Agrypnia excitata in a patient with progeroid short stature and pigmented Nevi (Mulvihill-Smith syndrome)

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Accepted in revised form 18 May 2005; received 14 December 2004

SUMMARY We report the video-polysomnographic sleep characteristics of a 25-year-old woman with the Mulvihill-Smith syndrome, a rare clinical condition characterized by progeria-like aspect, peculiar multiple pigmented nevi, low stature, and cognitive impairment. Among the various exams, two overnight video-polysomnographic recordings were carried out; moreover, cerebral MRI and molecular analysis of the prion protein gene (PRNP) were also performed. The video-polysomnographic recordings showed the absence of clear sleep episodes but the presence of periods during which the patient had poor contact with the environment, stereotyped afinalistic movements of the upper limbs and hands, irregular or periodic breathing (with central apnea episodes), heart rate arrhythmia, and rapid eye movements. Cerebral MRI showed only diffuse mild enlargement of the cortical sulci and the molecular genetics analysis of the PRNP was normal. Our clinical and neurophysiological study seems to indicate that a particular condition of severe sleep disruption, similar to some extent to that reported in the fatal familial insomnia and in the Morvan fibrillary chorea, which has been indicated as Agrypnia Excitata in recent literature, might be associated with the Mulvihill-Smith syndrome. The inclusion of a detailed study on the sleep characteristics of eventual additional patients will certainly help our understanding of this rare condition.

KEYWORDS agrypnia excitata, mulvihill-smith syndrome, prion protein gene, progeria, video-polysomnography

INTRODUCTION

The Mulvihill-Smith syndrome is a rare clinical condition characterized by progeria-like aspect, multiple pigmented nevi, lack of facial subcutaneous fat, microcephaly, low stature, and mental retardation (Baraitser et al., 1988). After the first reported cases of isolated male with no parental consanguinity (Baraitser et al., 1988; Elliott, 1975; Mulvihill and Smith, 1975; Shepard, 1971), Ohashi et al. (1993) reported the disorder in a 30-year-old woman who had immunodeficiency and whose parents were first cousins. They suggested autosomal recessive inheritance of the disorder in their patient and indicated that another female patient previously reported by Wong et al. (1979) might have been affected by the same syndrome. Another male patient with the Mulvihill-Smith syndrome and immunodeficiency was reported by Bartsch et al. (1994). de Silva et al. (1997) reported the seventh case of the Mulvihill-Smith progeria-like syndrome in a 5-year-old boy and reviewed all the cases published previously. Because of its rarity, the mutation responsible for the Mulvihill-Smith syndrome was not identified; therefore, the diagnosis was purely clinical. Moreover, there is no indication of sleep problems in the other seven cases reported in the literature or sleep recordings; even the simple EEG recording was not reported in these patients.

We report here a 25-year-old woman with the Mulvihill-Smith syndrome who was referred to us for her excessive
daytime sleepiness, severe nocturnal insomnia and movement disorder during the night.

CASE REPORT

The patient was a 25-year-old woman born from non-consanguineous parents who have also a 29-year-old healthy son. Pregnancy and delivery were uneventful; psychomotor development is reported as normal and the patient had successfully completed high school. During the school period, at the age of 6–7 years, the parents noticed growth delay and relapsing respiratory system infectious episodes.

At 10 years of age, pigmented lesions affecting trunk and limbs were first noticed; because of her growth delay, a series of hospital controls were performed between the ages of 10 and 13 years during which bone age was reported as being 2 years older than her actual age and a diagnosis of 'deficit of growth hormone (GH)' was also posed. For this reason the patient started synthetic GH therapy with very scarce effects on her growth rate.

Menarche occurred at 14 years of age while respiratory tract infections continued to relapse and the pigmented lesions progressively increased in number over the trunk and limbs. At 20 years of age, bilateral sensory neural hearing impairment developed and, 2 years later, she underwent surgical removal of the left part of her tongue because of the occurrence of squamous cell carcinoma; for this reason, radiotherapy was performed. This caused an involvement of her verbal skills and speech became poorly intelligible.

At 24 years of age, a new surgical intervention was carried out on her nose sept because of a chronic obstructive nose pathology and two pigmented lesions were removed, one from her back and the other from her left gluteus. Menopause occurred at the age of 24 years.

At the moment of our observation, the patient showed rounded face with atrophic skin, scarce subcutaneous adipose tissue, in the inferior part of her face, deep-set eyes, narrow nasal bridge, and retragnathia. Pigmented lesions were more numerous over her trunk skin (Fig. 1a) than over her limbs. The patient stature was 135.8 cm (<3rd centile), weight was 33.5 kg (<3rd centile); karyotype was 46, XX without chromosomal abnormalities. Laboratory blood tests showed the presence of microcytic anemia and decreased levels of IgG (400 mg dL\(^{-1}\); normal range 800–1800), IgA (50 mg dL\(^{-1}\); normal range 90–400), and \(\gamma\)-globulins (0.6 mg dL\(^{-1}\); normal range 0.9–1.4). Chest X-rays showed chronic bronchitis, congested hilum and occluded right costal-phrenic sinus. Different X-rays and ultrasound exams only disclosed a left double ureter. No cardiovascular system abnormalities were found while her eyes were both affected by hypermetropic astigmatism, ambylophic amblyopia, and posterior cortical cataract. A routine ECG recorded during wakefulness showed sinusal rhythm and was reported as normal by the cardiologist.

At neurological clinical examination the patient was found not to be well oriented in time, her gait was slightly ataxic with lateral oscillations and tendency to deviate towards the right side; fine postural tremor of both hands was also noticed. MRI scans were obtained from a 0.5 tesla superconducting magnet, Philips Gyrosan MR which only showed mild enlargement of the cortical sulci (Fig. 1b). A multisection spin-echo sequence (proton density, TR 1850 ms, TE 30 ms and T2-weighted, TR 1850 ms, TE 90 ms) was performed in the axial and coronal planes, and a multisection T1-weighted sequence (TR 520 ms, TE 30 ms) in the sagittal plane centered at the midline. The section thickness was 5 mm, with a gap of 1 mm between adjacent sections. Routine EEG was uninformative because of the poor collaboration of the patient.

Neuropsychological testing disclosed the presence of mild cognitive impairment and depression; a score of 20 (normal
values $\geq 24$) was obtained at Mini Mental State Evaluation (Folstein et al., 1975) and of 56 at the Wechsler Adult Intelligence Scale-Revised Performance (Wechsler, 1981). The patient also showed poor social interactions, sometimes agitation, and poor communication skills (gestural communication). The voice appeared to be high-pitched. The particular picture shown by the patient with a senile-like aspect, peculiar face, short stature, microcephaly, sensory neural hearing impairment, diffuse pigmented skin lesions and immunologic abnormalities allowed us to make the diagnosis of Mulvihill-Smith syndrome.

Excessive daytime sleepiness was noticed since the age of approximately 7 years but was mild and did not interfere with the normal activities until 24 years of age, 1 year before our observation, when it started to worsen gradually, with irresistible sleep attacks in the last 2 months.

After our observation, the clinical picture continued to worsen progressively and the patient started to show daytime fluctuations of her level of confusion and alertness with visual hallucinations. Finally, the patient died at the age of 26 years and 2 months.

**Neurophysiological recording**

The patient, who was drug-free at the time of our study and a few months before, underwent two overnight video-polysomnographic recordings which comprised EOG (two channels), EEG (F3, C3, and O1 referred to A2), EMG of the submentalis muscle, ECG, oronasal airflow with thermistors, chest and abdominal movements, and EMG of the right and left deltoids and tibialis anterior muscle. Peripheral oxygen saturation was not recorded because the patient detached the sensor soon after its placement. Both recordings were carried out using a Brain Quick Micromed System 98 recording machine and signals were sampled at 256 Hz and stored on hard disk for further analysis, synchronized with the video recording. EEG signals, in particular, were digitally band-pass filtered at 0.1–70 Hz, 12-bit A/D precision.

These video-polysomnographic recordings showed the absence of clear sleep episodes; most of the time was spent by the patient in a state with closed eyes, desynchronized EEG activity, presence of eye movements similar to those recorded during wakefulness, irregular breathing, heart arrhythmia and afinalistic movements of the upper limbs and hands (Fig. 2) which often simulated the movements needed to button up a shirt. More rarely, some short episodes were noticed, lasting for approximately 1 min, which were characterized by some slow-waves mixed with desynchronized EEG activity, low chin muscle tone, presence of slow eye movements, heart arrhythmia, regular breathing and absence of motor activity at the four limbs, during which the patient seemed to have poor contact with the environment (Fig. 3). Finally other short

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**Figure 2.** Video-polysomnographic recording showing desynchronized EEG activity, presence of eye movements similar to those recorded during wakefulness, irregular breathing, heart arrhythmia and afinalistic movements of the upper limbs and hands.
periods were noticed characterized by the presence of a periodic respiratory pattern characterized by the regular occurrence of central apnea episodes, heart rate arrhythmia, desynchronized EEG activity, high chin muscle tone and presence of rapid eye movements (Fig. 4); also during these episodes the patient seemed to have poor contact with the environment and stereotyped afinalistic movements of the upper limbs and hands.

The patient seemed to have sleep mentation associated with the motor activity during sleep with various content; however, because of her tongue postsurgical abnormalities and her cognitive status it was difficult to obtain a detailed description. Even the words pronounced during sleep were poorly intelligible. The different sleep stages detected (Figs 2–4) are described in Table 1 and their distribution (hypnogram) throughout the night is shown in Fig. 5, in comparison with the hypnogram from a sex- and age-matched normal control. Figure 5 also displays the histogram of the delta band (0.5–4.5 Hz) which shows the absence of the normal slow-wave sleep-related peaks, evident in the histogram from the normal control.

**Genetic study**

The EDTA blood of the patient was obtained by venepuncture after overnight fasting and genomic DNA was extracted using a Nucleon BACC 3 Kit (Amersham Pharmacia Biotech, Milan, Italy). All extraction procedures were performed according to the manufacturer’s recommendations. The entire open-reading frame of the prion protein gene (PRNP) was amplified by the polymerase chain reaction (PCR) and sequenced as described previously (Windl et al., 1996). We found no mutations in the coding region of the PRNP gene and the genotype at codon 129 was homozygous for the amino acid methionine.

**DISCUSSION**

The Mulvihill-Smith syndrome is a rare entity and, to our knowledge, only seven cases have been reported previously (de Silva et al., 1997); Thus, our patient seems to be the 8th case reported so far.

Autosomal recessive inheritance was suspected in one previous patient (Ohashi et al., 1993) because of the consanguinity of the parents; however, the other cases reported in the literature and our patient seem to be sporadic. Chromosomal abnormalities have never been found in the Mulvihill-Smith syndrome and also the karyotype of our patient was normal. Thus, we must consider that, most probably, a new dominant mutation might be the genetic basis of this syndrome.

In the few reports available, a certain variability in clinical severity of the different symptoms and signs of this syndrome is evident such as growth delay, mental retardation, immuno-
deficiency, age at onset, and sensory neural hearing loss, all of variable entity (de Silva et al., 1997).

Sleep problems have never been clearly reported and it is difficult to understand if they were not present or if, simply, they were not detected. Our clinical and neurophysiological study seems to indicate that a particular condition of sleep disruption (Montagna and Lugaresi, 2002), similar to some extent to the sleep alterations usually found in the fatal familial insomnia (Lugaresi et al., 1986) and in the Morvan fibrillary chorea (Josephs et al., 2004; Montagna and Lugaresi, 2002; Morvan, 1890), might be associated with the Mulvihill-Smith syndrome.

Fatal familial insomnia is caused by a mutation in the PRNP gene causing the substitution of asparagine for aspartic acid at codon 178, in conjunction with the methionine at polymorphic codon 129 (Gambetti et al., 1995). The contemporary presence of the dominant D178N mutation and the substitution of a valine at position 129 causes a dementing phenotype, the familial Creutzfeldt–Jakob disease, characterized by diffuse spongiosis and widely distributed pathogenic isoform of the prion protein (Goldfarb et al., 1992). Only a difference in size of the pathogenic isoform of the prion protein accounts for the different clinical characteristics of the familial

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### Table 1. Characteristics of the different sleep stages identified in the polysomnographic recording

<table>
<thead>
<tr>
<th>Stage</th>
<th>A (Fig. 2)</th>
<th>B (Fig. 3)</th>
<th>C (Fig. 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact</td>
<td>Normal</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Limb movements</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Eyes</td>
<td>Open or closed</td>
<td>Closed</td>
<td>Closed</td>
</tr>
<tr>
<td>EEG</td>
<td>Desynchronized</td>
<td>Desynchronized, mixed slow waves</td>
<td>Desynchronized</td>
</tr>
<tr>
<td>EOG</td>
<td>REM</td>
<td>Slow</td>
<td>REM</td>
</tr>
<tr>
<td>Chin EMG</td>
<td>+ +</td>
<td>Decreased</td>
<td>+ +</td>
</tr>
<tr>
<td>Respiration</td>
<td>Irregular</td>
<td>Regular</td>
<td>Central apnea</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Irregular</td>
<td>Irregular</td>
<td>Irregular</td>
</tr>
<tr>
<td>Duration [min (%)]</td>
<td>154 (38.1%</td>
<td>93.5 (23.1%)</td>
<td>157 (38.8%)</td>
</tr>
</tbody>
</table>

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Creutzfeldt–Jakob disease and fatal familial insomnia (Monari et al., 1994).

Our patient showed clinical traits which might have been caused by similar genetic alterations; in particular, her type of sleep disruption was very similar to that reported in patients with fatal familial insomnia (Harder et al., 1999; Lugaresi et al., 1986; Spacey et al., 2004) while her cognitive status was characterized by progeria and early-onset dementia. For this reason, we also analyzed the PRNP gene which resulted to be normal; thus, the clinical picture of our patient could not be explained by mutations of this gene and the genetic basis of the Mulvihill-Smith syndrome remains unknown.

Figure 5. Sleep hypnogram and histogram of the delta band (0.5–4.5 Hz) from our patient and that of a sex- and age-matched normal control. Sleep stages of the patients have been indicated as described in Table 1.
As introduced above, the sleep abnormalities shown by our patients are also similar to those reported in the Morvan fibrillary chorea (Morvan, 1890), characterized by almost complete lack of sleep (agrypnia), lasting for weeks or months, and autonomic abnormalities consisting of profuse perspiration with characteristic skin miliaria, tachycardia, increased body temperature and hypertension (Josephs et al., 2004; Montagna and Lugaresi, 2002). In addition, these patients display a fluctuating hallucinatory behavior, peculiar motor disturbances, reported under the term of ‘fibrillar chorea’ by Morvan, cramps and myoclonic jerks.

Sleep abnormalities of patients with fatal familial insomnia, Morvan fibrillary chorea and delirium tremens have been grouped under Agrypnia excitata (Montagna and Lugaresi, 2002); we propose that the particular sleep disruption presented by our patient, characterized by absence of sleep spindles and K-complexes, complete loss of slow-wave sleep and probably abnormal REM sleep with lack of muscle atonia, can be interpreted with the same mechanism proposed for Agrypnia Excitata and based on a severe and progressive dysfunction of the thalamo-limbic system.

The disruption of the sleep structure we found in our patient was profound and we could only observe states which we could not classify following the usual criteria for sleep staging (Rechtschaffen and Kales, 1968). We believe that this severe alteration of sleep can be considered at least as one of the most important factors determining the cognitive decline observed in our patient. In fact, very important learning and cognitive processes take place during all sleep stages, probably in a differential and sequential manner (Ambrosini and Giuditta, 2001; Giuditta, 1994; Jouvet, 1998; Smith, 2001), for which sleep integrity is important and cognitive impairment evolved more abruptly, in our patient, after the worsening of her excessive daytime sleepiness, probably connected with the worsening of her nocturnal sleep. However, this correlation is highly speculative and should be regarded with caution.

Because of the rarity of this syndrome, it is difficult to know when a new case will be described in the future literature; the inclusion of a detailed study on the sleep characteristics of these patients will certainly help our understanding of this rare condition.

ACKNOWLEDGEMENTS

We thank Dr Rosario S. Spada and Dr Giuseppe Toscano for their valued help and advice.

REFERENCES


