remembered as historical artifacts embedded in the circumstances and motivations of their framing. Furthermore, understanding these motivations may go a long way toward understanding the differences between the multiaxis system proposed by Lüders et al, so well suited to epilepsy surgery evaluations, and the ILAE system, intended to provide a common language to the broader medical and research community.[4]

ACKNOWLEDGMENTS

B.P.W. is supported by a Samuel R. McLaughlin Fellowship (Dalhousie University, Canada) and a Detweiler Travelling Fellowship (Royal College of Physicians and Surgeons of Canada).

DISCLOSURE

I have no conflict of interest to disclose. I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Benjamin P. Whatley

Department of Clinical and Experimental Epilepsy, Queen Square Institute of Neurology, University College London, London, UK

Email: b.whatley@ucl.ac.uk

ORCID

Benjamin P. Whatley https://orcid.org/0000-0001-8824-367X

REFERENCES

1. Lüders H, Akamatsu N, Amina S, et al. Critique of the 2017 epileptic seizure and epilepsy classifications. Epilepsia. 2019;60:1032–9.
2. Linnaeus C. Reflections on the study of nature. In: Smith J, ed. Tracts Relating to Natural History. London, UK: J. Davis; 1798:9–46.
3. Scott E. Evolution. In: Scott E, ed. Evolution vs Creationism: An Introduction. Westport, CT: Greenwood Press; 2009:23–51.
4. Fisher RS, Cross H, D'Souza C, et al. 2017 International League Against Epilepsy classifications of seizures and epilepsy are steps in the right direction. Epilepsia. 2019;60:1040–4.

DOI: 10.1111/epi.16292

Epilepsia®

Announcements

Epilepsia – July 2019 – Announcements

2019 Advanced San Servolo Epilepsy Course

7–18 July 2019
San Servolo, Venice, Italy
Information: https://www.ilae.org/congresses/2019-advanced-san-servolo-epilepsy-course

10th International Summer School for Neuropathology & Neuroimaging in Epilepsy (INES)

24–27 July 2019
State University of Campinas (UNICAMP) in Campinas, Brazil
Information: https://www.ilae.org/congresses/10th-international-summer-school-for-neuropathology-and-neuroimaging-in-epilepsy-ines

13th Baltic Sea Summer School on Epilepsy (BSSSE 13)

18–24 August 2019
Rostock, Germany
Information: https://www.ilae.org/congresses/13th-baltic-sea-summer-school-on-epilepsy-bssse-13

4th African Epilepsy Congress

22–24 August 2019
Entebbe, Uganda
Website: https://www.epilepsycongress.org/aec/

5th SuSIE – Summer School on Imaging in Epilepsy, Epilepsy Surgery and Epilepsy Research

25–28 August 2019
Teaching, scientific exchange, and marketplace
Bochum, Germany
Website: http://www.imaging-in-epilepsy.org/

Epilepsia en Atención Primaraia para América Latina: Curso Virtual

26 August–20 October
Epilepsy for Primary Care Online Course
Information: https://www.ilae.org/congresses/epilepsia-en-atenci-n-primaraia-para-am-rica-latina-curso-virtual

2nd International Congress on Mobile Devices and Seizure Detection in Epilepsy

6–7 September 2019
Lausanne, Switzerland
http://www.mhsdepilepsy2019.com/

4th International Epilepsy Symposium: Epilepsy and Psychology Seizures, Cognition, and Behavior

6–7 September 2019
Neue Schmiede, Bilefeld, Germany
Information: https://www.ilae.org/congresses/4th-international-epilepsy-symposium-epilepsy-and-psychology

4th International Symposium on Hypothalamic Hamartomas

12–14 September 2019
Washington, D.C., USA
Symposium website: http://www.hopeforhh.org/4th-international-symposium-on-hypothalamic-hamartomas/

Cleveland Clinic Neurological Institute Summit 2019: Epilepsy - Focal Cortical Displasia

12–15 September 2019
Cleveland, OH, US
Website: http://www.clevelandclinicmeded.com/live/courses/ni-summit-epilepsy/default.asp

ILAE British Branch 17th SpR Epilepsy Teaching Weekend

14–15 September 2019
The Mathematics Institute in Oxford, UK.
http://www.epilepsyteachingweekend.com/

Introduction to Neuropsychological Methods in the Diagnosis and Treatment of People with Epilepsy

18–22 September 2019
Hanoi, Vietnam
Information: https://www.ilae.org/congresses/introduction-to-neuropsychological-methods-in-the-diagnosis-and-treatment-of-people-with-epilepsy

Congreso LACE

19–20 September 2019
Buenos Aires, Argentina
Congress website: http://www.lace.org.ar/constructor.php?-categoria=1

9th Migrating Course on Epilepsy

19–22 September 2019
Vrdnik, Serbia
Information: https://www.ilae.org/congresses/9th-migrating-course-on-epilepsy

Canadian League Against Epilepsy 2019 Annual Scientific Meeting

20–22 September 2019
Winnipeg, Manitoba
Congress website: https://claegroup.org/2019-meeting

Philippine League Against Epilepsy 10th Biennial Epilepsy Congress: Epilepsy Across the Ages: Advancing the Science, Improving the Care

26–28 September 2019
Manilla, Philippines
Congress Programme: https://www.ilae.org/index.cfm?objectid=0A15EA80-35D7-11E9-B2E2204747814332

Masterclass on Resistant Epilepsy – Part 2

2 October 2019
Bucharest, Romania
Information: https://www.ilae.org/congresses/masterclass-on-resistant-epilepsies-m2

2019 ILAE British Branch Annual Scientific Meeting

2–4 October 2019
Birmingham, UK
Congress website - http://www.ilaebritishconference.org.uk/

Park City Epilepsy Meeting: Cutting Edge Approaches to Transform Epilepsy Therapy

6–8 October 2019
Utah, USA
Website: http://www.parkcityepilepsymeeting.com/

European Congress of NeuroRehabilitation 2019 (ECNR)

9–12 October 2019
Budapest Congress Center, Budapest, Hungary
https://www.ecnr-congress.org/

9th Caucasian Summer School on Clinical Epileptology

11–13 October 2019
Tbilisi, Georgia
Information: https://www.ilae.org/congresses/9th-caucasian-summer-school-on-clinical-epileptology-cssce-ix

EAN Autumn School 2019

17–20 October 2019
Loutraki, Greece
https://www.ean.org/Autumn-School.3752.0.html

ISPN 2019: 47th Annual Meeting of the International Society for Pediatric Neurology

20–24 October 2019
ICC Birmingham, Birmingham, UK
https://www.ispnmeeting.org/2019/

Epilepsy and Psychiatric Disorders throughout Life Educational Symposium of the Psychiatry Commission

25–26 October 2019
São Paulo, Brazil
Information: https://www.ilae.org/congresses/epilepsy-and-psychiatric-disorders-throughout-life

WCN 2019: XXIV World Congress of Neurology

27–31 October 2019
Dubai, United Arab Emirates
Congress website: https://2019.wcn-neurology.com/

Congreso Argentino de Neurología

19–22 November 2019
Mar del Plata, Argentina
Congress website: http://www.lace.org.ar/constructor.php?-categoria=1

Le 3ème Congrès Marocain de Neurophysiologie & La 4ème Session des Ecoles EEG & EMG

29 November–1 December 2019
Marrakech, Morocco
Information: https://www.ilae.org/congresses/le-3-me-congr-s-marocain-de-neurophysiologie

American Epilepsy Society

6–10 December 2019
Baltimore, MD, USA
Website: https://meeting.aesnet.org/abstracts

14th World Congress on Controversies in Neurology (CONy)

26–29 March 2020
London, UK
Congress website: http://cony.comtecmed.com/

3rd International Training Course on Neuropsychology in Epilepsy

29 March–3 April 2020
Bordeaux, France
Information: https://www.ilae.org/congresses/3rd-international-training-course-on-neuropsychology-in-epilepsy

14th European Congress on Epileptology (ECE)

4–8 July 2020
Geneva Switzerland
Website: http://www.epilepsycongress.org/ece/

ESTM 2020: Epilepsy Surgery Techniques Meeting

9–10 July 2020
Geneva, Switzerland
Website: https://www.estm2020.com/

First North American Epilepsy Congress (NAEC)

25–27 September 2020
Toronto, Canada
Call for session proposals: Session Proposal Form
https://www.surveymonkey.com/r/1stNAEC_Toronto2020

13th Asian and Oceanian Epilepsy Congress (AOEC)

8–11 October 2020
Fukuoka, Japan
Information: https://www.epilepsycongress.org/congresses/aoec2020/