Viscum Album in the Treatment of a Girl With Refractory Childhood Absence Epilepsy

Tido von Schoen-Angerer, René Madeleyn, Gunver Kienle, Helmut Kiene and Jan Vagedes

J Child Neurol published online 17 July 2014
DOI: 10.1177/0883073814541473

Journal of Child Neurology
1-5

DOI: 10.1177/0883073814541473
jcn.sagepub.com
SAGE

Viscum Album in the Treatment of a Girl With Refractory Childhood Absence Epilepsy

Tido von Schoen-Angerer, MD, MPH[1,4], René Madeleyn, MD[2], Gunver Kienle, MD[3], Helmut Kiene, MD[3], and Jan Vagedes, MD[1,2,5]

Abstract

Viscum album (European mistletoe) extracts have known immunomodulatory effects but little data exist on anticonvulsant activity despite its usefulness having been reported for centuries. A 4½-year-old girl with childhood absence epilepsy and global developmental delay was treated with different antiepileptic drugs and ketogenic diet but failed to become seizure free over a 2-year period. She also received different herbal remedies as part of an integrative medicine approach. Initial improvement occurred on valproate-ethosuximide, a further improvement was seen after adding clobazam to valproate. Final cessation of absence activity occurred after a dose increase of *V album*. She was still seizure free at the 12-month follow-up. *V album* appears to have been a necessary adjunct treatment for this child to become seizure free. We call on physicians to report their experiences of *V album* in epilepsy and suggest further study.

Keywords

absence epilepsy, *Viscum album*, European mistletoe, case reports, integrative medicine

Received April 14, 2014. Received revised May 21, 2014. Accepted for publication June 01, 2014.

Childhood absence epilepsy is the most common pediatric epilepsy syndrome. It occurs in otherwise normal children of school age (peak manifestation age 6-7 years) and is characterized by very frequent (several to many per day) absences and electroencephalographic (EEG) findings of bilateral, synchronous symmetrical spike waves, usually 3 Hz, on a normal background activity. Recommended antiepileptic drugs in order of priority are ethosuximide, valproate, and lamotrigine.[1] However, lack of response is common; in a key trial on childhood absence epilepsy, 16% of children on the best performing drug ethosuximide continued to have seizures at 12 months.[2] Ketogenic diet and drugs such as clobazam, sulthiame, levetiracetam or topiramate are options for refractory absence seizures but may not be successful.[3,4] Complementary medicine is widely used by parents for children with epilepsy[5] but it is rarely offered as an integrative medicine approach and its efficacy has not been thoroughly assessed.

Case Presentation

This white girl was born at 40 weeks' gestation as the second child of 2 children. Her infanthood was uneventful but motor delay became apparent when she started walking at 21 months of age. Severe speech delay, anxiety disorder in the form of social fear and extreme shyness, as well as suspicion for global developmental delay were diagnosed during her third year of life (International Classification of Disease, 10th edition, categories F80.1, F93.1, and F89). She had no febrile seizures. Furthermore, no epileptic disorders had occurred in the family.

During developmental follow-up at age 4½ years in September 2010, her parents reported brief periods of appearing absent, occurring since a few weeks. During physical examination, discrete eye blinking, slight grimacing, and moments of wide eye opening were noted. EEG recorded 2 generalized spike-and-wave complexes of 2 to 3 Hz and 10 seconds duration with discrete eye blinking, consistent with childhood absence epilepsy.

[1] ARCIM Institute, Filderklinik, Filderstadt, Germany
[2] Department of Pediatrics, Filderklinik, Filderstadt, Germany
[3] Institute for Applied Epistemology and Medical Methodology (IFAEMM), University of Witten/Herdecke, Fribourg, Germany
[4] Department of Pediatrics, Fribourg Hospital HFR, Fribourg, Switzerland
[5] Department of Pediatrics, University Hospital, Tübingen, Germany

Corresponding Author:
Tido von Schoen-Angerer, MD, MPH, ARCIM Institute, Filderklinik, Im Haberschlai 7, 70794 Filderstadt, Germany.
Email: tido.von.schoenangerer@gmail.com

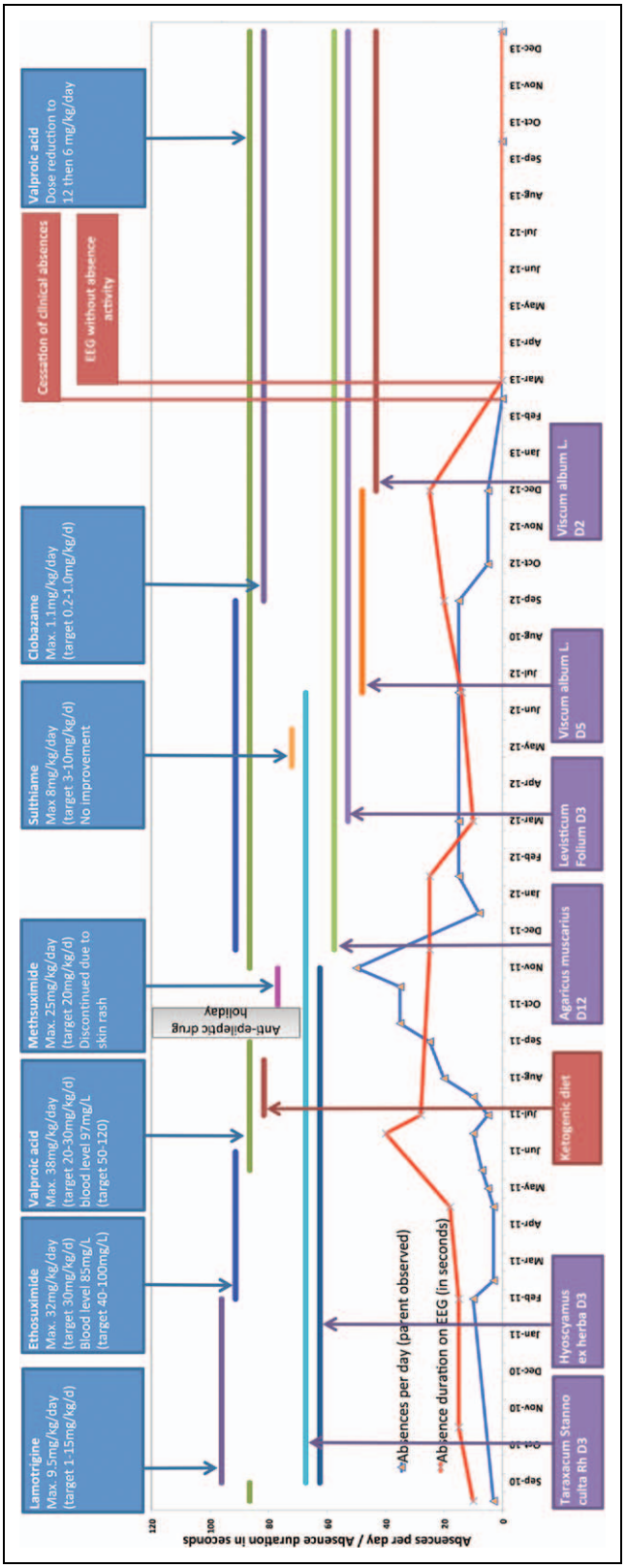

Figure 1. Timeline of seizure activity and treatment.

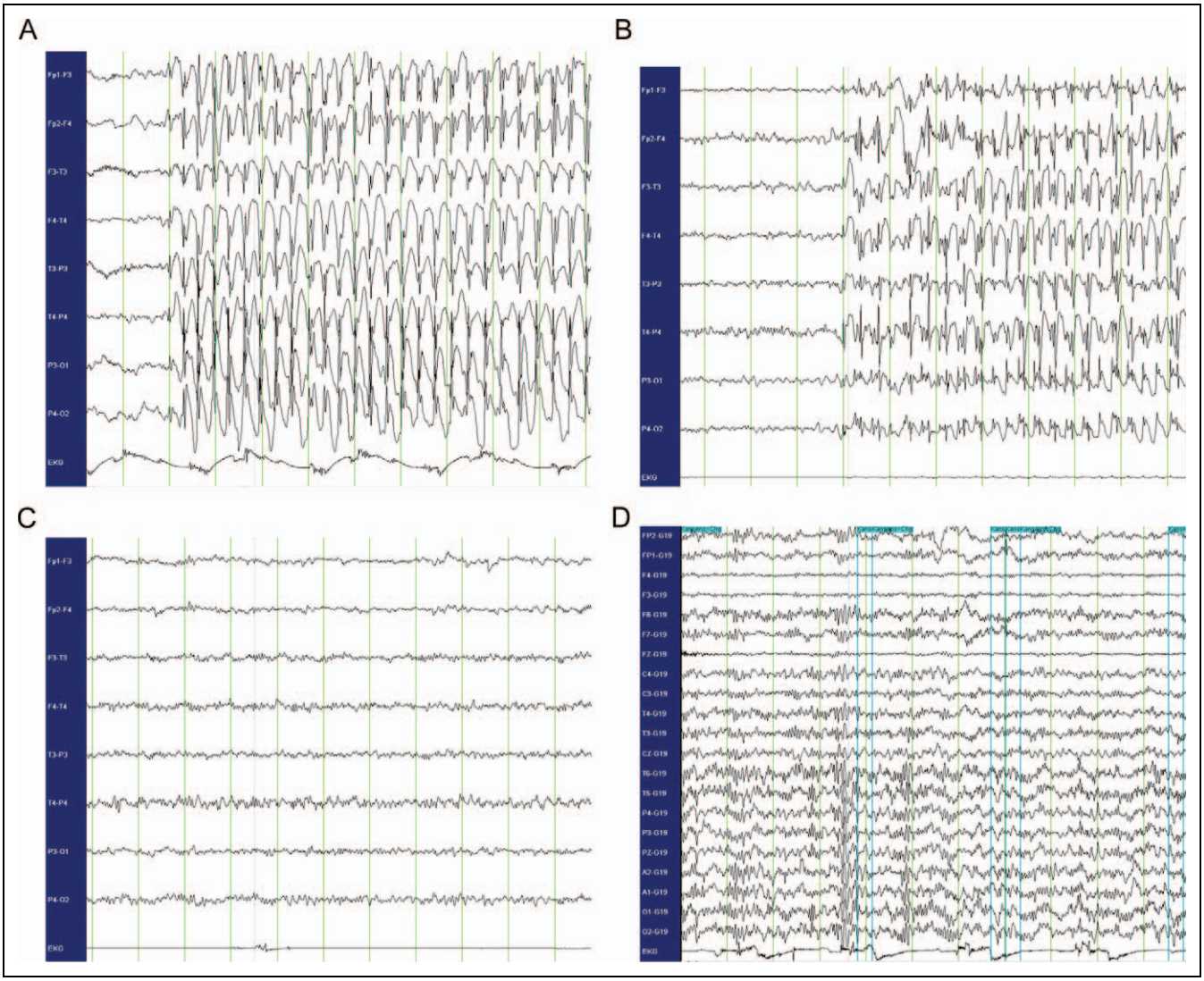

Figure 2. EEG recordings during different treatments. (A) Under lamotrigine treatment, October 2010: generalized spike wave complexes. (B) Under valproic acid, clobazam and Viscum Mali D5, November 2012: Right frontal spike waves generalizing during hyperventilation. (C) Under valproic acid, clobazam, Viscum Mali D2, March 2013 (bipolar montage): occasional solitary steep waves but no spike-wave complexes. (D) Under valproic acid, clobazam, Viscum Mali D2, December 2013: occasional solitary steep waves, no spike-wave complexes.

At this point, she was referred to our center, the Filderklinik. She could not yet draw a closed circle (expected latest by 4 years of age by Denver Developmental Screening Test II) and had difficulties with hand coordination and coordinated ball throwing. The remainder of her neurologic examination was normal. Height was 25th percentile, weight between the 25th and 50th percentiles, and head circumference 50th percentile for age. No dysmorphic features were noted. Complete blood count, liver, and thyroid function tests were within normal limits. Treatment with lamotrigine was initiated following 2 weeks of valproic acid prescribed by the referring physician. Lamotrigine was selected exceptionally, despite its lower antiepileptic activity, for its lower sedative properties in light of her developmental delay. The Filderklinik practices an integrative medicine approach with anthroposophic medicine, with an integrative treatment concept for childhood epilepsy[6,7]: treatment with plant extracts in low homeopathic dilutions of Hyoscyamus ex herba D3 (Wala GmbH, Bad Boll, Germany), 8 globules twice a day; and Taraxacum Stanno culta Rh D3 (Weleda AG, Schwäbisch Gmünd, Germany), 8 drops twice a day, were started simultaneously.

Figure 1 provides details on all antiepileptic treatment attempts, including maximum antiepileptic doses reached (after gradual increase)[8] and blood levels, where applicable. Figure 1 further provides absence durations as measured by spike-and-wave complexes on EEG and absence frequencies based on parent's estimates. EEGs were performed every 2 to 4 months and showed absence activity with or without hyperventilation on all occasions, until durable absence cessation was achieved 2 years after diagnosis. On several EEG recordings, right frontal and temporal spike waves, generalizing into spike-and-wave complexes were noted (see Figure 2 for sample EEG extracts).

Lamotrigine led to no clinical or EEG improvement. Slight reduction in absence frequency and duration were later noted on ethosuximide, and when valproic acid was given in combination with ethosuximide. A further improvement was noted when clobazam was added to valproic acid. Methsuximide had to be discontinued due to skin rash; sulthiame had no effect. No antiepileptic drug alone or in combination was able to achieve seizure freedom.

Ketogenic diet was attempted during the first year, in accordance with international recommendations.[3] Prior to the diet, laboratory investigations, including complete blood count, serum electrolytes, fasting lipid profile, serum acylcarnitine profile, serum and urine amino acids, and urine organic acids were all within normal limits. Magnetic resonance imaging (MRI) of the head, electrocardiogram, and abdominal ultrasonography revealed no pathologies. A 4 g fat to 1 g carbohydrate (4:1) diet with 1160 kcal/d and 16 g protein/d quickly led to ketosis but also nausea, fatigue, and slight weight loss. The diet was thus adjusted to 2.5:1, 1300 kcal/d and 17 g protein/d. No clinical or EEG improvements were noted and the diet was thus considered ineffective and stopped after 2 months.

Complementary treatment was also modified over time (see Figure 1), including with Agaricus muscarius D12, 10 globules twice a day (Deutsche Homöopathie-Union DHU, Karlsruhe, Germany); Levisticum Folium D3, 1 knife point twice a day (Weleda AG, Arlesheim, Switzerland); and Viscum Mali e planta tota (Wala GmbH, Bad Boll, Germany), an extract of *V album* L., European mistletoe, grown on apple tree (Mali). Weleda, DHU, and Wala products, except Levisticum Folium, are registered as homeopathic products without therapeutic indication with the German Federal Institute for Drugs and Medical Devices; Levisticum Folium is similarly registered with the Swiss Agency for Therapeutic Products. Viscum Mali was initially given in strength D5, 10 granules BID, equivalent to a 1:100,000 dilution of the whole plant extract, later increased to D2, equivalent to a 1:100 dilution, 10 granules twice a day.

Over the course of 8 to 12 weeks following the Viscum Mali dose change, absences disappeared gradually and permanently. During this time, the parents also noted their daughter to become more alert, active, and confident. There was no other medication change or any change in her living environment during this time. EEG about 1 month later recorded background activity dominated by 5- to 7-Hz theta waves and occasional superimposed beta wave activity (probably medication induced) but no spike-and-wave complexes at rest or during hyperventilation and no clinical absences (see Figure 2). EEG 6 and 9 months into seizure freedom still recorded no spike-and-wave complexes, including under hyperventilation and no clinical absences. Valproic acid dose reduction to 12 then 6 mg/kg/d was well tolerated. At the time of writing, our patient has remained seizure free for 12 months. At no point during her course did she have motor phenomena during her absences or generalized tonic-clonic seizures.

The patient made good developmental progress during the course described here but still has global developmental delay. At age 6, cognitive development with the Kaufmann Assessment Battery for Children (KABC-I) was <5th percentile for age and she began special school.

> Parents' perspective: We were relieved the Filderklinik combines conventional and homeopathic treatment. Dr M understood and supported us. In the weeks before her seventh birthday, L. changed in a positive way, becoming more confident and active and her absences disappeared. We do not know if seizures disappeared because of *Viscum* or if she simply grew out of it. In retrospect, we wonder if she could have been treated only with homeopathy.

Parents read this report and provided written consent. This case is reported according to CARE guidelines.[9]

Discussion

This girl suffered from refractory childhood absence epilepsy and developmental delay. Although right frontal and temporal seizure onset was sometimes observed, we still classify her absences as Childhood Absence Epilepsy because the focal pattern appeared during therapy and was not consistent.

We assumed idiopathic etiology, based on normal physical examination and a range of laboratory and imaging studies. No genetic studies were performed, as there was no specific clinical suspicion. Cerebrospinal fluid glucose levels to rule out Glut1 deficiency were not obtained as her absences were not associated with fasting or exercise, nor did she respond to a ketogenic diet.

Our patient was treatment refractory, failing to achieve seizure freedom with 3 recommended drugs for childhood absence epilepsy, 3 further antiepileptic drugs, drug combinations and ketogenic diet. Drug-resistant seizures are defined as lack of seizure freedom from 2 appropriate drugs of adequate duration and dose.[10]

Seizures disappeared over 10 to 12 weeks following the dose change of Viscum Mali from D5 to D2. Valproic acid and clobazam had led to some improvement but had not achieved seizure freedom despite sufficient treatment time (started 14 and 5 months, respectively, before seizure freedom). Clinical reduction in absences to 5 per day had already been noted following the addition of clobazam and Viscum Mali at lower dose (D5). We consider that the dose increase of Viscum Mali, in addition to an existing combination with valproic acid and clobazam, may have played a key role in achieving seizure freedom for this child.

Spontaneous remission is possible but seems less likely: drug-resistant seizures are associated with longer disease duration. In the Dutch childhood absence epilepsy cohort, outcome for children who needed >6 months to become seizure free was 7.2 years mean disease duration.[11]

European mistletoe is an old, traditional remedy for convulsions: Pliny the Elder mentions it in his "Natural History" (AD 77-79), Paracelsus recommends it around 1520, John Colebatch published "A dissertation concerning the mistletoe—a most

wonderful specific remedy for the cure of convulsive distempers," in 1720 and Christoph Wilhelm Hufeland published on it in 1830.[12] In recent literature, anticonvulsant activity of *V album* L. has been observed in animals[13] and has been reported in a child with myoclonic seizures.[6] Although a mechanism of action is unknown, unspecified immunomodulatory actions may play a role: *V album* extract contains a variety of biologically active compounds such as lectins, activating a variety of cellular and cytokine-mediated immune responses.[14] Favorable responses of refractory epilepsy syndromes to various immunomodulatory treatments have been observed.[15]

Finally, this case provides an example of integrative medicine in the treatment of pediatric seizures, including the range of anthroposophic medicines typically used with absence epilepsy.

Conclusions

Treatment refractory absence epilepsy poses a significant clinical challenge. *V album* L. (Mali) appears to have been a necessary adjunct to valproic acid and clobazam for this child with a 2-year history of refractory absence epilepsy to become seizure free. We call on physicians to report their experience of *V album* in seizures and suggest further investigation of a possible role of *V album* as potential adjunct in absence epilepsy.

Acknowledgments

The authors wish to thank PD Dr Thomas Bast and Dr Kavitha Kolappa for helpful comments on the manuscript.

Author Contributions

RM was the treating pediatric neurologist, provided patient information, and reviewed the manuscript. TvSA conceptualized the report, wrote the manuscript, and prepared the graph. GSK, HK, and JV critically reviewed the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Within the last 5 years IFAEMM (affiliation of GSK and HK) received restricted research grants from the pharmaceutical companies Wala and Weleda.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: TvSA is supported by a grant from the Mahle Stiftung for the writing of case reports.

References

1. Tenney JR, Glauser TA. The current state of absence epilepsy: can we have your attention? *Epilepsy Curr*. 2013;13:135-140.
2. Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months. *Epilepsia*. 2013;54:141-155.
3. Kossoff EH, Zupec-Kania BA, Amark PE, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. *Epilepsia*. 2009;50:304-317.
4. National Institute for Health and Care Excellence (NICE). The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. 2012. Available at: http://guidance.nice.org.uk/CG137. Accessed March 28, 2014.
5. Doering JH, Reuner G, Kadish NE, Pietz J, Schubert-Bast S. Pattern and predictors of complementary and alternative medicine (CAM) use among pediatric patients with epilepsy. *Epilepsy Behav*. 2013;29:41-46.
6. Madeleyn R. Gesichtspunkte zur Epilepsie und deren Behandlungsmöglichkeiten bei Kindern. *Der Merkurstab*. 1990;43:369-384.
7. Kienle GS, Albonico HU, Baars E, et al. Anthroposophic medicine: an integrative medical system originating in Europe. *Global Adv Health Med*. 2013;2:20-31.
8. Steinhoff B. *Vademecum Antiepileptikum 2013/2014—Pharmokotherapie der Epilepsie*, 22nd ed. Berlin: Deutsche Gesellschaft für Epileptologie e.V; 2013.
9. Gagnier JJ, Kienle G, Altman DG, et al. The CARE Guidelines: Consensus-Based Clinical Case Reporting Guideline Development. *Headache*. 2013;53:1541-1547.
10. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2010;51:1069-1077.
11. Callenbach PM, Bouma PA, Geerts AT, et al. Long-term outcome of childhood absence epilepsy: Dutch Study of Epilepsy in Childhood. *Epilepsy Res*. 2009;83:249-256.
12. Wilkens J. *Misteltherapie: differenzierte Anwendung der Mistel nach Wirtsbäumen*. Stuttgart: Georg Thieme Verlag; 2006.
13. Gupta G, Kazmi I, Afzal M, et al. Sedative, antiepileptic and antipsychotic effects of *Viscum album* L. (Loranthaceae) in mice and rats. *J Ethnopharmacol*. 2012;141:810-816.
14. Kienle GS, Kiene H. *Die Mistel in der Onkologie: Fakten und konzeptionelle Grundlagen*. New York: Schattauer; 2003.
15. Billiau AD, Wouters CH, Lagae LG. Epilepsy and the immune system: is there a link? *Eur J Paediatr Neurol*. 2005;9:29-42.