Tryptophan for the Treatment of Excessive Daytime Sleepiness in Prader-Willi Syndrome

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An 8-year old girl with Prader-Willi Syndrome presenting with excessive daytime sleepiness improved following treatment with tryptophan; possibly by consolidation of her fragmented sleep. Improvement was recorded on a follow-up sleep study, one year after initiating treatment with tryptophan. We conclude that tryptophan may be an useful medication for excessive sleepiness in children with Prader-Willi Syndrome.

Key words: *Excessive Daytime Sleepiness, Prader-Willi Syndrome, Tryptophan.*

Tryptophan is an essential amino acid and the metabolic precursor of serotonin, which has an important role in sleep. From the perspective of therapeutic use in children, there has been only one study which demonstrated the efficacy of low dose 5-hydroxytryptophan (5-HTP) i.e. another precursor of serotonin in children with sleep terror [1].

Various sleep complaints have been reported in Prader-Willi syndrome, including narcoleptic features like excessive daytime sleepiness (EDS), sleep onset REM period (SOREMP), sleep apnea syndrome (SAS), and fragmented nocturnal sleep [2]. Continuous positive airway pressure has been known to be useful treatment for SAS and its associated EDS in this syndrome. There is only one case report of clomipramine trial which showed improvement of his sleepiness by 2 minutes of sleep latency on multiple sleep latency test (MSLT) [3]. We tried tryptophan to reduce excessive daytime sleepiness in Prader – Willi syndrome.

CASE REPORT

An eight year-old girl diagnosed with Prader-Willi syndrome with deletion in the paternally derived chromosome 15 presented with excessive daytime sleepiness. She would fall asleep when she was in a car, or in the subway and had problems staying awake in class. She had no symptoms of cataplexy, sleep related hallucinations, sleep paralysis, or sleep apnea. There were no other symptoms suggestive of sleep apnea.

On physical examination, her height was 115cm (<5th centile), weight was 22.7 kg with a BMI of 17.2. She had a narrow face. Her systematic examination was normal and there was no hypertrophy of her tonsils or adenoids, and a structured interview of the child did not reveal any history suggestive of depression. Two overnight polysomnographic studies and two daytime tests (multiple sleep latency test; MSLT and maintenance of wakefulness test; MWT) were conducted on day 1 and 2. Polysomnographic findings on second night were used for her assessment. No significant sleep apnea episodes or snoring were recorded during her sleep. Even though she did not complain of difficulty with her nocturnal sleep, fragmented night time sleep (arousal index=9.8/h) was observed. Day time sleepiness on the MSLT was prominent (sleep latency on the MSLT was 4.4 minutes) and 3 SOREMPs were recorded in a four session MSLT.

After obtaining informed consent, she was

started on oral tryptophan starting with a dose of 750 mg and titrating to 4500 mg, by a 750 mg elevation at 2 weeks interval. Parents were instructed to choose and maintain the dosage at which the child felt best. After 4-weeks treatment her daytime sleepiness decreased. She was followed up every 3 months and her parents reported a significant improvement in the child's symptoms at a daily dose of 4500 mg of tryptophan taken in the evening for 1 year. Parents and teachers commented that she was able to learn more as a result of her increased alertness. Routine laboratory investigations including complete blood count, liver function tests and routine urine examination were unremarkable at follow-up after 1-year.

Sleep studies performed after 1-year of treatment showed a lower arousal index in her nocturnal polysomnography, and she stayed awake during all the four sessions without any SOREMP episode in MSLT compared to baseline findings. ***Table* I** shows results of her sleep studies at baseline and follow-up after taking tryptophan.

DISCUSSION

To our knowledge, this is the first report of tryptophan trial for treatment of excessive daytime sleepiness by consolidating fragmented sleep in a patient with Prader Willi syndrome. The underlying mechanism of narcolepsy symptoms in Prader-Willi syndrome still remains unclear. Hypothalamic dysfunction involved in hypocretin/orexin system was considered as one of possible causes [4]. Hypothalamic dysfunction in PWS can manifest as abnormal response to hypercarbia in conjunction with the dysregulation of REM sleep [5].

In this girl, tryptophan was effective for her sleepiness. One explanation of the improvement might be the hypnotic nature of tryptophan. In this case, the consolidation of fragmented nocturnal sleep with tryptophan could be verified by marked reduction of arousal index in the follow-up study. An increase in sleep efficiency and a decrease in wakefulness time after sleep onset also indicated improvement in her sleep. The improvement of her nocturnal sleep is the likely source for the positive impact on her excessive daytime sleepiness.

Serotonin as a wakefulness promoter might be another feasible explanation of tryptophan's effect on her sleep. Previous studies noted that serotonin facilitates wakefulness by its action on 5-HT_2 receptors and subsequently provokes sleep by sleep promoting mechanism in the regulation of arousal state by serotonin [6]. In animal models, the mechanism of serotonergic activation seems to be up to the timing of the administration of 5-hydroxytryptophan (5-HTP), when it is at dark onset or light onset. 5-HTP injected at dark onset increases NREM sleep, while administration at light onset initially provokes wakefulness with increase NREM sleep during the subsequent dark period [7]. This patient has taken the tryptophan in the evening, which was usually 2 hours before her bedtime, which was after dark onset. Therefore, the improvement of her sleepiness by the consolidation of her nocturnal sleep rather than by promoting wakefulness effect itself from the serotonergic activation might be more plausible explanation.

TABLE I COMPARISON OF SLEEP STUDY FINDINGS AT BASELINE AND FOLLOWING Tryptophan Therapy in Prader-Willi Syndrome

Overnight study	Baseline	Follow-up
Total time in bed (min)	536.5	558
Total sleep time (min)	495.5	546
Sleep period time (min)	534	555.5
Sleep latency (min)	1.5	1.5
Sleep efficiency (%)	92.4	98
REM latency (min)	72	76
WASO (%)	7.4	1.8
Stage 1 (%)	1.6	2.8
Stage 2 (%)	46.8	50
SWS (%)	25.6	21.3
REM (%)	17.9	22.9
Apnea hypopnea index (No./hour)	0.4	0
Arousal index (No./hour)	9.8	4.7
Daytime sleep study		
Mean sleep latency in MSLT (min)	4.4	Awake
No. of SOREMP in MSLT	3/4	0/4
Mean sleep latency in MWT (min)	19	18

WASO: Wake After Sleep Onset, SWS: Slow Wave Sleep, MSLT: Multiple Sleep Latency Test, SOREMP: Sleep Onset REM Period, MWT: Maintenance Wakefulness Test.

In this patient, the baseline MSLT had shown three SOREMPs of four sessions. There was no SOREMP on the follow-up MSLT with tryptophan. This result may be accounted for by the fact that tryptophan as the metabolic precursor of serotonin acted as a REM sleep suppressant [7]. Another explanation for the effect on REM sleep might be that hypothalamic prolactin, which exists in the same neurons as hypocretin/orexin, is considered to play important role in REM sleep regulation [8] and might have a hypnotic effect via another neurotransmitter *i.e.* VIP [9].

Some studies have reported the role of growth hormone treatment in improving the sleep-disordered breathing in PWS, but a subset of patients had worsening of symptoms 6 weeks after starting growth hormone [10]. However, the apnea index of this patient did not meet the diagnosis of sleep apnea.

We conclude that in PWS patients tryptophan might be a useful pharmacologic treatment for excessive daytime sleepiness.

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Umbilical Myiasis in Newborn

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Umbilical myiasis is rare in newborns. We are reporting two cases of umbilical myiasis from rural West Bengal (India) that were infected by larval forms of blow fly (*Chrysomya megacephala*). One of them subsequently developed septicemia while the other one was clinically well.

Keywords: *Myiasis, Neonate, Umbilical*.

Myiasis is an animal or human disease caused by the immature stage (maggots) of flies which feed on the host's necrotic or living tissue[1]. Myiasis may affect humans reared in poor hygienic conditions. It is more common in children less than five years of age and with a rural background [2]. Myiasis in the human neonatal period is a rare