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High prevalence of severe sleep cycle disruption in *de novo* acromegaly and underdiagnosis by common clinical screening tools: A prospective, observational, cross-sectional study

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Abstract

Context: Although sleep disordered breathing (SDB) is well-recognised in acromegaly, most studies have reported heterogeneous, often heavily treated, groups and few have performed detailed sleep phenotyping at presentation.

Objective: To study SDB using the gold standard of polysomnography, in the largest group of newly-diagnosed, treatment-naïve patients with acromegaly.

Setting and Patients: 40 patients [22 males, 18 females; mean age 54 years (range 23–78)], were studied to:

(i) establish the prevalence and severity of SDB

(ii) assess the reliability of commonly employed screening tools [Epworth Sleepiness Scale (ESS) and overnight oxygen desaturation index (DI)] to detect SDB

(iii) determine the extent to which sleep architecture is disrupted.

Results: Obstructive sleep apnoea (OSA), defined by the apnoea-hypopnoea index (AHI), was present in 79% of subjects (mild, $n = 12$; moderate, $n = 5$; severe, $n = 14$). However, in these individuals with OSA by AHI criteria, ESS (positive in 35% [$n = 11$]) and DI (positive in 71%: mild, $n = 11$; moderate, $n = 6$; severe, $n = 5$) markedly underestimated its prevalence/extent. Seventy-eight percent of patients exhibited increased arousal, with marked disruption of the sleep cycle, despite most (82%) having normal total time asleep. Fourteen patients spent longer in stage 1 sleep. Deeper sleep stages were severely attenuated in many subjects (reduced stage 2, $n = 18$; reduced slow wave sleep, $n = 24$; reduced rapid eye movement sleep, $n = 32$).

Conclusion: Our study provides strong support for clinical guidelines that recommend screening for sleep apnoea syndrome in patients with newly-diagnosed acromegaly. Importantly, however, it highlights shortcomings in commonly recommended screening tools (questionnaires, desaturation index) and

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demonstrates the added value of polysomnography to allow timely detection of obstructive sleep apnoea and associated sleep cycle disruption.

KEYWORDS
acromegaly, arousal index, polysomnography, sleep apnoea, sleep stages

1 | INTRODUCTION

Sleep disordered breathing (SDB), and in particular obstructive sleep apnoea (OSA), is a common finding in the general population, especially in overweight and obese subjects. It can result in impaired quality of life, with excessive daytime somnolence affecting 2% and 4% of middle-aged women and men respectively.[1,2] OSA is associated with metabolic and cardiovascular dysfunction, and has been independently linked to an increased risk of type 2 diabetes, dyslipidaemia, hypertension, cardiac failure, and possibly osteoporosis.[3–6]

Obstructive sleep apnoea is a common finding in acromegaly, affecting more than two thirds of patients, as reported in both prospective and retrospective studies.[7,8] It has been variably attributed to: increased craniofacial, pharyngeal and laryngeal soft tissue thickening,[9] facial skeletal abnormalities,[9] neuromuscular defects of the pharyngeal muscles,[9] co-existent obesity,[8] and thyroid dysfunction.[10] In contrast, central sleep apnoea is rare, and has been postulated to be a consequence of continuous exposure of central respiratory centres to elevated growth hormone (GH) and insulin-like growth factor-1 (IGF1) levels, as well as an increased ventilatory threshold for carbon dioxide.[11]

Untreated acromegaly is associated with increased cardiovascular morbidity and mortality, which is potentially exacerbated by the coexistence of OSA.[12,13] Importantly however, control of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) hypersecretion does not always correlate with reversal/resolution of sleep apnoea; many patients exhibit an overall improvement, but up to 40% still manifest OSA despite good biochemical control of their acromegaly.[9,14–16] In view of this, independent assessment for sleep disordered breathing is recommended.[17]

Although several studies have evaluated SDB in acromegaly, most groups of patients studied have been heterogeneous, often including subjects who have undergone one or more primary treatment interventions (pituitary surgery, radiotherapy and/or medical therapy). Surprisingly few studies have focussed on treatment-naïve patients,[7,18] and the primary method used to assess sleep apnoea has varied across studies, with only a small subset utilising the gold-standard of polysomnography. Furthermore, disturbance of sleep architecture (i.e., disruption of the normal stages of the sleep cycle) has been largely overlooked, which is a potentially important oversight given its suggested independent association with cardiovascular and metabolic dysfunction.[19–23]

Here, we report the largest and most comprehensive study to date of SDB in newly-diagnosed acromegaly. The performances of two screening tests, the Epworth Sleepiness Scale (ESS) questionnaire and overnight pulse oxygen desaturation index (DI), have been compared with the gold standard polysomnography. ESS screening demonstrates clinical variability in sleep apnoea studies in the general population and is not considered an ideal tool to prioritise sleep apnoea assessment, owing to its unreliability.[24–26] However, recent consensus guidelines on screening for sleep disordered breathing in acromegaly continue to suggest the ESS as a screening tool, before considering polysomnography.[27,28] Our study explores whether use of ESS has a similarly unreliable performance in SDB in newly-diagnosed acromegaly. We also provide a detailed analysis of sleep architecture in untreated acromegaly. Finally, a summary of previous studies that have assessed sleep in acromegaly is presented for comparison with our findings.

2 | PATIENTS AND METHODS

2.1 | Patients

Sequential patients with acromegaly referred to our university teaching hospital between March 2004 and July 2013 were invited to participate in the study. Patients who had received prior medical therapy, surgery or radiotherapy, or had sight-threatening tumours requiring urgent surgical decompression were excluded. 40 consecutive patients were recruited: 18 female, 22 male; mean age 54 year, range 23–78 year. No eligible patient declined entry, and all participants provided signed informed consent. Acromegaly was diagnosed on the basis of clinical features, failure to suppress serum GH concentrations to <0.4 mcgg/L after a 75 g oral glucose load, and elevated fasting IGF-1 (above the age- and sex-matched reference range [RR]). Limited data for a subset of this study group have previously been reported as part of a study examining the effects of pre-surgical somatostatin analogue therapy on radiological and biochemical parameters and the extent of comorbidity in acromegaly. This study is a secondary data analysis expanding from a previous single arm open label clinical trial.[16]

2.2 | Study protocol

All assessments were performed at initial diagnosis of acromegaly. Anthropometric measures included body mass index (BMI), and neck and waist circumference. Mean GH levels (GH_{mean}) during a day curve (GHDC) were determined from eight to 10 samples drawn at hourly intervals between 0800 and 1700 h. IGF-1, free thyroxine (FT4), thyrotropin (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (males), oestrogen (females), prolactin

and cortisol (pre- and 30 min post-250 μg Synacthen®) were measured on serum/plasma samples collected at 0900 h following an overnight fast. IGF-1 levels are shown as × upper limit of normal (×ULN).

2.3 | Biochemical measurements

Serum and plasma were stored at −20°C pending assay. All analytes were measured by a United Kingdom Accreditation Service (UKAS) laboratory with relevant internal and external quality assurance. Serum GH concentration was measured using a solid phase two-site time-resolved fluorometric assay (DELFIA®, PerkinElmer Life and Analytical Sciences Inc., Waltham, Massachusetts, USA) calibrated to IS 98/574 (analytical sensitivity 0.01 ng/ml; interassay coefficient of variation <5% across the range 0.025–25 ng/ml). Serum samples giving GH higher than this were diluted with zero standard as provided by the manufacturer. Serum IGF-1 was measured using a solid-phase enzyme labelled chemiluminescent immunometric assay (Siemens Immulite2000®—Siemens Medical Solutions Diagnostics Ltd., Llanberis, Gwynedd, UK) calibrated to IS 87/518 (analytical sensitivity 20 ng/ml; interassay coefficient of variation <10% across the range 25–1600 ng/ml).

Thyrotropin (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin were measured by two-site chemiluminescent immunometric assays using a Siemens Centaur® immuno-analyzer (Siemens Healthcare, Surrey, UK) with protocols and reagents provided by the manufacturer. Serum free thyroxine was measured using a one-step chemiluminescent analogue method on the Centaur® immuno-analyzer using reagents provided by the same manufacturer. Testosterone and cortisol were measured by competitive chemiluminescent immunoassay also using the Centaur®. Oestrogen was measured by competitive immunoassay on the Perkin-Elmer DELFIA® immunoanalyser (Waltham, MA, USA) using protocols and reagents provided by the manufacturer.

2.4 | Polysomnography

Subjects completed the Epworth sleepiness scale (ESS), a well-validated screening questionnaire designed to detect excessive daytime somnolence as an indicator of symptomatic underlying obstructive sleep apnoea.[29] Polysomnography was then performed with all sleep studies undertaken in the sleep laboratory at the Respiratory Support and Sleep Centre, Papworth Hospital, Papworth, UK. Data were recorded using the Embla® S7000 Recording System and analysed using Embla REMbrandt® software (Natus Neurology, Denver, USA). The recording montage for each study included C3-A1 and C4-A2 electroencephalogram derivations, bilateral electro-oculogram channels and submental EMG recordings. In addition, bilateral anterior tibialis EMG overnight recordings were made. The respiratory recordings included body position, chest and abdominal respiratory movements, pulse oximetry, snoring sensor and oral/nasal airflow. Synchronised video recordings were also performed. Studies were set up during the evening before data acquisition and signals were checked for quality. Participants were advised to switch their light out at their usual time and wake up times were dictated by their own natural sleep pattern. EEG arousal scoring was completed according to the recommendations of the Atlas Task Force of the American Sleep Disorders Association.[30]

Standard sleep variables and quality indices were assessed.[31,32] These included sleep latency, total sleep time (sleep period time [SPT], and time in bed [TIB]), sleep efficiency, apnoea-hyponoea index (AHI), arousal index (AI), periodic limb movements (PLMs) and the percentage and duration of different sleep stages (1, 2, slow wave sleep [SWS], rapid eye movement [REM]). Respiratory event marking was performed in line with guidance from the American Academy of Sleep Medicine Task Force.[33] The following criteria were used to ascertain the AHI score: apnoea (cessation of oronasal airflow ≥10 s) and hypopnoea (decrease in airflow of ≥50% for 10 s, associated with arousals and/or a decline in oxygen saturation of 3%). Severity of sleep apnoea was defined as follows: mild, AHI score 5–14/h; moderate, AHI score 15–29/h; severe, AHI score ≥30/h). Apnoea characteristics were determined from thoracic or abdominal movements (central, obstructive or mixed). Sleep stages were classified using Rechtschaffen and Kales 1968 sleep staging criteria.[34] Periodic limb movements (PLMs) were defined as the occurrence of ≥4 consecutive limb movements at intervals of 5–90 s and duration of 0.5–5 s, predominantly during light non-REM (NREM) stages 1 and 2. PLMs <5/h were considered to be normal.

2.5 | Study ethics

The study was approved by the Cambridgeshire Research Ethics Committee, and has been assigned the International Standard Randomised Controlled Trial Number: ISRCTN20365485. (Cambridge Local Research Ethics Committee: Ref 03/354; 09 Dec 2003).

3 | RESULTS

Patient characteristics at diagnosis are shown in Table 1. The median GH_{mean} level was 7.93 mcg/L (interquartile range [IQR] 5.27 to 16.44) and median IGF-1 ×ULN level was 3.41 (IQR 2.42 to 4.73). Estimated duration of acromegaly ranged from <1 year to >10 years (Table 1). Five of 18 females and eight of 22 males had a BMI ≥ 30 kg/m^2. Partial anterior hypopituitarism was present in 14 subjects, and comprised hypogonadism (n = 13) and hypoadrenalism (n = 3). Two patients had both deficiencies. One asymptomatic patient was diagnosed with coexistent Graves' hyperthyroidism. Comparison of acromegaly patients with OSA (n = 31) and without OSA (n = 8) showed significant differences in age and baseline hypogonadism (Table 2). However, there were no significant differences in BMI, waist circumference and neck circumference, duration of acromegaly, presence of macroadenoma, diabetes/IGT, mean GH or IGF-1(×ULN) (Table 2).

TABLE 1 Patient characteristics at study entry.

Subject	Age (yr)	Sex	BMI (kg/m^2)	WC (cm)	NC (cm)	Smoking status	Glycaemic status	Estimated acromegaly duration (yr)	Pituitary MRI findings	GH_{mean} (mcg/L)	IGF1 (×ULN)	Baseline pituitary deficits	AHI (episodes/h)
Females													
1	66	F	29.7	88	38	NS	-	10	ES	8.34	3.90	-	19.5
3	65	F	27.8	95	39	NS	IGT	unknown	Macro^2	22.32	4.10	-	13.9
4	68	F	25.9	84	37	ExS	T2DM	>5	Macro^1	30.79	5.97	-	12.5
6	75	F	34.1	98	42	ExS	-	>10	Micro	13.47	5.58	-	45.4
7	49	F	25.4	81	33.5	NS	-	2	Macro^1	9.79	2.42	-	18.7
8	76	F	26.5	77	39	NS	T2DM	unknown	Micro	5.16	1.84	-	17.4
13	74	F	23.7	75	34	NS	-	2	Macro^1	4.38	2.98	-	4.9
17	57	F	24.2	77	35	ExS	-	unknown	Macro^1	19.12	5.53	-	na
19	43	F	29.3	91	37	NS	-	>5	Macro^2	9.80	5.93	-	21.8
20	51	F	26.7	92	41	S	-	>5	Micro	3.32	2.42	-	0.8
21	30	F	30.6	94	40	NS	-	5	Macro^2	40.00	3.57	A	0.6
25	68	F	38.5	122	45	NS	-	1-2	Micro	3.05	5.10	-	53.4
27	51	F	34.1	94	42	NS	-	5	Macro^1	5.69	3.24	-	12.1
29	48	F	20.9	77	35	S	-	3	Macro^1	45.26	2.09	-	6.6
30	23	F	30.0	87	34.7	NS	-	0.5	Macro^2	3.74	1.97	Gn	2.1
32	49	F	22.6	75.5	34.5	NS	IGT	10	Macro	6.6	2.32	-	5.7
33	63	F	28.4	96	37.5	NS	T2DM	2	Micro	6.26	1.66	-	31.9
39	56	F	26.2	78	36.4	NS	T2DM	5	Macro	15.54	2.82	-	6.8
Males													
2	39	M	31.3	97	33.5	S	-	unknown	Macro^2	7.53	4.93	A, Gn	32.2
5	78	M	30.8	120	43	ExS	IGT	>5	Macro^2	8.86	5.65	A, Gn	58.6
9	61	M	28.8	93	44	S	T2DM	unknown	Macro^2	37.28	3.02	-	8.24
10	66	M	32.2	107	43	ExS	-	unknown	Micro	3.34	3.10	-	44.5
11	64	M	29.0	99	43.5	NS	T2DM	unknown	Macro^2	38.22	3.86	Gn	46.4
12	29	M	30.4	94	41.5	NS	-	unknown	Macro^1	20.59	3.61	Gn	4.5
14	40	M	28.6	96	43	NS	T1DM	unknown	Macro^1	7.18	2.33	Gn	1.0
15	58	M	30.3	111	44	NS	T2DM	3	Micro	7.30	4.70	Gn	34.9
16	54	M	27.4	99	40	ExS	T2DM	>5	Macro^1	6.13	2.59	-	7.9
18	46	M	30.0	98	45	NS	IGT	7	Macro^1	5.31	4.03	Gn	11.3
22	52	M	25.3	90	42	S	-	>5	Macro^1	11.37	2.42	-	12.5
23	76	M	27.3	105	41	ExS	T2DM	5	Macro^2	237.44	9.06	-	24.2
24	56	M	30.0	102	42	NS	-	4	Micro	10.24	4.70	Gn	44.4
26	66	M	25.8	93	41	S	-	0.5	Micro	4.19	1.80	-	10.5
28	46	M	23.1	87	41	S	-	>10	Macro^1	13.75	4.20	-	63.2
31	47	M	30.0	115	47	NS	-	>10	Macro	2.25	3.73	Gn	45.0
34	60	M	34.0	115	43.5	S	-	unknown	Macro	6.6	2.44	Gn	47.4
35	23	M	26.9	90	42.5	NS	-	6	Macro	9.52	2.62	-	8.5
36	48	M	24.7	99	40	NS	-	5	Macro	2.6	2.94	Gn	4.3

TABLE 1 (Continued)

Subject	Age (yr)	Sex	BMI (kg/m^2)	WC (cm)	NC (cm)	Smoking status	Glycaemic status	Estimated acromegaly duration (yr)	Pituitary MRI findings	GH_{mean} (mcg/L)	IGF1 (×ULN)	Baseline pituitary deficits	AHI (episodes/h)
37	44	M	23.0	86	36.5	NS	-	>10	Macro	2.87	2.08	Gn	3.1
38	64	M	27.2	94	42	ExS	IGT	5	Macro	6.12	5.51	-	60.3
40	45	M	30.5	na	na	ExS	-	>5	Macro^2	34.8	4.81	- (*)	68.3

Abbreviations: A, adrenocorticotrophic hormone deficiency; AHI, apnoea-hypopnoea index; BMI, body mass index; ES, empty sella; ExS, ex-smoker; F, female; GH, growth hormone; Gn, gonadotrophin deficiency; IGF-1, insulin-like growth factor 1; IGT, impaired glucose tolerance; M, male; Macro^1, maximum tumour diameter <2 cm and no parasellar extension; Macro^2, maximum tumour diameter >2 cm and/or parasellar extension; Micro, microadenoma; MRI, magnetic resonance imaging; na, not available; NC, neck circumference; NS, never smoked; S, current smoker; T2DM, type 2 diabetes mellitus; WC, waist circumference.

*signifies patient with coincidental Graves' disease.

TABLE 2 Baseline characteristics according to presence or absence of OSA.

Baseline Characteristics	Patients with OSA (n = 31)	Patients without OSA (n = 8)	p-Value
Age (years)	57.35 ± 12.4	42.38 ± 16.1	.007
Gender (n, %)			
Male	18 (58.1)	4 (50.0)	.709
Female	13 (41.9)	4 (50.0)	
BMI (kg/m^2)	28.69 ± 3.7	27.21 ± 3.1	.306
WC (cm)	95.72 ± 12.5	90.38 ± 7.6	.261
NC (cm)	40.46 ± 3.6	38.84 ± 3.3	.259
Smoking status (including Ex-smokers and current smokers) (n, %)	15 (48.4)	1 (12.5)	.109
IGT/diabetes mellitus (n, %)	14 (45.2)	1 (12.5)	.121
Acromegaly duration (yr)	5 (3.5 to 6.5)	5 (2 to 5)	.532
Pituitary macroadenoma (n, %)	23 (74.2)	7 (87.5)	.653
GH_{mean} (mcg/L)	8.86 (6.1 to 15.5)	4.06 (3.1 to 13.9)	.095
IGF-1 (×ULN)	3.88 ± 1.6	2.74 ± 0.6	.064
Baseline hypogonadism (n, %)	8 (25.8)	6 (75.0)	.016
ESS ≥ 11 (n, %)	10 (34.5)	3 (42.9)	.686

Note: All quantitative variables are expressed in mean ± SD or median with interquartile range and all categorical values are represented as frequencies and percentage.

Abbreviations: BMI, body mass index; ESS, Epworth sleepiness scale; GH, growth hormone; IGF-1, insulin-like growth factor 1; IGT, impaired glucose tolerance; NC, neck circumference; OSA, obstructive sleep apnoea; ULN, upper limit of normal; WC, waist circumference.

3.1 | Prevalence of sleep apnoea and comparison of ESS and DI with polysomnography

Sleep apnoea (SA) was a common finding with 31 of 39 patients (79%) exhibiting an AHI ≥ 5 episodes/h on polysomnography (no AHI data were available for one female subject due to a technical failure) (Figure 1A). Twelve patients (31%) had mild SA (5–14 episodes/h), five (13%) had moderate SA (15–29 episodes/h), and fourteen (36%) had severe SA (≥ 30 episodes/h). In contrast, using DI as a screening test only 22 of the 31 (71%) patients with SA according to AHI criteria were identified as having SA (Figure 1B). Stratifying these by severity, eleven patients (27.5%) had mild SA (5–14 episodes/h), six (15%) had moderate SA (15–29 episodes/h) and just five (12.5%) had severe SA (≥30 episodes/h). Therefore, DI markedly underestimated the extent of SA when compared with AHI. There were no false positive results for DI when compared with AHI. ESS predicted possible sleep disordered breathing (score ≥11) in only 11 of the 31 patients (35%) who had confirmed sleep apnoea by AHI criteria,

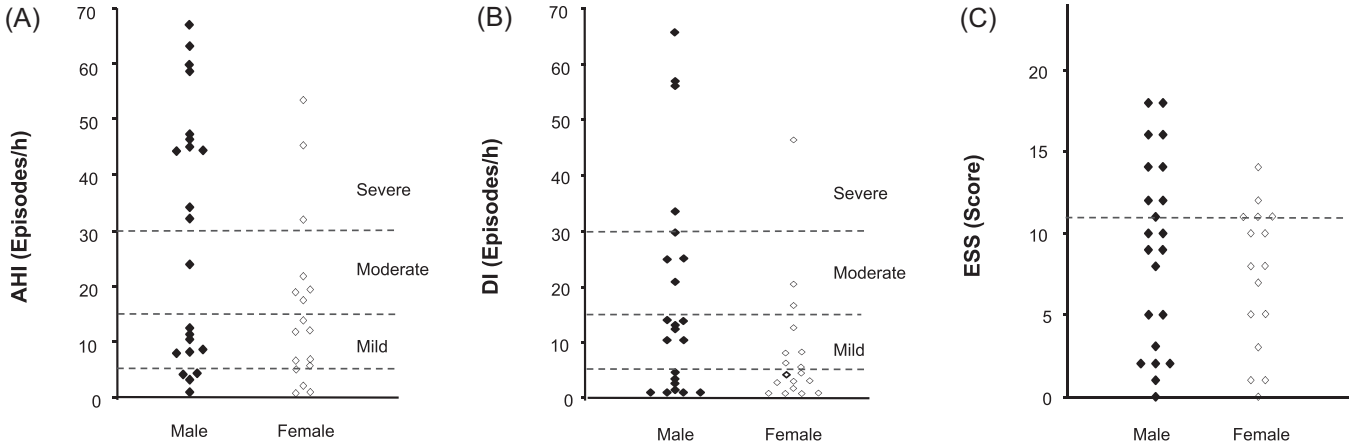

FIGURE 1 Screening for sleep apnoea in *de novo* acromegaly. (A) apnoea-hypopnoea index (AHI; $n = 39$), (B) oxygen desaturation index (DI, $n = 40$) and (C) Epworth Sleepiness Scale score (ESS, $n = 38$) at presentation in 40 subjects with acromegaly. Results are shown separately for male (solid diamonds) and female (open diamonds) subjects. Dashed lines denote respective reference ranges for each parameter (ESS score ≥11 is suggestive of sleep apnoea. DI and AHI threshold values: <5 events/hour, normal; 5–14, mild sleep apnoea; 15–29, moderate sleep apnoea; ≥30 severe sleep apnoea).

thereby failing to detect OSA in the majority of affected individuals (Figure 1C). In addition, a further three subjects with ESS ≥ 11 were subsequently shown not to have sleep apnoea.

3.2 | Sleep latency & sleep time

Thirteen of 39 patients (33%) demonstrated normal sleep latency (i.e., the time taken to first fall asleep; reference range 10–20 min) (Figure 2A). Fifteen of 39 patients (38%) had a sleep latency longer than 20 min. Overall time spent asleep during the night (sleep period time) was within the expected range (350–550 min) in the majority of the study group (31 of 38 patients [82%] for whom data were available) (Figure 2B).

3.3 | Arousal index and periodic limb movements

Reference ranges for arousal index vary with age (e.g., up to 12/h for young adults compared with up to 22/h for older subjects). The majority of patients had no difficulty falling asleep (as demonstrated by normal or reduced sleep latency), and exhibited normal sleep duration. However, their nights were frequently disturbed, with 29 of 37 patients (78%) demonstrating an increased arousal index (up to 70 events/h) (Figure 2C). In addition, we observed an excess of periodic limb movements (≥15/h) in 10 of 38 individuals (26%) (Figure 2D).

3.4 | Sleep architecture

Consistent with regular sleep arousal, there was marked disruption of the normal sleep cycle. Fourteen of 38 patients (37%) spent longer than predicted in stage 1 sleep (Figure 3), and progression through the sleep cycle to the deeper sleep stages was dramatically attenuated in many patients ([reduced stage 2, $n = 18$ (47%); reduced slow wave sleep, $n = 24$ (63%); reduced REM sleep, $n = 32$ (84%)]).

4 | DISCUSSION

This is the largest prospective and comprehensive study of sleep disordered breathing in newly-diagnosed, treatment-naïve, acromegaly reported to date. Using the gold standard of polysomnography, we have found a high prevalence of obstructive sleep apnoea, which is associated with frequent arousals, and marked disruption of sleep architecture in the majority of patients. Importantly, we have also shown that two of the most commonly employed screening tools for the detection of sleep apnoea in the general population have significant limitations when used in patients with acromegaly.

Although a number of workers have published primary sleep findings in acromegaly, the majority of studies have included patients who have previously received treatment (Supplementary Table S1 - studies published between 1980 and 2022). In fact, only 26 studies recruited subjects with no prior treatment and, of these, 16 included <50% *de novo* cases. Accordingly, for the most part, reported prevalence rates do not provide an accurate estimate of SDB in newly diagnosed acromegaly. Moreover, for those studies including previously treated subjects, additional factors such as new onset hypopituitarism and weight gain are potential confounding factors. In addition, more than half of the reported studies have relied on methodology (e.g., capnography, polygraphy, MESAM4, PolyMESAM, overnight DI) (Supplementary Table S1) that did not include the gold standard of full polysomnography, or were heterogeneous in the techniques used. Consistent with this, sleep architecture has been formally assessed in only ten studies (Supplementary Table S1). Importantly this is the largest study with a comprehensive assessment of sleep disordered breathing including sleep cycle

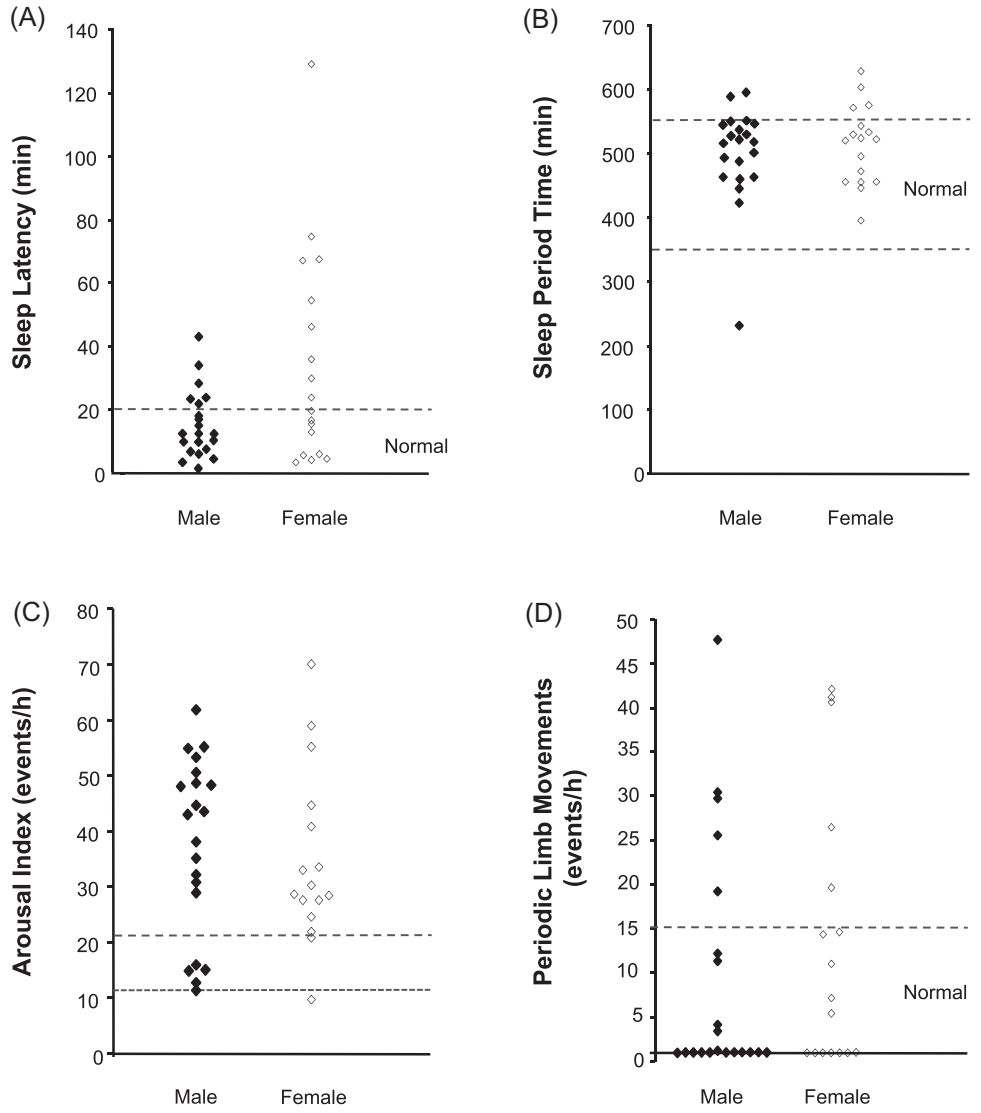

FIGURE 2 Sleep indices in *de novo* acromegaly. (A) sleep latency (SL, *n* = 39), (B) sleep period time (SPT, *n* = 38), (C) arousal index (AI, *n* = 37) and (D) periodic limb movement (PLM, *n* = 38) were assessed in 40 subjects with newly diagnosed acromegaly. Results are shown separately for male (solid diamonds) and female (open diamonds) subjects. Dashed lines denote respective reference ranges for each parameter (sleep latency, <20 min; sleep period time, 350–550 min; arousal index, up to 12/h for young adults and up to 22/h for older subjects; total periodic limb movement, <15 per hour).

disturbances, as defined using the gold standard of polysomnography, in a study group exclusively comprising newly-diagnosed treatment naïve subjects.

In this study, we have confirmed a high prevalence of obstructive sleep apnoea, in line with the findings of previous investigators: overall prevalence 79%, mild OSA 31%, moderate OSA 13%, severe OSA 36% (Figure 1A). However, we observed significant discrepancies between the findings of methods commonly used to screen for OSA and the gold standard of polysomnography. In many centres, screening for sleep-disordered breathing involves an initial symptom questionnaire, such as the Epworth Sleepiness Scale. If a threshold score is exceeded (≥11 in the case of the ESS), further investigation is triggered. In the UK, this is most frequently overnight pulse oximetry (which yields a desaturation index, DI). This approach has the advantage of being relatively affordable and simple, as it can be undertaken at home. Full polysomnography is generally not performed as a first line investigation, largely due to cost implications; the study requires involvement of a specialist unit and skilled technicians.

In our study, subjective reporting of excessive daytime somnolence was a poor predictor of the presence of OSA in patients with *de novo* acromegaly, with just 31% of those with a diagnosis of OSA by AHI returning an ESS score of ≥11 (Figure 1C). Similarly, desaturation index underestimated the prevalence of sleep apnoea in the study group, with only 55% returning a DI ≥ 5. It also significantly underestimated severity, classifying just 27.5% as having moderate or severe sleep apnoea, in contrast to 49% identified by AHI (Figure 1A & B). Interestingly, the majority of patients exhibited normal or reduced sleep latency (time to fall asleep) (Figure 2A) and sleep period time (total time asleep) (Figure 2B),

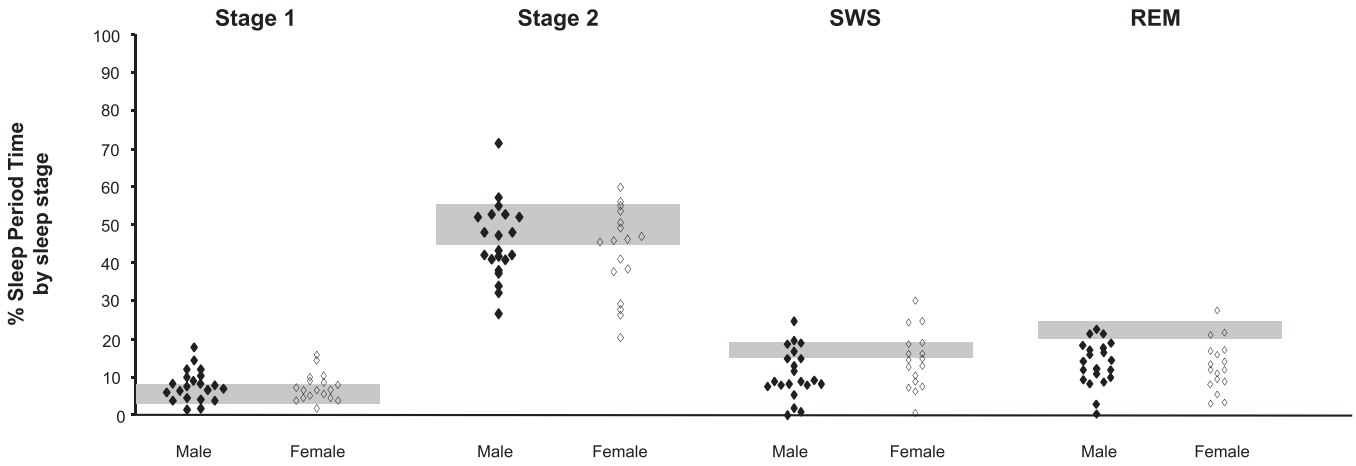

FIGURE 3 Sleep architecture in *de novo* acromegaly. Percentage of total sleep time spent in each sleep stage (stage 1, stage 2, slow wave sleep [SWS] and rapid eye movement [REM] sleep; $n = 39$). Results are shown separately for male (solid diamonds) and female (open diamonds) subjects. Grey boxes denote respective reference ranges for each parameter (stage 1, 3%–8%; stage 2, 45%–55%; SWS, 15%–20%; REM, 20%–25%).

and had a normal ESS score, and it seems likely therefore that many patients were unaware of their sleep disordered breathing even in the presence of severe OSA. Given the increased morbidity and mortality associated with OSA independent of acromegaly, we therefore propose that ESS and DI should no longer be employed as screening tests for OSA in this setting, but rather all patients should proceed directly to polysomnography. As is the case in our study, ESS has previously been shown to be variable and an unreliable tool for sleep apnoea assessment in the general population.[24–26] However, consensus guidelines for acromegaly continue to suggest ESS as an initial tool for obstructive sleep apnoea.[27,28]

Sleep architecture has not been widely reported in previous studies of patients with acromegaly (11 studies since 1980—Supplementary Table S1). Findings in other populations show that disruption of the sleep cycle, and diminution of the deep slow wave and REM sleep stages, have significant effects on cardiovascular and metabolic morbidity.[19–23] In our study we have demonstrated a greatly increased level of arousal in patients with acromegaly (Figure 2C), consistent with their high rate of sleep apnoea. Such arousals are known to be associated with sympathetic pathway activation and the release of catecholamines and corticosteroids, which may in part account for their detrimental effect.[35,36] Notably, the consequence of these arousals is a severe attenuation of the deeper sleep stages, such that subjects spend far longer in stage 1 sleep, and far less time in slow wave and REM sleep (Figure 3). This provides additional support for full polysomnographic assessment in acromegaly.

Treatment for obstructive sleep apnoea is most readily achieved with continuous positive airway pressure (CPAP) ventilatory support, providing a 'splinting' effect to the airways during inspiration, and reducing collapse and loss of inspiratory airflow. Given that treatment of acromegaly and attainment of GH and IGF-1 targets only partially ameliorate sleep apnoea,[9,14–16] it is important that co-existent OSA in acromegaly is appropriately screened for and identified. There are then sound reasons for believing that treatment of OSA in acromegaly is appropriate, even in those with relatively few symptoms, given the overall excess of cardiovascular risk associated with acromegaly. There is currently, however, a lack of evidence to confirm that treatments such as CPAP change this risk.

It is likely that OSA in the context of acromegaly has a multifactorial aetiology when compared with that in the general population, where obesity is the most common association.[37] In acromegaly, although obesity may be present, there are other unique abnormalities, most notably the expansion of soft tissues in the oropharynx, craniofacial skeletal abnormalities and neuromuscular dysfunction. The potential direct effects of GH and IGF-1 on the sleep centres are also poorly understood. However, whether these differences contribute to the lack of sensitivity of ESS and DI for the detection of OSA in acromegaly remains unclear.

In conclusion, this study supports the evidence for the use of polysomnography in all patients with newly-diagnosed acromegaly to allow early identification and treatment of sleep disordered breathing.

AUTHOR CONTRIBUTIONS

SM, AJW, DJH, JMS and MG designed the study. ASP, AKA, SM, AJW, JG, NK and OK performed the study assessments. ASP, AKA, LB, JMS and MG undertook data analysis. ASP, AKA, JMS and MG wrote the manuscript. All authors revised and approved the final version of the manuscript.

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REFERENCES

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328:1230-1235.
2. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med*. 2002;165:1217-1239.
3. Bonsignore MR, Borel AL, Machan E, Grunstein R. Sleep apnoea and metabolic dysfunction. *Eur Respir Rev*. 2013;22:353-364.
4. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. *The Lancet*. 2009;373:82-93.
5. Adedayo AM, Olafiranye O, Smith D, et al. Obstructive sleep apnea and dyslipidemia: evidence and underlying mechanism. *Sleep Breath*. 2014;18:13-18.
6. Luboshitzky R, Aviv A, Hefetz A, et al. Decreased pituitary-gonadal secretion in men with obstructive sleep apnea. *J Clin Endocrinol Metab*. 2002;87:3394-3398.
7. Grunstein RR, Ho KY, Sullivan CE. Sleep apnea in acromegaly. *Ann Intern Med*. 1991;115:527-532.
8. Weiss V, Šonka K, Pretl M, et al. Prevalence of the sleep apnea syndrome in acromegaly population. *J Endocrinol Invest*. 2000;23:515-519.
9. Attal P, Chanson P. Endocrine aspects of obstructive sleep apnea. *J Clin Endocrinol Metab*. 2010;95:483-495.
10. Grunstein RR, Sullivan CE. Sleep apnea and hypothyroidism: mechanisms and management. *Am J Med*. 1988;85:775-779.
11. Grunstein RR, Ho KY, Berthon-Jones M, Stewart D, Sullivan CE. Central sleep apnea is associated with increased ventilatory response to carbon dioxide and hypersecretion of growth hormone in patients with acromegaly. *Am J Respir Crit Care Med*. 1994;150:496-502.
12. Colao A, Ferone D, Marzullo P, Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endocr Rev*. 2004;25:102-152.
13. Orme SM, Orme SM, McNally RJQ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. *J Clin Endocrinol Metab*. 1998;83:2730-2734.
14. Davi MV, Carbonare LD, Giustina A, et al. Sleep apnoea syndrome is highly prevalent in acromegaly and only partially reversible after biochemical control of the disease. *Eur J Endocrinol*. 2008;159:533-540.
15. Roemmler J, Gutt B, Fischer R, et al. Elevated incidence of sleep apnoea in acromegaly-correlation to disease activity. *Sleep Breath*. 2012;16:1247-1253.
16. Annamalai AK, Webb A, Kandasamy N, et al. A comprehensive study of clinical, biochemical, radiological, vascular, cardiac, and sleep parameters in an unselected cohort of patients with acromegaly undergoing presurgical somatostatin receptor ligand therapy. *J Clin Endocrinol Metab*. 2013;98:1040-1050.
17. Powlson AS, Gurnell M. Cardiovascular disease and sleep-disordered breathing in acromegaly. *Neuroendocrinology*. 2016;103:75-85.
18. Saeki N, Isono S, Nishino T, Iuchi T, Yamaura A. Sleep-disordered breathing in acromegalics—relation of hormonal levels and quantitative sleep study by means of bedside oximeter. *Endocr J*. 1999;46:585-590.
19. Anothaisintawee T, Reutrakul S, Van Cauter E, Thakkinstian A. Sleep disturbances compared to traditional risk factors for diabetes development: systematic review and meta-analysis. *Sleep Med Rev*. 2016;30:11-24.
20. Van Cauter E. Sleep disturbances and insulin resistance. *Diabetic Med*. 2011;28:1455-1462.
21. Briançon-Marjollet A, Weiszenstein M, Henri M, Thomas A, Godin-Ribuot D, Polak J. The impact of sleep disorders on glucose metabolism: endocrine and molecular mechanisms. *Diabetol Metab Syndr*. 2015;7:25.
22. Haba-Rubio J, Marques-Vidal P, Andries D, et al. Objective sleep structure and cardiovascular risk factors in the general population: the HypnoLaus Study. *Sleep*. 2015;38:391-400.
23. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J*. 2011;32:1484-1492.
24. Campbell AJ, Neill AM, Scott DAR. Clinical reproducibility of the Epworth Sleepiness Scale for patients with suspected sleep apnea. *J Clin Sleep Med*. 2018;14:791-795.
25. Taylor E, Zeng I, O'Dochartaigh C. The reliability of the Epworth Sleepiness Score in a sleep clinic population. *J Sleep Res*. 2019;28:e12687.
26. Lee JL, Chung Y, Waters E, Vedam H. The Epworth sleepiness scale: reliably unreliable in a sleep clinic population. *J Sleep Res*. 2020;29:e13019.
27. Melmed S, Bronstein MD, Chanson P, et al. A consensus statement on acromegaly therapeutic outcomes. *Nat Rev Endocrinol*. 2018;14:552-561.
28. Giustina A, Barkan A, Beckers A, et al. A consensus on the diagnosis and treatment of acromegaly comorbidities: an update. *J Clin Endocrinol Metab*. 2020;105:e937-e946.
29. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14:540-545.
30. (1992) EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep* 15, 173-184.
31. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep*. 2004;27:1255-1273.
32. Dijk DJ. Regulation and functional correlates of slow wave sleep. *J Clin Sleep Med*. 2009;5:S6-S15.
33. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep*. 1999;22:667-689.
34. Rechchtshaffen A KA. *A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects*. Brain Information Service/Brain Research institute, UCLA; 1968.
35. Bisogni V, Pengo MF, Maiolino G, Rossi GP. The sympathetic nervous system and catecholamines metabolism in obstructive sleep apnoea. *J Thorac Dis*. 2016;8:243-254.
36. Balbo M, Leproult R, Van Cauter E. Impact of sleep and its disturbances on hypothalamo-pituitary-adrenal axis activity. *Int J Endocrinol*. 2010;2010:1-16.
37. Hooper RG. The relation between sleep and weight in a suburban sleep center: observations and speculations on apnea and weight. *Nat Sci Sleep*. 2016;8:315-320.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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