Eur J Pediatr (2004) 163: 402–407
DOI 10.1007/s00431-004-1444-7

ORIGINAL PAPER

Oliviero Bruni · Raffaele Ferri · Silvia Miano
Elisabetta Verrillo

L -5-Hydroxytryptophan treatment of sleep terrors in children

Received: 14 November 2003 / Revised: 18 February 2004 / Accepted: 23 February 2004 / Published online: 14 May 2004

Abstract To test the hypothesis that the administration of L -5-hydroxytryptophan (L -5-HTP) might exert beneficial effects on sleep terrors, we carried out an open pharmacological trial in a group of children with sleep terrors compared to a group of children with the same disorder but without L -5-HTP treatment. Participants in the trial were 45 children (34 males and 11 females; age range 3.2–10.6 years), referred to the Sleep Centre of the Department of Developmental Neurology and Psychiatry of the University of Rome "La Sapienza", affected by sleep terrors. All subjects underwent: (1) complete medical and sleep history; (2) complete neurological examination and EEG recording whilst awake and sleeping, (3) a structured sleep diary for 2 months, (4) after 1 month, all subjects were examined again from the clinical and EEG points of view and (5) after 6 months, a structured interview in order to evaluate the clinical outcome. After the first visit, L -5-HTP was administered (2 mg/kg per day) at bedtime to 31 randomly selected patients for a single period of 20 consecutive days. After 1 month of treatment, 29/31 (93.5%) of patients showed a positive response. In the comparison group without drug therapy, after 1 month, the episodes disappeared only in four children (28.6%) while ten children (71.4%) showed the persistence of episodes with the same frequency as before. After 6 months, 26/31 (83.9%) of children treated with L -5HTP were sleep terror-free, while in five children (16.1%) sleep terror episodes persisted. Of the children in the comparison group, ten (71.4%) continued to show sleep terrors at 6-month follow-up. *Conclusion*: To our knowledge, this is the first study demonstrating the efficacy of a new drug treatment for sleep terrors. These results confirm our initial hypothesis and represent evidence that treatment with L -5-hydroxytryptophan is able to modulate the arousal level in children and to induce a long-term improvement of sleep terrors.

Keywords Arousal disorders · L -5-Hydroxytryptophan · Serotoninergic system · Sleep terrors

Abbreviations EMS: eosinophilia-myalgia syndrome · HSDWA: hypersynchronous high voltage delta waves arousal · HVMD: high voltage monomorphic delta · L -5-HTP: L -5-hydroxytryptophan · NREM: non rapid eye movement · PLMs: periodic limb movements during sleep · SDB: sleep-disordered breathing

O. Bruni (✉) · E. Verrillo
Centre for Paediatric Sleep Disorders,
Department of Developmental Neurology and Psychiatry,
University of Rome "La Sapienza",
Via dei Sabelli 108, 00185 Rome, Italy
E-mail: oliviero.bruni@uniroma1.it
Tel.: +39-06-44712257
Fax: +39-06-4957857

R. Ferri · S. Miano
Sleep Research Centre, Department of Neurology, Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Troina, Italy

Introduction

Sleep terrors are characterised by sudden waking from slow-wave sleep with persistent fear or terror, screaming, sweating, confusion, and increased heart rate. The subjects affected by this sleep disorder usually do not report dreams or nightmares but might have a vague sense of frightening images. Sleep terrors show a prevalence rate ranging from 1% to 6.5% [9]. Sleep terrors can affect also adults; however, they show a peak of prevalence between 5 and 7 years of age and their frequency reaches its maximum soon after the onset of the disorder.

As shown by Di Mario and Emery [9], children suffering from sleep terrors with age at onset less than 3.5 years attain a peak frequency of at least one episode per week, while children with age at onset between 3.5 and 7.5 years usually reach a peak frequency of 1–2 episodes per month; in the same study, the disorder mean

duration was 3.9 years, with a tendency for longer duration in children with positive family history for sleep walking. In the same study, sleep terrors stopped by the age of 8 years in 50% of cases; 36% continued into adolescence.

Different therapeutic strategies have been proposed for sleep terrors: a behavioural approach, reinforcing age-appropriate sleep patterns, reassuring and guiding parents [32]; an approach based on psychotherapy or hypnosis [10,19]; waking treatment [20]; and a pharmacological approach using different classes of medication such as benzodiazepines and tricyclic antidepressants [3, 5, 6, 23, 25]. However, drugs are only rarely used in clinical practice.

It has been suggested that the manifestations of arousal disorders, such as sleep terrors, may be due to a conflict between the mechanisms generating slow-wave sleep and arousal, dependent on a dysfunction in the serotoninergic system [1,16]. It is also known that high doses of L-5-hydroxytryptophan (L-5-HTP), a precursor of serotonin, might cause the production of sleep-promoting factors [15].

In order to collect preliminary data on the eventual efficacy of L-5-HTP on sleep terrors, we carried out an open-label study with the aim of treating a group of children affected by sleep terrors with this compound and to compare their outcome with that of a group of children with the same disorder but without L-5-HTP treatment.

Subjects and methods

Subjects

A total of 45 consecutive children (34 males and 11 females; age range 3.2–10.6 years), referred to the Sleep Centre of the Department of Developmental Neurology and Psychiatry of the University of Rome "La Sapienza", affected by sleep terrors were included in this study. All parents of the children who were seen and monitored in the sleep clinic were asked to sign a consent form approved by the institution for use of clinical data for research purposes.

The diagnosis of sleep terrors was based on the criteria reported in the International Classification of Sleep Disorders [2] and all subjects presented the following features:

1. sleep terrors (sudden arousal during the first third of the night with a piercing scream or cry, accompanied by autonomic and behavioural manifestations of intense fear)
2. partial or total amnesia for the events during the episode
3. at least 3 episodes during the last month
4. presence of sleep terror episodes for at least 3 months
5. absence of seizures

None of the children had taken medications for their sleep disorders.

Protocol

Each child underwent the same standardised evaluation protocol. A complete medical history and a detailed sleep history were taken. Parents and children were interviewed about the children's schooling, psychological difficulties, medication intake, and family history of medical and sleep disorders. Medical histories included systematic assessment of variables relevant to early life sleep disorders, such as allergies and asthma. Family histories included inquiries about parasomnias and other sleep disorders, and affected relatives were examined when possible. All children underwent a complete neurological examination and EEG recording whilst awake and sleeping in order to rule out any neurological conditions which might cause or might be confounded with sleep terrors. A structured sleep diary for 2 months was completed and the eventual occurrence of sleep terror episodes recorded. After 1 month, all subjects were examined and a structured interview was conducted in order to quantify the frequency of sleep terror episodes and to evaluate their clinical outcome. After 6 months, parents of patients were contacted by telephone and invited to our Department. On this occasion the same structured interview was conducted in order to evaluate the frequency of sleep terror episodes and the clinical outcome.

Patients were randomly assigned to two groups: group A treated with L-5-HTP and group B in which no drug therapy was given and parents were told that the disturbance usually shows a benign course, disappearing during adolescence. No behavioural treatment or any other non-pharmacological therapy was suggested to patients of group B.

After the neurological evaluation and the recording of the EEG, a dosage of 2 mg/kg per day of L-5-HTP [13, 24, 30] was administered at bedtime to all patients of group A for a single period of 20 consecutive days. Blood samples were monitored on a regular basis every month in order to detect the eventual occurrence of eosinophilia, with the aim of avoiding the development of eosinophilia-myalgia syndrome (EMS), previously reported during treatment with L-tryptophan [21, 22].

Patients were considered as responders if they showed a $>50\%$ reduction in the number of reported sleep terror episodes with respect to their individual baseline value.

Results

Group A was composed of 31 subjects (22 males, 9 females; mean age 6.8 years, SD 2.6) and group B was composed of 14 subjects (12 males, 2 females; mean age 7.4 years, SD 3.0). The clinical characteristics of the whole group of children, who were behaviourally and developmentally normal, are given in Table 1. Family history for arousal disorders was reported in 32 out of the 45 children (71%). The frequency of sleep terror

Table 1 Clinical characteristics of the children with sleep terrors ($n = 45$)

Mean age at observation (years)	7.3 (range 3.2–10.6)
Mean age at onset (years)	3.4 (range 1.6–5.9)
Gender	
males	34 (75.5%)
females	11 (25.5%)
Frequency of episodes (per month)	6.6 ± 3.4
Positive family history	32 (71.1%)
Snoring	9 (20%)
Sleepwalking	4 (8.8%)
Enuresis	3 (6.6%)
Restless sleep	18 (40%)
Night awakenings	3 (6.6%)

Table 2 Evolution of sleep terrors at 1 month and at 6 months in relation to treatment. Responders are patients with a reduction in sleep terror episodes > 50% from baseline

	After 1 month	After 6 months
L-5-HTP treatment	Responders 29 (93.5%)	No episodes 26 (83.9%)
		Episodes recurrence 3 (9.7%)
	Non responders 2 (6.5%)	Enduring 2 (6.4%)
No treatment	Improvement 4 (28.6%)	No episodes 3 (21.4%)
		Episodes recurrence 1 (7.1%)
	No improvement 10 (71.4%)	Enduring 9 (64.3%)
		No episodes 1 (7.1%)

episodes per month was 6.6 ± 3.4. No seizures were reported in the patient histories and all EEGs were normal.

No significant differences between the two groups were found for age ($t = -0.69$; $P = 0.49$) and sex (Yates corrected Chi-square $= 0.48$; $P = 0.49$). All children of group A completed the basic treatment prescribed. No variation of the schedule was required due to side-effects. Also no alterations in the number of eosinophilic cells were observed. Table 2 shows, schematically, the course of sleep terrors in both groups of patients.

In group A, treatment with L-5-HTP gave a positive response in 29/31 (93.55%) of cases evaluated at the follow-up visit after 1 month. The complete disappearance of sleep terrors was achieved in 16/31 (51.6%) cases whereas 13 children showed a reduction > 50% in frequency of episodes. In only two patients (6.45%) had L-5-HTP no effect. Table 3 shows that the mean number of episodes per month decreased from 6.6 to 0.5.

In group B, after 1 month, ten children (71.43%) showed the persistence of episodes with the same frequency as before; in two children (14.29%) the episodes disappeared and in the remaining two there was a reduction > 50% in frequency of events. The mean number of episodes per month decreased from 6.6 to 3.2 (Table 3).

After 6 months, at follow-up visit, 24/31 (77.42%) of children treated with L-5-HTP were sleep terror-free, and another two (6.45%) had a reduction in frequency of attacks > 50%; sleep terrors were still present in five children (16.12%). The improvement was long-lasting in all the 16 subjects who had shown a positive response after 1 month and no new sleep terror episodes were reported by their parents.

Of the 13 children who showed a decrease of episode frequency > 50% at 1 month, 8 (61.54%) were sleep terror-free after 6 months (for the last 3 months, at least), in another two (15.38%) the frequency of sleep terrors was still below 50% of baseline and, in the remaining three (23.08%), the episodes relapsed after the interruption of the treatment. In the two children who did not respond to L-5-HTP at 1 month, parents reported the persistence of sleep terrors with the same rate of recurrence preceding the treatment. No long-term side-effects were reported by parents. Table 3 shows that the mean number of episodes per month remained low at 0.4.

Of the ten children in group B who had sleep terrors at 1-month follow-up, nine (90%) continued to show sleep terrors at 6-months follow-up, the remaining patient showed a reduction > 50% of the attacks. One out of the two children who had shown disappearance of sleep terrors at 1-month follow-up, presented a re-occurrence of episodes at 6 months. The remaining two children who had shown episode frequency decrease at 1 month continued to be affected by sleep terrors with the same rate of recurrence. Also in this group, the mean number of episodes per month remained stable at 3.4 (Table 3).

Table 4 shows the statistical analysis (Yates corrected Chi-square test) of the difference in response to the two treatments in both groups of patients at 1-month and at 6-months follow-up revealing a significant improvement only in the group treated with L-5-HTP.

Table 3 Statistical analysis of response to treatment or follow-up in terms of episodes of sleep terrors per month after 1 month and 6 months. All values expressed as mean ± SD

	Baseline	After 1 month	After 6 months	Friedman ANOVA
Group A	6.6 ± 3.31	0.5 ± 1.09	0.4 ± 0.92	$P < 0.00001$
Group B	6.6 ± 3.97	3.2 ± 3.00	3.4 ± 2.84	$P < 0.001$

Table 4 Statistical analysis of response to treatment in both groups of patients at 1 month and at 6 months follow-up. Responders are patients with a reduction in sleep terror episodes > 50% from baseline

	Responders	Non responders	Chi-Square	*P*
1 month follow-up				
Group A	29 (93.5%)	2 (6.5%)	17.63	< 0.00001
Group B	4 (28.6%)	10 (71.4%)		
6 month follow-up				
Group A	26 (83,9%)	5 (16.1%)	10.90	< 0.001
Group B	4 (28.6%)	10 (71.4%)		

Discussion

To our knowledge, this is the first study attempting to test the efficacy of a new drug treatment for sleep terrors, in an open label fashion. The results suggest that the treatment with L-5-HTP is highly effective in reducing the number of episodes after 1 or 6 months follow-up, with 84% of responders versus 28.6% in the non-treated group. Also the mean number of episodes decreased to a great extent with only 0.4 episodes per month in the L-5-HTP group. In the non-treated group there was a decrease of the frequency of the episodes according to the natural history of sleep terrors [9] but the mean number of episodes was still 3.4 per month at 6 months follow-up. The period of observation of this study was short (6 months) and one would not expect a decrease in attacks in such a short time without treatment. However, our control group was formed mainly by subjects with ages closer to the upper limit of their age range (4 to 10 years) when the probability that the condition begins to fade away increases.

The results suggest that the treatment with L-5-HTP might be able to modulate the arousal level in children and to induce a long-term improvement of sleep terrors. This is confirmed by other studies on insomnia which reported that the administration of L-5-HTP resulted in a long-lasting improvement of sleep [29], at least for several months.

It has been demonstrated that the number and the duration of high voltage monomorphic delta (HVMD) activity or of hypersynchronous high voltage delta waves arousal (HSDWA) during sleep is increased in adults and children with sleep terrors [4, 10,11] and that an increase in sleep instability and in arousal oscillation during stage 3–4 non-rapid eye movement (NREM) sleep is a typical microstructure feature of delta sleep-related parasomnias and probably plays a role in triggering abnormal motor episodes during sleep in these patients [35]. The reduction of intermittent awakenings produced by L-5-HTP [34] could act, in sleep terrors, through a stabilisation of the sleep microstructure, modulating the frequency band and the spectra of delta waves and preventing the occurrence of the HVMD bursts that precede the clinical episodes [35]. There is also experimental evidence that L-5-HTP is able to reduce NREM sleep intensity irrespective of its changes in duration [29, 34].

It should be emphasised that children with chronic parasomnias may often also present sleep-disordered breathing (SDB) or, to a lesser extent, periodic limb movements (PLMs) during sleep; furthermore, the disappearance of the parasomnias after the treatment of the SDB or PLMs suggests that the latter may trigger the former, at least in some cases [14]. However, this mechanism does not seem to explain the majority of cases showing a natural disappearance of episodes after puberty [9]. No polysomnographic studies were performed in our group of patients; thus, we can not exclude the presence of SBD and/or PLMs.

It has been reported that L-tryptophan (not L-5-HTP) determined an epidemic of a new disease, termed EMS which occurred in the United States in 1989. This syndrome was linked to the consumption of L-tryptophan manufactured by a single company utilising a fermentation process. All the findings indicate that the illness was probably triggered by an impurity formed when the manufacturing conditions were modified and linked to ingestion of tryptophan contaminated with 1,1′-ethylidene-bis[L-tryptophan] [22]. Since then, several reports have examined the methodology of the epidemiological studies of the association between L-trytophan and EMS and contest the validity of the conclusions from these studies [7,31], although the debate about the cause-effect relationship is still open. In comparison with synthetic antidepressants and hypnotics, L-tryptophan and L-5-HTP are characterised by a particularly low level of side-effects [27].

To our knowledge, EMS has rarely been associated with L-5-HTP in the literature [18, 21,33] and, again, this was due to impurities in the preparation of the drug; on the other hand, there are several recent reports on the use of L-5-HTP in children without the occurrence of side-effects [8, 17, 26, 28].

The substances contaminating previous pharmaceutical preparations of L-5-HTP are no longer present in measurable amounts in the preparations now available on the market because of improved purification and analysis methods. We used Trypt-OH (Sigma-Tau, Italy), which, to our knowledge, has been associated with EMS only in one adult patient who was affected by chronic alcohol abuse and severe liver dysfunction [12]. Accordingly, in our study there was no evidence of symptoms related to the EMS.

At therapeutic doses, this substance does not affect the normal distribution of sleep stages in both acute and chronic treatment [29,34]. The absence of side-effects and lack of development of tolerance in long-term use are important factors in the decision to embark upon a trial of L-5-HTP treatment. Although the relatively small number of cases and the absence of a control group treated with placebo cannot allow us to suggest that the use of L-5-HTP in sleep terrors might be a real possibility, the results of this study are promising and represent the basis for the arrangement of a new investigation in which a double-blind and placebo-controlled protocol should clarify the real effectiveness and mechanisms of this new treatment for sleep terrors.

References

1. Adrien J (1995) The serotoninergic system and sleep-wakefulness regulation. In: Kales A (ed) The pharmacology of sleep. Springer, Berlin Heidelberg New York, pp 91–116
2. American Sleep Disorders Association (1997) International classification of sleep disorders, revised: diagnostic and coding manual. American Sleep Disorders Association, Rochester, Minnesota
3. Balon R (1994) Sleep terror disorder and insomnia treated with trazodone: a case report. Ann Clin Psychiatry 6: 161–163
4. Bastuji H, De Villard R, Garde P, Challamel MJ (1991) High voltage monomorphic delta activity during sleep in children with pavor nocturnus or somnambulism, and in normal controls. Sleep Res 20A: 285
5. Cameron OG, Thyer BA (1985) Treatment of pavor nocturnus with alprazolam. J Clin Psychiatry 46: 504
6. Dahl RE (1992) The pharmacologic treatment of sleep disorders. Psychiatric Clin North Am 15: 161–178
7. Daniels SR, Hudson JI, Horwitz RI (1995) Epidemiology of potential association between L-tryptophan ingestion and eosinophilia-myalgia syndrome. J Clin Epidemiol 48: 1413–1427
8. De Giorgis G, Miletto R, Iannuccelli M, Camuffo M, Scerni S (1987) Headache in association with sleep disorders in children: a psychodiagnostic evaluation and controlled clinical study - L-5-HTP versus placebo. Drugs Exp Clin Res 13: 425–433
9. DiMario FJ Jr, Emery ES III (1987) The natural history of sleep terrors. Clin Pediatr 26: 505–511
10. Driver H, Shapiro C (1993) Parasomnias. BMJ 306: 921–924
11. Espa F, Ondze B, Deglise P, Billiard M, Besset A (2000) Sleep architecture, slow wave activity, and sleep spindles in adult patients with sleepwalking and sleep terrors. Clin Neurophysiol 111: 929–939
12. Farinelli S, Mariani A, Grimaldi A, Mariani M, Iannessi A, De Rosa F (1991) Eosinophilia-myalgia syndrome associated with 5-OH-tryptophan. Description of a case. Recenti Prog Med 82: 381–384
13. Gijsman HJ, van Gerven JM, de Kam ML, Schoemaker RC, Pieters MS, Weemaes M, de Rijk R, van der Post J, Cohen AF (2002) Placebo-controlled comparison of three dose-regimens of 5-hydroxytryptophan challenge test in healthy volunteers. J Clin Psychopharmacol 22: 183–189
14. Guilleminault C, Palombini L, Pelayo R, Chervin RD (2003) Sleepwalking and sleep terrors in prepubertal children: what triggers them? Pediatrics 111: e17–e25
15. Imeri L, Mancia M, Bianchi S, Opp MR (2000) 5-hydroxytryptophan, but not L-tryptophan, alters sleep and brain temperature in rats. Neuroscience 95: 445–452
16. Jacos BL, Azmitia EC (1992) Structure and function of the brain serotonin system. Physiol Rev 72: 165–229
17. Kaufman J, Birmaher B, Perel J, Dahl RE, Stull S, Brent D, Trubnick L, Al-Shabbout M, Ryan ND (1998) Serotonergic functioning in depressed abused children: clinical and familial correlates. Biol Psychiatry 44: 973–981
18. Klarskov K, Johnson KL, Benson LM, Cragun JD, Gleich GJ, Wrona M, Jiang X-R, Dryhurst G, Naylor S (2003) Structural characterization of a case-implicated contaminant, "peak x," in commercial preparations of 5-hydroxytryptophan. J Rheumatol 30: 89–95
19. Kohen DP, Mahowald MW, Rosen GM (1992) Sleep-terror disorder in children: the role of self-hypnosis in management. Am J Clin Hypn 34:233–244
20. Lask B (1988) A novel and non-toxic treatment for sleep terrors. BMJ 297: 592
21. Michelson D, Page SW, Casey R, Trucksess MW, Love LA, Milstien S, Wilson C, Massaquoi SG, Crofford LJ, Hallett M et al (1994) An eosinophilia-myalgia syndrome related disorder associated with exposure to L-5-hydroxytryptophan. J Rheumatol 21: 2261–2265
22. Philen RM, Hill RH Jr, Flanders WD, Caudill SP, Needham L, Sewell L, Sampson EJ, Falk H, Kilbourne EM (1993) Tryptophan contaminants associated with eosinophilia-myalgia syndrome. The Eosinophilia-Myalgia Studies of Oregon, New York and New Mexico. Am J Epidemiol 138: 154–159
23. Popoviciu L, Corfariu O (1983) Efficacy and safety of midazolam in the treatment of night terrors in children. Br J Clin Pharmacol 16[Suppl 1]: 97S–102S
24. Ramaekers VT, Senderek J, Haeusler M, Haering M, Abeling N, Zerres K, Bergmann C, Heimann G, Blau N (2001) A novel neurodevelopmental syndrome responsive to 5-hydroxytryptophan and carbidopa. Mol Genet Metab 73: 179–187
25. Reimao R, Lefevre AB (1982) Evaluation of flurazepam and placebo on sleep disorders in childhood. Arq Neuropsiquiatr 40: 1–13
26. Ribeiro CA (2000) L-5-Hydroxytryptophan in the prophylaxis of chronic tension-type headache: a double-blind, randomized, placebo-controlled study. For the Portuguese Head Society. Headache 40: 451–456
27. Riemann D, Vorderholzer U (1998) Treatment of depression and sleep disorders. Significance of serotonin and L-tryptophan in pathophysiology and therapy. Fortschr Med 116: 40–42
28. Ryan ND, Birmaher B, Perel JM, Dahl RE, Meyer V, Al-Shabbout M, Iyengar S, Puig-Antich J (1992) Neuroendocrine response to L-5-hydroxytryptophan challenge in prepubertal major depression. Depressed vs normal children. Arch Gen Psychiatry 49: 843–851
29. Schneider-Helmert D, Spinweber CL (1986) Evaluation of L-tryptophan for treatment of insomnia: a review. Psychopharmacology 89: 1–7
30. Schruers K, van Diest R, Nicolson N, Griez E (2002) L-5-Hydroxytryptophan induced increase in salivary cortisol in panic disorder patients and healthy volunteers. Psychopharmacology 161: 365–369

31. Shapiro S (1996) Epidemiologic studies of the association of L -tryptophan with the eosinophilia-myalgia syndrome: a critique [see comments]. J Rheumatol Suppl 46: 44–58
32. Weissbluth M (1984) Is drug treatment of sleep terrors warranted? Am J Dis Child 138: 1086
33. Williamson BL, Klarskov K, Tomlinson AJ, Gleich GJ, Naylor S (1998) Problems with over-the-counter 5-hydroxy- L -tryptophan. Nat Med 4: 983
34. Wyatt RJ, Engelamn K, Kupfer DJ, Fram DH, Sjoerdsma A and Snyder F (1970) Effects of L -tryptophan (a natural sedative) on human sleep. Lancet 7678: 842–845
35. Zucconi M, Oldani A, Ferini-Strambi L, Smirne S (1995) Arousal fluctuations in non-rapid eye movement parasomnias: the role of cyclic alternating pattern as a measure of sleep instability. J Clin Neurophysiol 12: 147–154