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## Obstructive sleep apnea in a case of ehlers-danlos syndrome

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## ABSTRACT

Ehlers-Danlos Syndrome (EDS) is a group of rare connective tissue disorders characterized by genetic defects in collagen and connective tissue synthesis and structure, with manifestations ranging from asymptomatic or mild skin and joint hyperlaxity to severe physical disability.

Mild asymptomatic forms of Ehlers-Danlos syndrome seems to be under diagnosed and may have severe systemic complications mainly cardio vascular. Cartilaginous defects in the head and neck region increase the risk of Sleep-Disordered Breathing (SDB) especially Obstructive Sleep Apnea (OSA). It is well admitted now that OSA has many, frequently cardiovascular, adverse effects which are added to the risk of Ehlers-Danlos Syndrome's itself cardiovascular complications.

We report a case of EDS diagnosed since childhood with a long history of fatigue, daytime somnolence, snoring and unrefreshing sleep. Although the diagnosis of sleep apnea was suspected because of worsening of his symptoms ten years prior to his referral to our sleep laboratory, he was never investigated for Sleep-disordered breathing and was lost to follow up.

This case report relays what is stated in the literature regarding the association of SDB, mainly OSA, with EDS and its toll on the health of such individuals.

## 1. Background

Ehlers-Danlos Syndrome (EDS) is a group of connective tissue disorders with heterogeneous inherited, clinical and genetic characteristics. It involves a spectrum of genetic defects in collagen and connective tissue synthesis and structure, with multi systemic and variable clinical manifestations affecting primarily the skin, ligaments and joints, blood vessels and internal organs. It is part of the joint hypermotility syndrome, which includes several specific disorders as EDS, Marfan Syndrome (MFS), Osteogenesis Imperfecta and other rare syndromes [1].

This syndrome is clinically heterogeneous and had been classically divided into six types (classical, hypermobile, vascular, kyphoscoliotic, arthroclasis and dermatosparaxis) with the underlying collagen abnormality being different for each type. Since then, new diagnostic parameters became available and classification has evolved with description of new subtypes in recent years.

In 2017 a new international classification was proposed with 13 different subtypes transmitted through autosomal dominant or recessive genes [1]. The nine point Beighton scale helps to screen suspected cases of hypermobility.

*Abbreviations:* EDS, Ehler Danlos Syndrome; OSA, Obstructive Sleep Apnea; SDB, Sleep Disordered Breathing; MFS, Marfan Syndrome; ENT, Ear Nose Throat; CPAP, Continuous Positive Airway Pressure.

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Clinical manifestations vary from asymptomatic or mild skin and joint hyperlaxity to severe physical disability and life-threatening complications. Mild asymptomatic forms and Ehlers-Danlos syndrome (particularly the hypermobile type previously benign familiar hypermobile form: type III) seem to be under diagnosed and are the most common phenotypes. They should not be regarded as curiosities as they may have severe systemic complications. Symptoms are usually present in early childhood [2].

Cartilaginous defects including the nasal, maxillary cartilages, craniofacial abnormalities such as mandibular retrognathia, high arched palate, increased pharyngeal collapsibility, scoliosis or kyphosis and vocal cord abnormalities, increase the risk for Sleep-Disordered Breathing (SDB) particularly Obstructive Sleep Apnea (OSA) which in turn can be a risk for worsening of the cardiovascular conditions of these patients.

Prevalence of EDS, including all subtypes in the general population, is 1 for 5000, the EDS hypermobility type is the most common subtype with an incidence of 1 in 10 000 and 1 in 15 000. Prevalence is difficult to evaluate as it is directly related to physician awareness and changes in the classification hence varied among studies [3].

We report a case of EDS diagnosed since childhood with a long history of symptoms related to his disease associated with fatigue, daytime somnolence, snoring, unrefreshing sleep but who was never treated adequately or worked up for Sleep-Disordered Breathing (SDB).

We did a literature review about the OSA in EDS underlying the underdiagnosis of the association of these two disorders.

## 2. Case presentation

We report a case of a 50 years old male, nonsmoker, BMI: 27.2 Kg/m<sup>2</sup> referred by an ENT specialist because of excessive daytime sleepiness (the Epworth Sleepiness Score is 17), severe snoring worsened for the last year, with dizziness and morning headache. Sleep Apnea was clinically suspected by his treating physician at age 40, but was never worked up. However he was given, at that time, an autoCPAP treatment which he tried for few nights, did not tolerate it and was lost to follow up. His PMH is relevant for:

- Diagnosis of Ehlers-Danlos Syndrome since childhood (No details of the classification and the type were available),
- Recurrent joint dislocations,
- Recurrent injuries with fractures and recurrent surgeries.
- Hypotonic bladder with urethral stenosis necessitating multiple daily catheterizations,
- HTN, DL, GERD, chronic musculoskeletal pain,
- The Otolaryngology examination revealed a normal neck, no masses. The fiberoptic nasopharyngolaryngoscopy did not reveal any significant nasal obstruction, no nasopharyngeal lesions or collapse; the hypopharynx was normal, the tongue base was not particularly large and the Larynx revealed a normal epiglottis and bilaterally normally functioning vocal cords. There were no lesions or masses.

The patient underwent an attended, in lab, Polysomnography which showed a severe obstructive sleep apnea/hypopnea syndrome the AHI was 107 with severe Oxygen desaturation (O<sub>2</sub> saturation was below 90% during 16% of the sleep duration) and sleep fragmentation.

## 3. Discussion

Diagnosis of Ehlers-Danlos Syndrome relies mainly on clinical features. Because type 2: Mitis, skin, form and 3: Benign Familiar hypermobile form are the most frequent but mild and asymptomatic forms, they are often underdiagnosed if not searched for systematically by physicians with high degree of awareness [3,4].

Fatigue, daytime sleepiness, joint pain, dislocation and recurrent injuries, dizziness, chronic pain, anxiety, dysautonomia and phobic states are common symptoms of EDS and are considered by some as an overlap with chronic fatigue syndrome, they are also frequent symptoms in patients with sleep-disordered breathing (SDB).

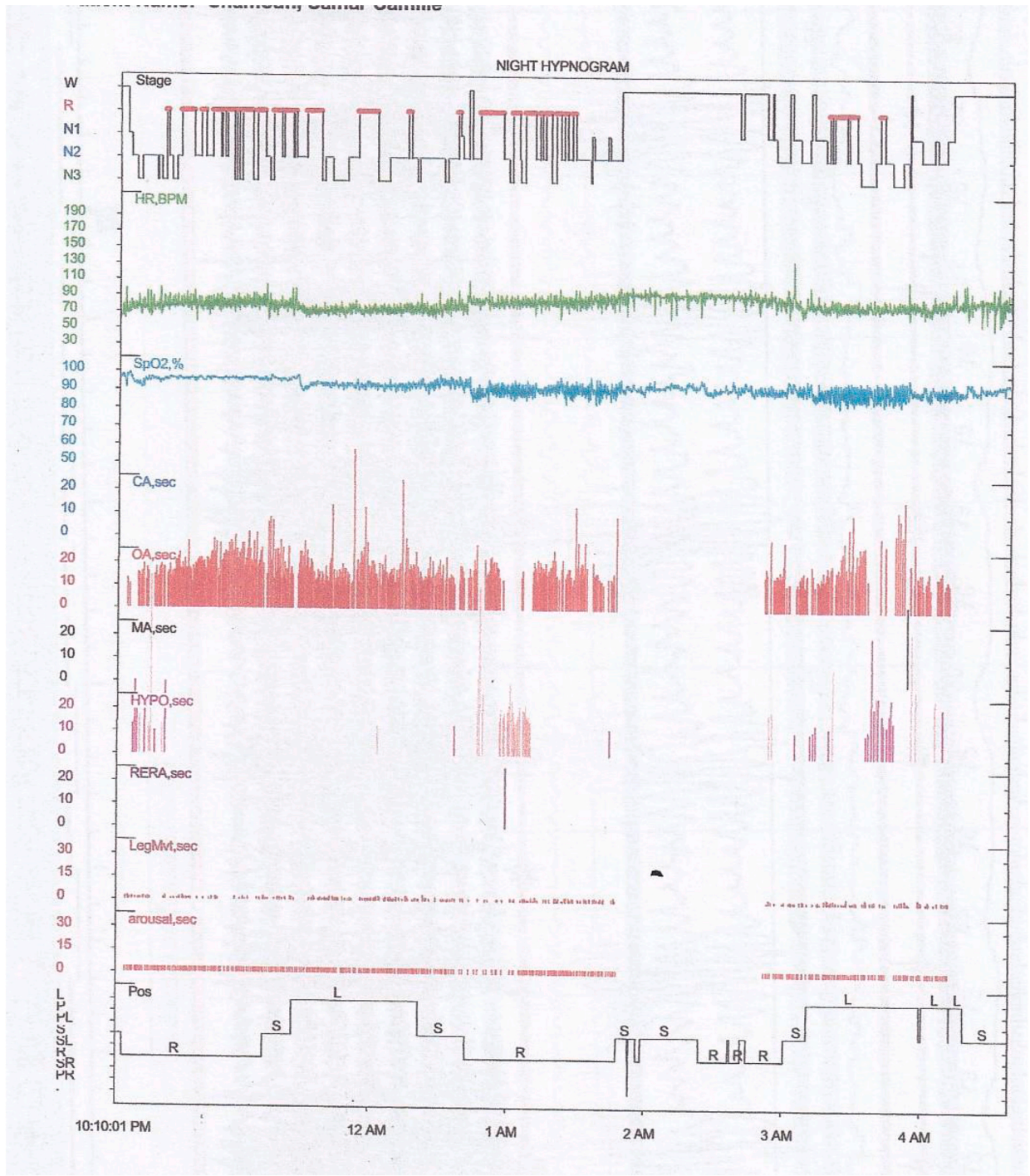
Research has focused on EDS and MFS and studies have shown that these patients with connective tissue disorders are at high risk to develop aortic aneurysms and cardio vascular complications [10].

Multiple studies have shown that untreated OSA can lead also to a variety of adverse effects mainly cardio vascular complications including aortic complications [5–10].

A recent meta-analysis [3] (Sedky K; J of clin sleep Med; 2019) on the prevalence of OSA in joint hypermotility syndrome showed that OSA in patients with EDS/Marfan syndrome (MFS) was underestimated: the prevalence of OSA among EDS patients was 39.4% and, when directly compared to the general population, they were on average 6 times more likely to have a diagnosis of OSA (OR: 6.28 [95% confidence interval: 3.31–11.93; p < 0.001])

Gaisl et al.; Thorax 2017 [4], evaluated the prevalence of OSA and QOL in a parallel cohort study of 100 EDS patients matched to healthy controls. They showed that 23% of these patients suffered from symptomatic OSAS compared to 3% of healthy controls.

An interesting study (Guilleminault C; Chest 2013 [11]) showed that: SDB were frequent not only in a referred sleep clinic population with EDS, but also in a sample of patients with EDS presenting for routine medical care in an internal medicine clinic: these patients had symptoms of fatigue, poor sleep and daytime sleepiness but they were never referred for evaluation of SDB. Moreover nasal CPAP treatment led to improvement of their complaints [13,15]. EDS may be a genetic model for OSA because of the craniofacial



growth abnormalities [12].

**In summary** these data suggest that the high prevalence of OSA in patients with EDS may contribute to the fatigue, daytime sleepiness, impaired QOL which are frequent complaints in these patients [14] and to significant adverse health outcomes such as worsening of vascular abnormalities. Robust data are now available about the cardiovascular adverse effects of OSA and about the treatment of OSA which successfully improve and prevent these adverse effects.

#### 4. Conclusion

This case illustrates the lack of awareness about EDS and its association with a high prevalence of OSA, despite the fact that they are frequently symptomatic. The above discussion highlights the importance of early diagnosis and treatment to improve symptoms, QOL and prevent adverse effects mainly cardio vascular. A high degree of awareness in the medical community is very important as the diagnosis of Ehlers-Danlos Syndrome relies mainly on clinical features. EDS may be a genetic model for OSA.

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#### Declaration of competing interest

The authors declare no conflict of interest.

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