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Acromegaly in sleep apnoea patients: a large observational study of 755 patients

To the Editor:

Acromegaly is a rare, chronic and progressive disease characterised by excess secretion of growth hormone with raised insulin-like growth factor I (IGF-I) levels and usually caused by a pituitary adenoma [1, 2]. Its prevalence is estimated at 40–480 cases per million, depending on the study [1, 3]. The diagnosis of acromegaly, frequently made late because of the insidious nature of the disease, is generally based on symptoms of excess growth hormone, such as acral enlargement, soft-tissue swelling, arthralgia, jaw prognathism, hyperhidrosis, osteoarthritis and frontal bossing, or symptoms of a pituitary adenoma, such as headaches, visual defects or pituitary insufficiency. Owing to prolonged untreated progression of the condition, patients often exhibit established systemic complications at diagnosis, such as diabetes mellitus (19–56%) [2], hypertension (30–40%) and respiratory/cardiac failure (60%) [4, 5], which are the main determinants of prognosis and premature mortality [1]. The majority of new diagnoses of acromegaly are detected by primary care physicians, or specialists other than endocrinologists. The therapeutic options for acromegaly include endoscopic surgery, medical therapies (long-acting somatostatin analogues; dopamine agonists; growth hormone receptor antagonists) and pituitary radiotherapy [6, 7]. 45–80% of acromegaly

patients have sleep apnoea syndrome (SAS) [4, 5], compared to 5% in the general population. Because of swelling of the uvula, macroglossia and maxillofacial modifications, obstructive sleep apnoea (OSA) is the prevailing form of SAS [8]. The combination of OSA and acromegaly increases the risk of systemic comorbidities and mortality [9]. The high prevalence of acromegaly-related comorbidities and its often late diagnosis [10], when valid treatment options exist, make screening for acromegaly in at-risk populations necessary. The OSA population might constitute a target group for the earlier detection of acromegaly, thereby preventing the late complications of the disease. Moreover, early treatment of acromegaly may favour the resolution of associated SAS. We prospectively assessed the prevalence of undiagnosed acromegaly in new patients suspected of suffering from OSA.

Between November 2013 and October 2014, we prospectively included adults referred for clinical suspicion of OSA to a tertiary teaching hospital or to one of 10 sleep clinics. All participants signed a written informed consent and the study was approved by the Grenoble Ethics Committee (CPP Sud-Est V, Grenoble, France; institutional review board number: 13-CHUG-37). During the baseline visit for suspected OSA, the Sleep registry of the French Federation of Pneumology (www.osfp.fr) was completed: sleep study results; Epworth Sleepiness Scale; fatigue and depression scales; medications; and pulmonary function test results. We also collected the clinical symptoms of acromegaly: acral enlargement; headache or visual field defects; facial changes; widely spaced teeth; diabetes; hyperhidrosis; arthralgia and/or arthritis; asthenia; menstrual disorders or galactorrhoea; carpal tunnel syndrome and acroparaesthesia; cardiovascular comorbidities (hypertension, diabetes); and prescribed lipid profile, fasting blood glucose and IGF-I tests. When serum IGF-I was elevated for age and sex, a new blood sample was requested and analysed for IGF-I level together with growth hormone monitoring during an oral glucose tolerance test (OGTT). If abnormal, patients were referred to an endocrinologist.

Assuming a prevalence of acromegaly of 0.04% in the general population [3] with a 10-fold higher prevalence in the OSA population, we needed 880 patients (risk α 0.10; margin of error±0.35). We actually included 873 patients: 817 had laboratory IGF-I measurements and 755 underwent sleep studies to diagnose SAS and determine its severity. The study population had a median (interquartile range) age of 53 (44–61) years, were overweight or obese (median body mass index 29.8 $kg \cdot m^{-2}$ (26.1±4.5)), predominantly male (63.9%) and had a median (interquartile range) apnoea–hypopnoea index (AHI) of 25.3 (15–41) $events \cdot h^{-1}$. OSA was confirmed in 567 patients (moderate-to-severe OSA, AHI $\geqslant$15 $events \cdot h^{-1}$).

Eight patients had IGF-I levels >110% of the expected values for age and sex, including four with normal growth hormone profile during OGTT. Two patients were diagnosed with acromegaly after consultation with an endocrinologist and in both cases magnetic resonance imaging revealed a pituitary macroadenoma. Both also had severe OSA. The overall prevalence of acromegaly in patients with suspected SAS was 0.25% (90% CI 0.05–0.93%). Among patients with confirmed OSA, the prevalence of acromegaly was 0.35% (90% CI 0.08–1.19%).

More than 50% patients (both confirmed OSA and others) reported at least three symptoms suggesting growth hormone/IGF-I hypersecretion (table 1). Hypertension, diabetes and facial changes were significantly more frequent in those with AHI $\geqslant$15 $events \cdot h^{-1}$. The prevalence of headaches and fatigue was very high in the whole study population but significantly higher in the non-OSA population, these symptoms being frequently reasons for referral to a sleep specialist.

Previous studies that screened for acromegaly in the general population [11], and in hypertensive [12], diabetic [3] or carpal tunnel syndrome patients [13] found similar results to ours. In patients with existing comorbidities, the only clinical indicators of acromegaly are obvious facial dysmorphism and enlargement of the extremities. This is reflected in the current guidelines for diagnosis that recommend IGF-I assays only in patients presenting typical acral and facial manifestations of acromegaly [7].

In view of the lack of compelling evidence supporting the value of systematic serum IGF-I measurement in the most commonly encountered comorbidities of acromegaly, the current consensus statement is relatively vague. It suggests "measurement of IGF-1 in patients without the typical manifestations of acromegaly, but who have several of these associated conditions: SAS, type 2 diabetes mellitus, debilitating arthritis, carpal tunnel syndrome, hyperhidrosis, and hypertension" [7]. The statement supports the use of a combination of signs, symptoms and comorbidities to screen for acromegaly but, to date, the exact cluster of comorbidities has not been validated.

Nevertheless, the at-risk OSA population seems one of the most promising for efficient screening of acromegaly. Our finding of an 8–30-fold increased prevalence of acromegaly in the OSA population compared to previously published data on other populations is explained by the fact that, over time, raised levels of IGF-I directly impact on craniofacial structures and swelling of soft tissues that are central to the pathophysiology of OSA. We recognise that the two patients diagnosed with acromegaly already exhibited

TABLE 1 Comparison of symptoms and clinical signs of acromegaly in non-OSA and moderate-to-severe OSA groups (with insulin-like growth factor I measurement and sleep studies)[#]

Symptoms/clinical signs of acromegaly	AHI <15 events·h^{-1}[¶]	AHI ⩾15 events·h^{-1}	OR (95% CI)	p-value
Patients	567	188	–	–
Enlargement of hands, increased ring size %	10.7	10.1	1.07 (0.61–1.88)	0.81
Enlargement of feet, increased shoe size %	7.6	8.4	1.23 (0.65–2.31)	0.52
Arterial hypertension %	30.1	43.1	1.86 (1.30–2.68)	0.001
Headache, visual field defects %	36.3	22.1	0.54 (0.38–0.79)	0.001
Facial changes, macroglossia %	11.9	19.3	1.80 (1.05–3.08)	0.032
Widely spaced teeth %	9.9	8.2	0.82 (0.45–1.47)	0.50
Diabetes mellitus %	3.7	8.8	2.96 (1.30–6.73)	0.010
Sweats, hyperhidrosis %	54.8	53.8	0.91 (0.64–1.28)	0.57
Joint pain, arthralgia %	42.2	42.7	1.32 (0.92–1.88)	0.13
Fatigue/asthenia %	76.1	69.3	0.66 (0.45–0.98)	0.038
Carpal tunnel syndrome, acroparaesthesia %	26.4	23.5	0.87 (0.59–1.30)	0.51
⩾3 symptoms and comorbidities %	56.7	56.6	1.07 (0.74–1.56)	0.71

[#]: n=755; [¶]: the non-OSA group consisted of the patients referred for suspicion of sleep apnoea syndrome, but with a diagnosis of no or only mild OSA (AHI <15 events·h^{-1}). AHI: apnoea–hypopnoea index; IGF-I: insulin-like growth factor I; OSA: obstructive sleep apnoea.

facial and acral dysmorphism. Such a small number of cases with typical acromegaly did not allow us to address the true challenge: detecting the very early phase of the disease. Not only would early diagnosis of acromegaly prevent irreversible comorbidities and facilitate surgical cures, but it would also permit the normalisation of OSA thereby avoiding long-term continuous positive airway pressure treatment. Trans-sphenoidal surgery and long-acting somatostatin analogues [8] are associated with a significant improvement in OSA severity, although up to 40% of those with cured or controlled acromegaly continue to exhibit significant OSA.

The level of awareness and training of sleep specialists and respiratory physicians needs to be improved to enable them to recognise the typical acromegaly phenotype in routine practice, so as to indicate an IGF-I measurement. In France, to measure IGF-I in 1000 patients would cost about USD 33 000. If IGF-I screening permitted early diagnosis of acromegaly leading to a complete surgical cure, the cost-saving for society would be considerable (cost of surgery *versus* lifetime somatostatin analogue monotherapy: USD 15 216 and USD 1 938 000, respectively) [14]. The justification for more general screening, especially in the absence of the typical phenotype, requires well-conducted, cost-effectiveness studies.

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Among patients with confirmed obstructive sleep apnoea the prevalence of acromegaly was 0.35%
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Introduction of the 13-valent pneumococcal conjugate vaccine in an isolated pneumococcal vaccine-naïve indigenous population

To the Editor:

The introduction of pneumococcal conjugate vaccines (PCVs) has the greatest impact in populations that are most affected by pneumococcal carriage and disease, such as indigenous children [1]. Although ∼10% of the South American population consists of indigenous people living in remote settings, to our knowledge PCVs have not been evaluated in native South American children. The Warao people are an Amerindian population residing in wooden houses along the Orinoco River delta in Venezuela. Almost one-third of Warao children die during childhood and respiratory tract infections are a major cause of death [2]. This study is the first to evaluate the impact of 13-valent (PCV13) vaccination on nasopharyngeal colonisation rates and antibody response in PCV-naïve indigenous South American children.

From May to November 2012, 504 Warao children aged 6 weeks to 59 months residing in nine communities were vaccinated. Before and at a median 6.7 weeks after primary PCV13 series we obtained nasopharyngeal swabs (n=424) and serum samples (n=421). The primary series consisted of three vaccine doses for children