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Pseudoacromegaly—A challenging entity in the endocrine clinic: A systematic review

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Abstract

Objective: Pseudoacromegaly encompasses conditions with features of acromegaly/gigantism, but no growth hormone (GH) or insulin-like growth factor-1 (IGF-1) excess. We aimed to review published pseudoacromegaly cases evaluated due to clinical suspicion of acromegaly.

Design/Patients: PubMed/Medline search was conducted to identify reported pseudoacromegaly cases, which were systematically reviewed to ensure they met eligibility criteria: (1) presentation suggestive of acromegaly; (2) acromegaly excluded based on normal GH, IGF-1 and/or GH suppression on oral glucose tolerance test (OGTT-GH); (3) diagnosis of the pseudoacromegaly condition was established. Data were retrieved from each case and analysed collectively.

Results: Of 76 cases, 47 were males, mean ages at presentation and at first acromegaloid symptoms were 28 ± 16 and 17 ± 10 years, respectively. Most common conditions were pachydermoperiostosis (47%) and insulin-mediated pseudoacromegaly (IMP) (24%). Acromegaloid facies (75%) and acral enlargement (80%) were the most common features. Measurement of random GH was reported in 65%, IGF-1 in 79%, OGTT-GH in 51%. GH excess was more frequently excluded based on two tests (53%). Magnetic resonance imaging (MRI) was performed in 30 patients, with pituitary adenoma or hyperplasia being reported in eight and three patients, respectively. Investigations differed between cases managed by endocrine and non-endocrine specialists, the former requesting more often IGF-1, OGTT-GH and pituitary MRI.

Conclusions: Pseudoacromegaly is a challenging entity that may be encountered by endocrinologists. Pachydermoperiostosis and IMP are the conditions most often mimicking acromegaly. Adequate assessment of GH/IGF-1 is crucial to exclude acromegaly, which may be better performed by endocrinologists. Pituitary incidentalomas are common and require careful judgement to prevent unnecessary pituitary surgery.

KEYWORDS

acromegaloidism, acromegaloid facial appearance, acromegaly, pseudoacromegaly

1 | INTRODUCTION

Pseudoacromegaly encompasses conditions in which patients have clinical features of acromegaly or gigantism, but no excessive levels of growth hormone (GH) or insulin-like growth factor-1 (IGF-1). Therefore, pseudoacromegaly cases are often referred to paediatric or adult endocrinologists with suspected pituitary gigantism or acromegaly for investigation of possible GH/IGF-1 excess.[1,2]

The differential diagnosis of pseudoacromegaly is challenging due to the long list of disorders that may be associated with acromegaly-related manifestations, including acromegaloid facial appearance, acral enlargement, overgrowth/tall stature, macroglossia, arthralgia, skin manifestations, hyperhidrosis, hypertension, diabetes, among others.[1,3] Such pseudoacromegaly conditions are rare and sometimes have overlapping features, which impose further challenges to the differential diagnosis, however some have distinctive features facilitating the establishment of the diagnosis of the underlying condition.[2,4–6]

Although the list of conditions associated with acromegaloid features but normal GH/IGF-1 axis may be extensive, not all pseudoacromegaly conditions mimic closely acromegaly or pituitary gigantism. Hence, some of these pseudoacromegaly cases are more prone to first present to adult or paediatric endocrinologists, while others with lower likelihood of masquerading acromegaly are typically referred to other medical specialists.[1,2] The variety of pseudoacromegaly disorders that may be more often encountered by endocrinologists remains unknown, in part due to the lack of studies or large series given the rarity of such cases. We reviewed the published pseudoacromegaly cases who presented/were evaluated due to a clinical suspicion of acromegaly aiming to provide a comprehensive overview about the spectrum of pseudoacromegaly conditions that may be referred to the endocrine clinic.

2 | MATERIALS AND METHODS

2.1 | Search methodology, eligibility criteria and selection of cases

We undertook a thorough systematic review of the cases published in the literature encompassing pseudoacromegaly patients presented and/or evaluated due to a clinical suspicion of acromegaly, in which the biochemical assessment of the GH/IGF-1 axis ruled out acromegaly, and the diagnosis of the underlying was then subsequently established. A PubMed search was performed using the terms "pseudoacromegaly," "acromegaloidism," "masquerade acromegaly," "mimic acromegaly," "resemble acromegaly," "simulate acromegaly," "masquerading acromegaly," "mimicking acromegaly," "resembling acromegaly," "simulating acromegaly," "pseudoacromegalic," "acromegaly-like," "acromegaloid," "acromegaloid facial appearance," and "differential diagnosis of acromegaly." Related articles and reference lists in each publication were also reviewed. All papers indexed in the Medline database and PubMed published in English until 1 November 2023 were evaluated. There was no funding source for this study.

All case reports and small series of cases were analysed, to ensure that all patients included in our manuscript met the eligibility criteria: (i) had a clinical presentation suggestive of acromegaly, and were investigated because of the acromegaly-related manifestations; (ii) presented to an endocrinologist or to an internal medicine or other specialized departments with the presumption of possible diagnosis of acromegaly; (iii) had a biochemical assessment of the GH/IGF-1, and acromegaly was confidently excluded based on normal serum GH, serum IGF-1 and/or GH suppression on an oral glucose tolerance test (OGTT-GH) and (iv) a definitive diagnosis of the underlying pseudoacromegaly condition has been established.

Pseudoacromegaly patients who presented with a distinctive presentation not raising an obvious clinical suspicion for acromegaly and/or patients who were investigated based on the suspicion of other differential diagnosis rather than acromegaly in the first place were excluded, even if these had concurrent acromegaloid features. Additionally, pseudoacromegaly patients who had no biochemical assessment of the GH/IGF-1 axis, as well as no definitive diagnosis for the underlying pseudoacromegaly condition, were also excluded.

2.2 | Demographic, clinical, biochemical and radiological features

We screened all published contents per case, including the case description in the manuscripts as well as the figures and tables related to each patient. We retrieved the relevant demographic and clinical features, as well as biochemical data regarding the GH/IGF-1 axis and pituitary-related radiological data, as reported in the original manuscript. We focused on the main and most reported features that closely resemble acromegaly and/or are typically found in an acromegaly patient, as per each case description. The acromegaloid features we considered for the purpose of statistical analysis were coarse facial features, acral enlargement, tall stature, macroglossia, widely-spaced teeth, prognathism, pachydermia, cutis verticis gyrata, acanthosis nigricans, oily skin, thick skin, hirsutism, arthralgia, headache, fatigue, hypertension, diabetes, sleep apnoea, deep voice, hepatomegaly, and oligomenorrhea and polycystic ovaries in women. Tall stature was mainly defined based on a height of more than 2 standard deviations (SD) above the mean for age and sex, or a height greater than the 95th percentile,[7,8] in accordance with each individual publication. The referral clinic/department was assumed based on the authors affiliations as well as on the description/information available in each publication.

Laboratorial data were reviewed to ensure that all included cases had at least one biochemical test concerning the GH/IGF-1 axis (random serum GH, serum IGF-1, and/or OGTT-GH) confirming a normal somatotroph axis, as reported in each publication. Adequate suppression of GH on an OGTT was considered when the GH nadir on an OGTT was reported as normal, suppressed or <1.0 μg/L. The exclusion of acromegaly based on serum IGF-1 was considered when the levels of IGF-1 were below the upper limit of the normal range, or when serum IGF-1 was reported as normal or low, in accordance with each individual case report.

We also analysed the reported radiological investigations of the pituitary gland: any form of pituitary/sellar imaging should be intended as a radiological exam performed to directly assess the pituitary or sellar region, which included skull or sellar X-ray, brain or pituitary computed tomography (CT) scan, and/or brain or pituitary magnetic resonance imaging (MRI) scan. However, considering the inaccuracy of some imaging exams for studying the pituitary gland (especially X-ray), the structural appearance of the pituitary was only analysed for cases who had a pituitary MRI. Other non-acromegaloid and/or endocrine-related clinical and biochemical features were also recorded, and are shown in detail, case-by-case, in Table S1.

2.3 | Data analysis

Data are presented as absolute number or percentages for categorical variables, and as mean and standard deviation (SD) for continuous variables. Comparisons involving qualitative variables were performed using the chi-squared test, while quantitative variables were tested for Gaussian distribution with the Shapiro-Wilk test, and non-parametric and parametric data were further analysed with Mann–Whitney *U* and Student's *t* tests, respectively, with application of post hoc Bonferroni test as appropriate for variables with 3 categories. Statistical analysis was carried out using the SPSS software version 20 (IBM). p Values < 0.05 were considered statistically significant.

3 | RESULTS

3.1 | General demographic and nosological characteristics of the study population

Our study population consisted of 76 published pseudoacromegaly cases who met the inclusion criteria. Presentation and clinical features, particularly those resembling acromegaly, as well as the main endocrine-related investigations and pseudoacromegaly diagnosis are described in detail in Table S1, while the overall demographic/nosological characteristics and clinical features of the study population are summarized in Tables 1 and 2. Of the 76 cases, 47 (61.8%) were males, and the mean age at presentation was 27.9 ± 15.7 years, with 75.7% of them presented at ≥ 18 years old. Mean age at first acromegaloid symptoms was 16.5 ± 10.3 years, and the delay in diagnosing the pseudoacromegaly condition since the appearance of the first acromegaloid symptoms was estimated at 11.1 ± 11.8 years. Thirty-two cases (42.1%) were reported from Asia (predominantly India, China and South Korea), while 20 and 15 cases were reported by groups in Europe (mainly United Kingdom) or North America, respectively. The most common pseudoacromegaly conditions were pachydermoperiostosis (47.4%) and insulin-mediated pseudoacromegaly (23.7%), followed by Cantú syndrome, Berardinelli-Seip syndrome, primary hypothyroidism, chromosome 11 pericentric inversion and anorexia nervosa (Table 1). A summary of the pathophysiology, major clinical features, and diagnostic criteria of the different pseudoacromegaly conditions is provided in Table S2.

3.2 | Presentation and clinical features of the study population

Of 70 pseudoacromegaly cases for whom referral or affiliation data were available, the majority were directly referred to an Endocrinology or Paediatric Endocrinology department (n = 40, 57.1%), followed by the departments of Dermatology (12 cases, 17.2%), Internal Medicine (11 cases, 15.7%), Neurosurgery (3 cases), Cardiology (2 cases), and then Genetics and Dentistry (1 case each) (Table 1).

Acromegaloid facial appearance (Figure 1) and acral enlargement (Figure 2) were the most common features across the study population leading to clinical suspicion of acromegaly. Coarsening of facial appearance was reported in 57 cases (75%) and acral enlargement in 61 cases (80.3%) (Table 2). The prevalence of other acromegaloid features as reported in the published cases were: macroglossia, 25%; widely-spaced teeth, 7.9%; prognathism, 25%; pachydermia, 31.6%; cutis verticis gyrata, 15.8%; tall stature, 19.7%; acanthosis nigricans, 25%; oily skin, 27.6%; thick skin, 40.8%; hirsutism, 15.8%; hyperhidrosis, 35.5%; arthralgia, 28.9%; headache, 6.6%; deep voice, 2.6%; sleep apnoea, 4%; hypertension, 11.8%; diabetes, 18.4%; hepatomegaly, 4.0%. Oligomenorrhoea and polycystic ovaries have been reported in 7 of 29 females. The coexistence of tall stature and acromegaloid physical features were reported in 15 (19.7%) cases (Table 2).

Other non-acromegaloid features have been commonly reported, some of those useful in identifying the respective pseudoacromegaly condition: digital clubbing, n = 28 (36.8%), and blepharoptosis, n = 9 (11.8%), which are distinctive features of pachydermoperiostosis; congenital generalized hypertrichosis, n = 6 (7.9%), which is characteristic of Cantú syndrome; weight gain, n = 7 (9.2%) and obesity, n = 11 (14.5%), more often (but not exclusively) seen in insulin-mediated pseudoacromegaly; diffuse lipoatrophy, n = 3 (4.0%), and muscle hypertrophy, n = 3 (4.0%) both typical of Berardinelli-Seip syndrome (Table 2).

3.3 | Somatotroph axis and pituitary radiological investigations in the study population

Biochemical assessment of the GH/IGF-1 axis has been done in all 76 cases, although in a heterogeneous manner. The measurement of random serum GH was reported in 49 cases (64.5%); serum IGF-1 was assessed in 60 patients (78.9%); OGTT with GH nadir has been performed in 39 cases (51.3%). GH excess was more frequently ruled out based on the combination of two tests, which was employed in 40 cases (52.6%), of which the most frequent combination was random serum GH plus serum IGF-1 (n = 22, 28.9%) followed by serum IGF-1 plus OGTT-GH (n = 16, 21.1%); the combination of three tests were applied to 17 cases (22.4%), while 17 patients underwent only one test (Table 2). The laboratory tests were not detailed in two cases, but these were reported as having normal endocrinological studies, including a negative GH assay.[9] All 60 patients who had serum IGF-1 measured, had the levels of IGF-1 below the upper limit of the normal range. Five of these cases had only serum IGF-1 measured,[10–13] while the other 55 cases had IGF-1 measured in

TABLE 1 General demographic and nosological characteristics of the study population consisting of 76 pseudoacromegaly patients.

General demographic and nosological characteristics	Study population (*n* = 76)
Gender, *n* (%)	
Male	47 (61.8%)
Female	29 (38.2%)
Age at presentation (years), mean ± SD (range)	27.9 ± 15.7 (2; 64)
Age at presentation according to cut-off 18 years old, *n* (%)	
<18 years old	18 (24.3%)
≥18 years old	56 (75.7%) *(age unknown in 2 cases)*
Age at first acromegaloid symptoms (years), mean ± SD (range)	16.5 ± 10.3 (2; 60)
Delay in the diagnosis of pseudoacromegaly condition since first acromegaloid symptoms (years), mean ± SD (range)	11.1 ± 11.8 (1; 44)
Pseudoacromegaly diagnosis, *n* (%)	
Pachydermoperiostosis	36 (47.4%)
Insulin-mediated pseudoacromegaly	18 (23.7%)
Cantú syndrome	6 (7.9%)
Berardinelli-Seip syndrome	3 (4.0%)
Primary hypothyroidism	3 (4.0%)
Chromosome 11 pericentric inversion	2 (2.6%)
Anorexia nervosa	2 (2.6%)
Sotos syndrome	1 (1.3%)
Klippel-Trénaunay syndrome	1 (1.3%)
Minoxidil-induced pseudoacromegaly	1 (1.3%)
X-Tetrasomy	1 (1.3%)
Klinefelter syndrome	1 (1.3%)
Epiphyseal chondrodysplasia Miura type	1 (1.3%)
Referral clinical department, *n* (%)	
Endocrinology/Paediatric endocrinology	40 (57.1%)
Dermatology	12 (17.2%)
Internal medicine	11 (15.7%)
Neurosurgery	3 (4.3%)
Cardiology	2 (2.9%)
Genetics	1 (1.4%)
Dentistry	1 (1.4%) *(referral department unknown in 6 cases)*
Distribution of the cases per continent, *n* (%)[a]	
Asia	32 (42.1%)
Europe	20 (26.3%)
North America	15 (19.7%)
Africa	4 (5.3%)

TABLE 1 (Continued)

General demographic and nosological characteristics	Study population ($n = 76$)
South America	3 (4.0%)
Europe-Asia (Turkey)	2 (2.6%)

Abbreviation: SD, standard deviation.

[a]The distribution of the published pseudoacromegaly cases per country (following an alphabetical order): Algeria, $n = 1$ (1.3%); Brazil, $n = 1$ (1.3%); Canada, $n = 2$ (2.6%); China, $n = 4$ (5.3%), Colombia, $n = 1$ (1.3%); Egypt, $n = 2$ (2.6%); Germany, $n = 1$ (1.3%); Ghana, $n = 1$ (1.3%); India, $n = 13$ (17.1%); Iran, $n = 1$ (1.3%); Ireland, $n = 1$ (1.3%); Italy, $n = 1$ (1.3%); Japan, $n = 3$ ($n = 4.0\%$); Jordan, $n = 2$ (2.6%); Malaysia, $n = 1$ (1.3%); Nepal, $n = 1$ (1.3%); Netherlands, $n = 1$ (1.3%); Poland, $n = 1$ (1.3%); Saudi Arabia, $n = 2$ (2.6%); South Korea, $n = 4$ (5.3%); Spain, $n = 1$ (1.3%); Sweden, $n = 1$ (1.3%); Turkey, $n = 2$ (2.6%); United Kingdom, $n = 13$ (17.1%); United States of America, $n = 13$ (17.1%); Uzbekistan, $n = 1$ (1.3%); Venezuela, $n = 1$ (1.3%).

combination with random GH and/or GH measured on an OGTT. GH nadir on an OGTT was reported as normal, suppressed or <1.0 μg/L in all 39 patients who underwent this test, except in one subject with pachydermoperiostosis where the GH nadir during an OGTT was 1.7 ng/mL.[14] Based on lack of GH suppressibility on an OGTT and clinical suspicion of acromegaly, he underwent hypophysectomy, but no pituitary tumour was seen on the histological analysis. After surgery, the patient was noted with hands and forearms thickening digital clubbing as well as facial furrowing indicative of pachydermoperiostosis, and his brother also had with similar features. The pachydermoperiostosis diagnosis was genetically confirmed in both of them after the identification of a mutation in the gene *SLCO2A1*.[14]

More than half of the pseudoacromegaly cases underwent any form of pituitary/sellar imaging (56.6%), while a pituitary MRI was performed in 30 cases (39.5%). Out of these 30 patients who had pituitary MRI, a normal pituitary gland was reported in 63.3%, while a pituitary adenoma or pituitary hyperplasia has been reported respectively in 8 (27%) and 3 (10%) cases (Table 2). Of the eight cases with pituitary adenomas on MRI (5 females, 3 males), five corresponded to microadenomas (62.5%), and the underlying pseudoacromegaly diagnoses were insulin-mediated pseudoacromegaly ($n = 3$), pachydermoperiostosis ($n = 3$), and Cantú syndrome ($n = 2$). The mean adenoma diameter was estimated at 8.1 ± 3.3 mm (range 5–13 mm), and mean age at diagnosis was 25.0 ± 8.8 years, ranging from 14 up to the maximum age of 44 (Table S3). Pituitary hyperplasia was described in 1 female with insulin-mediated pseudoacromegaly[15] and in two males with primary hypothyroidism-related pseudoacromegaly.[16,17]

3.4 | Pseudoacromegaly cases referred to adult and paediatric endocrinologists versus non-endocrine departments

Of the 76 pseudoacromegaly cases, 40 (57.1%) were referred directly to endocrinologists or paediatric endocrinologists (Table 1), with mean ages at presentation and at onset of acromegaloid symptoms of 24.9 ± 15.5 and 14.4 ± 10.4 years, respectively, and with an estimated delay in the diagnosis since first symptoms of about 10.8 ± 12.4 years, neither of these differing significantly from cases referred to non-endocrine departments (Table 4). Patients with insulin-mediated pseudoacromegaly and other causes of pseudoacromegaly were more often referred to endocrine departments, whereas pachydermoperiostosis cases presented more to non-endocrine departments (63.9 vs. 32.5%; $p = .024$) (Table 3).

The prevalence of acromegaloid facies and acral enlargement did not differ among pseudoacromegaly cases observed in endocrine versus non-endocrine departments. However, thick skin, pachydermia, oily skin and cutis verticis gyrata were more prevalent in the non-endocrine setting, whereas acanthosis nigricans and diabetes were more common in the subgroup first referred to endocrine specialists, reflecting the differences in the distribution of pseudoacromegaly diagnosis (Table 3).

Tall stature/overgrowth coexisted with acromegaloid physical features in 15 of the 76 pseudoacromegaly patients (19.7%) included in our study. The characteristics of these 15 cases who presented with acromegaloid physical features and tall stature are summarized in Table S4. The prevalence of acromegaloid physical features plus tall stature was significantly higher in the cases referred to adult and paediatric endocrinologists ($n = 13$, 32.5%) than in those referred to non-endocrine doctors ($n = 2$, 5.6%) (Table 3). Of the 13 cases with tall stature referred to endocrine departments, six (2 males, 4 females) presented to adult endocrinologists, had ages at presentation comprised between 19 and 53 years, and had the following underlying diagnosis: insulin-mediated pseudoacromegaly ($n = 2$), Sotos syndrome ($n = 1$), X-tetrasomy ($n = 1$), epiphyseal chondrodysplasia Miura type ($n = 1$) and pachydermoperiostosis ($n = 7$). On the other hand, of the seven patients (2 males, 5 females) who presented to paediatric endocrinologists, 5 had insulin-mediated pseudoacromegaly and two cases were diagnosed with a chromosome 11 pericentric inversion (Table S4).

The pattern of laboratorial and imaging investigations across the pseudoacromegaly cases differed between those encountering endocrine and non-endocrine medical specialists. Pseudoacromegaly cases referred to endocrinologists or paediatric endocrinologists had serum IGF-1 and OGTT-GH in a higher proportion of cases in comparison to the non-endocrine setting (90.0 vs. 61.1%; $p = .013$, and 65.0 vs. 36.1%; $p = .012$, respectively). Moreover, the proportion of cases with combined tests for GH/IGF-1 axis was higher in cases overseen by endocrine specialists. Although the proportion of cases with any form of pituitary/sellar radiological investigation did not differ among patients in endocrine and non-endocrine settings, a pituitary MRI was more often requested to patients seen by endocrine specialists (57.5 vs. 19.4%; $p = .001$) (Table 3).

TABLE 2 Clinical features, biochemical assessment of the somatotroph axis, and pituitary radiological investigations as reported in the study population of 76 pseudoacromegaly patients.

Clinical features, biochemical assessment of GH/IGF-1 axis, and pituitary radiological investigation	Study population ($n = 76$)
Prevalence of acromegaloid features, *n* (%)	
Acral enlargement	61 (80.3%)
Coarse facial features	57 (75.0%)
Thick skin	31 (40.8%)
Hyperhidrosis	27 (35.5%)
Pachydermia	24 (31.6%)
Arthralgia	22 (28.9%)
Oily skin	21 (27.6%)
Macroglossia	19 (25.0%)
Prognathism	19 (25.0%)
Acanthosis nigricans	19 (25.0%)
Tall stature	15 (19.7%)
Diabetes	14 (18.4%)
Cutis verticis gyrata	12 (15.8%)
Hirsutism	12 (15.8%)
Hypertension	9 (11.8%)
Widely-spaced teeth	6 (7.9%)
Headache	5 (6.6%)
Fatigue	5 (6.6%)
Sleep apnoea	3 (4.0%)
Deep voice	2 (2.6%)
Hepatomegaly	3 (4.0%)
Oligomenorrhea	7 of 29 females (24.1%)
Polycystic ovaries	7 of 29 females (24.1%)
Presence of tall stature + acromegaloid physical features, *n* (%)	15 (19.7%)
Prevalence of other non-acromegaloid features, *n* (%)	
Weight gain	7 (9.2%)
Obesity	11 (14.5%)
Digital clubbing	28 (36.8%)
Blepharoptosis	9 (11.8%)
Congenital generalized hypertrichosis	6 (7.9%)
Diffuse lipoatrophy	3 (4.0%)
Muscle hypertrophy	3 (4.0%)
Laboratorial tests performed to assess the GH/IGF-1 axis, *n* (%)	
Random GH	49 (64.5%)
Serum IGF-1	60 (78.9%)
GH suppression on OGTT	39 (51.3%)
Full laboratorial investigation of the GH/IGF-1 axis, *n* (%)	
GH	8 (10.5%)
IGF-1	5 (6.6%)
OGTT-GH	4 (5.3%)
GH + IGF-1	22 (28.9%)
GH + OGTT-GH	2 (2.6%)
IGF-1 + OGTT-GH	16 (21.1%)
GH + IGF-1 + OGTT-GH	17 (22.4%)
Not specified	2 (2.6%)
Radiological investigation of the pituitary gland, *n* (%)	
Any form of pituitary/sellar imaging	43 (56.6%)
Pituitary MRI	30 (39.5%)
Pituitary structural appearance on cases who underwent MRI, *n* (%)	
Normal pituitary gland	19 (63.3%)
Pituitary hyperplasia	3 (10.0%)
Pituitary adenoma	8 (26.7%) ($n = 30$)

Abbreviations: GH, growth hormone; IGF-1, insulin-like growth factor-1; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; OGTT-GH, GH suppression on OGTT.

3.5 | Characteristics and phenotypic differences across pachydermoperiostosis versus insulin-mediated pseudoacromegaly versus other causes of pseudoacromegaly

The characteristics and phenotypic differences across the main causes of pseudoacromegaly are shown in Table 4. Pachydermoperiostosis cohort is mainly composed of male and adult patients (94.4% and 88.9%, respectively), while the female gender predominates in the subgroup of insulin-mediated pseudoacromegaly (83.3%). Most pachydermoperiostosis cases concerned Asian patients, contrasting with other pseudoacromegaly causes where cases were more often described by European and North American groups. Pachydermoperiostosis cases had a less thorough investigation of the GH/IGF-1 axis, with only 64% of cases having a serum IGF-1 measured, when compared with insulin-mediated pseudoacromegaly or other causes of pseudoacromegaly where more than 90% of cases had a serum IGF-1 (Table 4).

The pachydermoperiostosis cohort had higher rates of thick skin, oily skin, hyperhidrosis, pachydermia, arthralgia and cutis verticis gyrata. Insulin-mediated pseudoacromegaly was associated with higher proportions of acanthosis nigricans, hirsutism, diabetes, macroglossia, prognathism and widely-spaced teeth. Coexistence of tall stature and acromegaloid features was higher in the insulin-mediated pseudoacromegaly subgroup than in the subgroups of

FIGURE 1 Acromegaloid facial appearance in published patients with pachydermoperiostosis (A–H) and with insulin-mediated pseudoacromegaly (I–L). The sources from the facial pictures are: (A) Donnelly 1991 *Ir J Med Sci* [PMID: 1885289]; (B) Chentli 2014 *Indian J Endocrinol Metab* [PMID: 24944954]; (C) Kim 2015 *J Dermatol* [PMID: 25810087]; (D) Karimova 2017 *J Endocr Soc* [PMID: 29264471]; (E) Prerna 2018 *Indian Dermatol Online J* [PMID: 29854639]; (F) Li 2019 *Br J Dermatol* [PMID: 26875533]; (G) Li 2019 *Indian J Dermatol Venereol Leprol* [PMID: 30880718]; (H) Salah 2019 *Clin Case Rep* [PMID: 30847204]; (I) Famuyiwa 1993 *Ann Saudi Med* [PMID: 17590683]; (J) Kumar 1996 *J Clin Endocrinol Metab* [PMID: 8855786]; (K) Moradi 2019 *Diabetes Metab Syndr* [PMID: 31336543]; (L) Stone 2020 *J Endocr Soc* [PMID: 33210059]. [Color figure can be viewed at wileyonlinelibrary.com]

pachydermoperiostosis or other causes of pseudoacromegaly (respectively, 44.4 vs. 2.8 vs. 27.3%; $p = .001$). Acral enlargement tended to be more common in pachydermoperiostosis (86.1%) and insulin-mediated pseudoacromegaly (88.9%) than in other conditions causing pseudoacromegaly (63.6%), and there were no differences regarding the prevalence of coarse facies (Table 4, Figures 1 and 2).

4 | DISCUSSION

We reviewed the pseudoacromegaly cases that presented/were evaluated due to a clinical suspicion of acromegaly, providing an overview about the spectrum and characteristics of pseudoacromegaly conditions that may be encountered by adult or paediatric endocrinologists. Our data compiling a total of 76 cases presented with suspected acromegaly confirm that pseudoacromegaly is a challenging entity in the endocrine clinic, with pachydermoperiostosis and insulin-mediated pseudoacromegaly being the conditions most often encountered by endocrinologists. An adequate assessment of GH/IGF-1 axis is crucial to conclusively rule out acromegaly, which may be better performed by endocrine specialists, as a higher number of combined biochemical tests of the GH/IGF-1 axis has been performed in the endocrine setting. Pituitary incidentalomas may be common in pseudoacromegaly and require careful judgement to prevent unnecessary pituitary surgery.

The adequate management of a pseudoacromegaly patient is much more than only ruling out acromegaly, as establishing the underlying diagnosis in a timely manner is key for the treatment of some disease-specific manifestations, but also to avoid a misdiagnosis or repetition of unnecessary investigations[17–23]; moreover, it is important for the appropriate testing and treatment of affected family members, as many of these disorders are genetically inherited.[2] The mean delay in the diagnosis of the pseudoacromegaly condition since the appearance of the first acromegaloid symptoms was higher than 10 years. Such delay was even higher than the

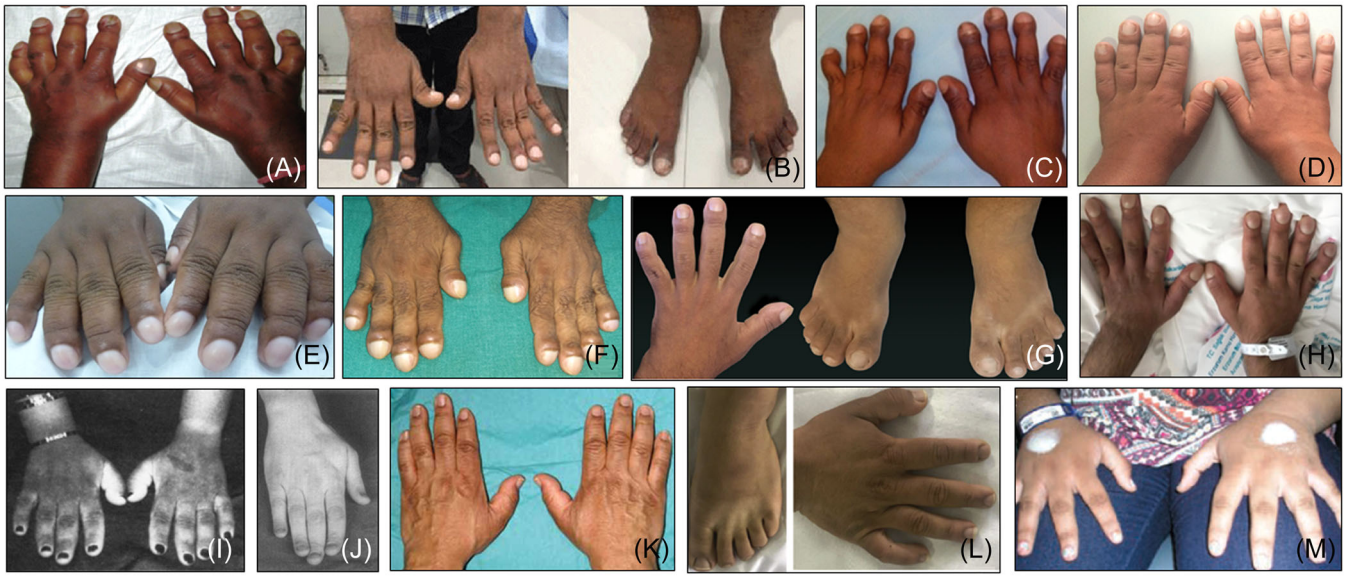

FIGURE 2 Acral appearance in published patients with pachydermoperiostosis (A–H) and with insulin-mediated pseudoacromegaly (I–M). The sources from the pictures are: (A) Ghatnatti 2012 *Indian J Endocrinol Metab* [PMID: 23565412]; (B) Narendra 2015 *J Assoc Physicians India* [PMID: 26710410]; (C) Rahaman 2016 *Indian J Endocrinol Metab* [PMID: 27730089]; (D) Karimova 2017 *J Endocr Soc* [PMID: 29264471]; (E) Mangupli 2017 *Endocrinol Diabetes Metab Case Rep* [PMID: 28469926]; (F) Prerna 2018 *Indian Dermatol Online J* [PMID: 29854639]; (G) Honório 2020 *An Bras Dermatol* [PMID: 31889594]; (H) Baykan 2022 *J Clin Res Pediatr Endocrinol* [PMID: 34027406]; (I) Famuyiwa 1993 *Ann Saudi Med* [PMID: 17590683]; (J) Kumar 1996 *J Clin Endocrinol Metab* [PMID: 8855786]; (K) Sam 2011 *Hormones (Athens)* [PMID: 16832583]; (L) Moradi 2019 *Diabetes Metab Syndr* [PMID: 31336543]; (M) Stone 2020 *J Endocr Soc* [PMID: 33210059]. [Color figure can be viewed at wileyonlinelibrary.com]

diagnostic delay recognized in acromegaly,[24,25] which illustrates the challenges associated with the differential diagnosis of pseudoacromegaly. Most pseudoacromegaly conditions are rare and heterogeneous with a wide phenotypic variability within the same disease, and they often have overlapping features with other disorders, which imposes diagnostic difficulties. Moreover, these cases may present to different medical specialists with distinct degrees of awareness and experience for pseudoacromegaly conditions, which may lead to further diagnostic delays, in some cases longer than 30 years,[14,15,18,26] or in others the underlying disorder may never be identified.[27–32]

Adult and paediatric endocrinologists may be referred with pseudoacromegaly patients, thus it is important to be aware of this entity and recognize the most common conditions, or at least those that more likely mimicking acromegaly (pachydermoperiostosis and insulin-mediated pseudoacromegaly). Forty cases (57%) were referred to endocrinologists, predominantly insulin-mediated pseudoacromegaly cases, which may be explained, at least in part, by the common occurrence of metabolic disorders such as obesity, diabetes or dyslipidemia, while other endocrine-related issues may also coexist, including amenorrhoea, polycystic ovaries or hirsutism.[12,15,20,33–37] Moreover, the coexistence of tall stature/overgrowth with acromegaloid physical features seem to be more prevalent in insulin-mediated pseudoacromegaly than in other pseudoacromegaly conditions, which may further explain the increased referrals of such cases to paediatric/adult endocrinologists for the evaluation of excessive growth. In contrast, pachydermoperiostosis cases were mainly referred to non-endocrine specialists, including dermatologists and internists, given the prominent skin and skeletal manifestations typical of this condition[11,38–42]; however, many reported pachydermoperiostosis patients were first referred and diagnosed by endocrinologists.[5,23,43–50] Endocrinologists should be familiar with these conditions and always consider them in the work-up of a pseudoacromegaly case. Besides the GH/IGF-1 axis assessment to rule out acromegaly, the investigation should include thyroid function tests, glucose, insulin, HbA1c and lipid profile.[2] Other tests such as full blood count, liver or kidney function tests may identify problems seen in some conditions, such as pachydermoperiostosis or Cantú syndrome.[2] Pachydermoperiostosis diagnosis made on clinical grounds can be genetically confirmed by testing for mutations in *HPGD* and *SLCO2A1* genes.[1,51,52]

In our cohort, we found no differences in the diagnostic delay between endocrine and non-endocrine doctors, even though endocrinologists were referred with a higher proportion of cases with other (rare) causes of pseudoacromegaly rather than pachydermoperiostosis or insulin-mediated pseudoacromegaly, which tend to be associated with longer diagnostic delay. Pseudoacromegaly cases referred to endocrinologists had more often measured IGF-1 and OGTT-GH, and a higher rate of combined biochemical tests. These findings support the relevance of endocrine specialists in the management of pseudoacromegaly patients, where adequate assessment of GH/IGF-1 axis is crucial to conclusively rule out (or diagnose) acromegaly.[53–55] Endocrinologists must ensure that

TABLE 3 Demographic, clinical, biochemical and imaging features of the pseudoacromegaly cases referred directly to endocrinologists or paediatric endocrinologists versus cases presenting to non-endocrine departments.

	Cases referred to endocrinologists or paediatric endocrinologists ($n = 40$)	Cases referred to non-endocrine departments ($n = 36$)	p Value
Gender,*n* (%)			
Male	21 (52.5%)	26 (72.2%)	.077
Female	19 (47.5%)	10 (27.8%)	
Age at presentation (years), mean ± SD	24.9 ± 15.5	30.9 ± 15.4	.100
Age at presentation according to cut-off 18 years old, *n* (%)			
<18 years old	15 (39.5%)	3 (8.3%)	**.002**
≥18 years old	23 (60.5%) *(age unknown in 2 cases)*	33 (91.7%)	
Age at first acromegaloid symptoms (years), mean ± SD	14.4 ± 10.4	19.2 ± 9.8	.131
Delay in the diagnosis of pseudoacromegaly condition since first acromegaloid symptoms (years), mean ± SD	10.8 ± 12.4	11.5 ± 11.1	.853
Pseudoacromegaly diagnosis, *n* (%)			
Pachydermoperiostosis	13 (32.5%)	23 (63.9%)	**.024**
Insulin-mediated pseudoacromegaly	12 (30.0%)	6 (16.7%)	
Other causes of pseudoacromegaly	15 (37.5%)	7 (19.4%)	
Prevalence of acromegaloid features, *n* (%)			
Acral enlargement	31 (77.5%)	30 (83.3%)	.523
Coarse facial features	31 (77.5%)	26 (72.2%)	.596
Thick skin	12 (30.0%)	19 (52.8%)	**.044**
Hyperhidrosis	16 (40.0%)	11 (30.6%)	.390
Pachydermia	8 (20.0%)	16 (44.4%)	**.022**
Arthralgia	11 (27.5%)	11 (30.6%)	.769
Oily skin	7 (17.5%)	14 (38.9%)	**.037**
Macroglossia	11 (27.5%)	8 (22.2%)	.596
Prognathism	17 (42.5%)	2 (5.6%)	**<.001**
Acanthosis nigricans	14 (35.0%)	5 (13.9%)	**.034**
Diabetes	11 (27.5%)	3 (8.3%)	**.031**
Cutis verticis gyrata	2 (5.0%)	10 (27.8%)	**.007**

(Continues)

TABLE 3 (Continued)

	Cases referred to endocrinologists or paediatric endocrinologists ($n = 40$)	Cases referred to non-endocrine departments ($n = 36$)	p Value
Hirsutism	9 (22.5%)	3 (8.3%)	.091
Hypertension	6 (15.0%)	3 (8.3%)	.369
Widely-spaced teeth	5 (12.5%)	1 (2.8%)	.117
Headache	5 (12.5%)	0	**.028**
Fatigue	5 (12.5%)	0	**.028**
Presence of tall stature + acromegaloid physical features, *n* (%)	13 (32.5%)	2 (5.6%)	**.003**
Lab tests performed to assess the GH/IGF-1 axis, *n* (%)			
Random GH	22 (55.0%)	27 (75.0%)	.069
Serum IGF-1	36 (90.0%)	22 (61.1%)	**.013**
GH suppression on OGTT	26 (65.0%)	13 (36.1%)	**.012**
Combined investigations of the GH/IGF-1 axis, *n* (%)			
GH + IGF-1	9 (22.5%)	13 (36.1%)	**.043**
IGF-1 + OGTT-GH	13 (32.5%)	3 (8.3%)	
GH + IGF-1 + OGTT-GH	11 (27.5%)	6 (16.7%)	
Radiological investigation of the pituitary gland, *n* (%)			
Any form of pituitary/sellar imaging	25 (62.5%)	18 (50.0%)	.272
Pituitary MRI	23 (57.5%)	7 (19.4%)	**.001**
Pituitary structural appearance on cases who had MRI, *n* (%)			
Normal pituitary gland	14 (60.9%)	5 (71.4%)	.601
Pituitary hyperplasia	3 (13.0%)	0	
Pituitary adenoma	6 (26.1%) *(n = 23)*	2 (28.6%) *(n = 7)*	

Note: Data are presented as absolute number and percentages for categorical variables, or as mean and SD for continuous variables. Comparisons involving qualitative variables were performed with the chi-squared test, while quantitative non-parametric and parametric variables were analysed with Mann–Whitney *U* and Student's *t* tests, respectively.

Abbreviations: GH, growth hormone; IGF-1, insulin-like growth factor-1; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; OGTT-GH, GH suppression on OGTT; SD, standard deviation.

TABLE 4 Characteristics and main differences across the patients with pachydermoperiostosis, insulin-mediated pseudoacromegaly or other causes of pseudoacromegaly.

	Pachydermoperiostosis (*n* = 36)	Insulin-mediated pseudoacromegaly (*n* = 18)	Other causes of pseudoacromegaly (*n* = 22)	*p* Value
Gender, *n* (%)				
Male	34 (94.4%)	3 (16.7%)	10 (45.5%)	**<.001**
Female	2 (5.6%)	15 (83.3%)	12 (54.5%)	
Age at presentation (years), mean ± SD	28.6 ± 12.9	22.7 ± 15.6	31.4 ± 19.4	.220
Age at presentation according to cut-off 18 years, *n* (%)				
<18 years old	4 (11.1%)	8 (44.4%)	6 (30.0%)	**.021**
≥18 years old	32 (88.9%)	10 (55.6%)	14 (70.0%) *(age unknown in 2 cases)*	
Age at first acromegaloid symptoms (years), mean ± SD	16.2 ± 4.8	16.3 ± 12.2	18.4 ± 23.5	.991
Delay in the diagnosis of pseudoacromegaly condition since first acromegaloid symptoms (years), mean ± SD	10.3 ± 10.2	8.4 ± 10.2	21.8 ± 8.3	.084
Distribution of the cases per continent, *n* (%)				
Asia	23 (63.9%)	5 (27.8%)	4 (18.2%)	**.003**
Europe	3 (8.3%)	6 (33.3%)	11 (50.0%)	
North America	4 (11.1%)	7 (38.9%)	4 (18.2%)	
Africa	2 (5.6%)	0	2 (9.1%)	
South America	2 (5.6%)	0	1 (4.5%)	
Europe-Asia (Turkey)	2 (5.6%)	0	0	
Prevalence of acromegaloid features, *n* (%)				
Acral enlargement	31 (86.1%)	16 (88.9%)	14 (63.6%)	.065
Coarse facial features	28 (77.8%)	13 (72.2%)	16 (72.7%)	.868
Thick skin	21 (58.3%)	4 (22.2%)	6 (27.3%)	**.012**
Hyperhidrosis	23 (63.9%)	3 (16.7%)	1 (4.5%)	**<.001**
Pachydermia	22 (61.1%)	0	2 (9.1%)	**<.001**
Arthralgia	20 (55.6%)	0	2 (9.1%)	**<.001**
Oily skin	18 (50.0%)	1 (5.6%)	2 (9.1%)	**<.001**
Macroglossia	2 (5.6%)	8 (44.4%)	9 (40.9%)	**.001**
Prognathism	4 (11.1%)	8 (44.4%)	7 (31.8%)	**.019**

(Continues)

TABLE 4 (Continued)

	Pachydermoperiostosis (*n* = 36)	Insulin-mediated pseudoacromegaly (*n* = 18)	Other causes of pseudoacromegaly (*n* = 22)	*p* Value
Acanthosis nigricans	0	16 (88.9%)	3 (13.6%)	**<.001**
Diabetes	0	9 (50.0%)	5 (22.7%)	**<.001**
Cutis verticis gyrata	12 (33.3%)	0	0	**<.001**
Hirsutism	1 (2.8%)	10 (55.6%)	1 (4.5%)	**<.001**
Hypertension	2 (5.6%)	2 (11.1%)	5 (22.7%)	.145
Widely-spaced teeth	0	4 (22.2%)	2 (9.1%)	**.016**
Headache	1 (2.8%)	2 (11.1%)	2 (9.1%)	.433
Fatigue	0	2 (11.1%)	3 (13.6%)	.085
Presence of tall stature + acromegaloid physical features, *n* (%)	1 (2.8%)	8 (44.4%)	6 (27.3%)	**.001**
Lab tests performed to assess the GH/IGF-1 axis, *n* (%)				
Random GH	23 (63.9%)	9 (50.0%)	5 (22.7%)	0.199
Serum IGF-1	23 (63.9%)	17 (94.4%)	20 (90.9%)	**0.009**
GH suppression on OGTT	16 (44.4%)	13 (72.2%)	10 (45.5%)	0.127
Combined investigations of the GH/IGF-1 axis, *n* (%)				
GH + IGF-1	8 (22.2%)	3 (16.7%)	11 (50.0%)	**0.023**
IGF-1 + OGTT-GH	6 (16.7%)	6 (33.3%)	4 (18.2%)	
GH + IGF-1 + OGTT-GH	7 (19.4%)	6 (33.3%)	4 (18.2%)	
Radiological investigation of the pituitary gland, *n* (%)				
Any form of pituitary/sellar imaging	19 (52.8%)	9 (50.0%)	15 (68.2%)	0.420
Pituitary MRI	10 (27.8%)	7 (38.9%)	13 (59.1%)	0.061
Pituitary appearance on cases who had MRI, *n* (%)				
Normal pituitary gland	7 (70.0%)	3 (42.9%)	9 (69.2%)	0.484
Pituitary hyperplasia	0	1 (14.3%)	2 (15.4%)	
Pituitary adenoma	3 (30.0%) *(n = 10)*	3 (42.9%) *(n = 7)*	2 (15.4%) *(n = 13)*	

Note: Data are presented as absolute number and percentages for categorical variables, or as mean and SD for continuous variables. Comparisons involving qualitative variables were performed with the chi-squared test, while quantitative non-parametric and parametric variables were analysed with Mann–Whitney *U* and Student's *t* tests, respectively. Post hoc Bonferroni test was applied for comparisons regarding continuous variables between the three subgroups of pachydermoperiostosis, insulin-mediated pseudoacromegaly or other causes of pseudoacromegaly.

Abbreviations: GH, growth hormone; IGF-1, insulin-like growth factor-1; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; OGTT-GH, GH suppression on OGTT; SD, standard deviation.

every pseudoacromegaly case have a normal GH/IGF-1 axis before assuming a certain condition as the cause of acromegaloid features,[56,57] as acromegaly may coexist with other pseudoacromegaly disorders, as reported in Seip-Berardinelli syndrome,[58] Tatton-Brown-Rahman syndrome,[59] pachydermoperiostosis,[60] and Klinefelter syndrome,[61] or in families with both GH-related pituitary and non-pituitary gigantism.[62] Endocrine specialists are also important to avoid erroneous diagnosis of acromegaly,[17–20] and prevent inadequate pituitary surgery in pseudoacromegaly cases with pituitary incidentalomas.[14,17]

The biochemical assessment of GH/IGF-1 axis was performed/reported in a heterogeneous manner in the cases we studied, which may be explained by different factors. First, different medical specialists (endocrinologists and non-endocrinologists) have been involved in the work-up of the published cases. Second, there is a phenotype variability within the clinical entity of pseudoacromegaly, as well as within the same pseudoacromegaly condition, which may result into different degrees of clinical suspicion for acromegaly, and thus, justifying a more or less comprehensive biochemical work-up depending on each case. Third, cases were reported from different countries spread across Asia, Europe, North America, South America and Africa, where local diagnostic resources and medical practices may be distinct. The chronological amplitude of the case reports should be also taken into account, as we included few cases from the decades 80 and 90, where the diagnostic work-up for acromegaly is different from recent cases, as a result of the evolution of laboratorial tests and advancement of the scientific knowledge. These aspects, together with the intrinsic limitations associated with GH and IGF-1 immunoassays, including issues on the lack of standardization between different laboratories, technical differences between manufacturers or antibodies used in the different assays, difficulties in establishing the normal reference intervals of GH and IGF-1 assays,[54,63] impose some caution in the interpretation of the biochemical-related findings regarding the somatotroph axis in our cohort of pseudoacromegaly cases.

More than half of the patients we studied had any form of pituitary/sellar imaging despite normal GH/IGF-1 axis, showing that pituitary radiological studies are often inappropriately requested to pseudoacromegaly patients. Where the biochemical assessment of GH/IGF-1 axis is normal, pituitary imaging is not indicated, and should be discouraged. Thirty cases underwent a pituitary MRI, with a pituitary adenoma or hyperplasia being found in 8 (27%) and 3 (10%) patients, respectively. These data suggest that pituitary abnormalities may be found in more than one-third of cases, while adenomas can be incidentally found in about a fourth of cases. Most pituitary adenomas in the pseudoacromegaly setting have been detected in young patients (as early as 14 years old; mean age at diagnosis 25 years), population where incidentalomas are less common.[64–66] Pituitary incidentalomas seem common in pseudoacromegaly (more than in the general population[67,68]), and typically correspond to small nonfunctioning adenomas without clinical significance.[4,32,34,36,38,45,48,69] Nevertheless, such pituitary incidentalomas require careful judgement to prevent inappropriate surgery.[14] Pituitary hyperplasia was reported in a 57-year-old female with insulin-mediated pseudoacromegaly,[15] and in two males (ages 22 and 64) with pseudoacromegaly due to long-standing primary hypothyroidism in whom the hyperplasia resolved following euthyroidism restoration[16,17]; hence, none of these were related to normal pituitary hypertrophy that is common in adolescents and young women.[70]

Acromegaloid facies and acral enlargement were the most common acromegaloid features, described in 75% and 80% of cases, respectively. Other frequent clinical features include hyperhidrosis, pachydermia, arthralgia, macroglossia, prognathism, acanthosis nigricans and tall stature, features also very common in acromegaly.[53,55] The overall prevalence of these features in our cohort is intrinsically associated with the predominance of the most represented pseudoacromegaly causes, namely pachydermoperiostosis and insulin-mediated pseudoacromegaly. The main features of pachydermoperiostosis (also known as primary hypertrophic osteoarthropathy) are digital clubbing, joint problems and pachydermia (thickening and furrowing of the skin). Digital clubbing is the most specific sign of this condition, while joint manifestations typically include arthralgia, synovial effusions, periosteal changes, acroosteolysis and interosseous membranes ossification, affecting mainly the knees, ankles and wrists.[1,2] Skin involvement is characterized by facial coarsening, skin hypertrophy and pachydermia of the forehead, face, and scalp (cutis verticis gyrata).[1,3] Other features of pachydermoperiostosis includes hyperhidrosis, seborrhoea, acne, blepharoptosis, hypoalbuminemia, chronic gastritis, peptic ulcer, episodes of watery diarrhoea, anaemia and myelofibrosis.[1,2] In insulin-mediated pseudoacromegaly, the major features are weight gain/obesity, acanthosis nigricans, skin tags, acne, seborrhoea, hirsutism, hyperhidrosis, hyperglycaemia/diabetes, dyslipidemia, acromegaloid facial features (coarsening, frontal bossing, separated teeth, prognathism), macroglossia, acral enlargement, oligomenorrhea and polycystic ovaries.[1,2] This clinical picture together with the demonstration of a normal GH/IGF-1 axis and high basal levels of serum insulin, with or without hyperglycaemia, support a diagnosis of insulin-mediated pseudoacromegaly; an OGTT may further aid to confirm this diagnosis as, typically, there is a marked elevation of insulin levels after an oral glucose load related with the severe insulin resistance characteristic of insulin-mediated pseudoacromegaly.[2]

The phenotypic characterization of pseudoacromegaly as a whole, we provide here may be useful to have an overview of the main manifestations in pseudoacromegaly, particularly in the subgroup of disorders with higher likelihood of mimicking acromegaly. However, the clinical data we report should be interpreted cautiously, as it is dependent on the quality and level of detail from each published case. In some case reports, there might have been features underreported, which will give inaccurate figures, while other cases there was no information on some clinical aspects. Moreover, the cases were published by a wide range of medical specialists, hence some endocrine-related features may have been overlooked or not described. This may explain prevalence differences concerning some symptoms between cases referred to endocrinologists and cases referred to non-endocrine departments, together with the different distribution of pseudoacromegaly causes between these two subgroups. The prevalence of acromegaloid features and tall stature was higher in cases referred to endocrine specialists, as

expected given their expertise in assessing growth-related issues, highlighting the need for endocrinologists to be familiar with pseudoacromegaly conditions associated with acromegaloid appearance and overgrowth/tall stature.[1,2] Another limitation of this study relates with the amplitude of the case report publication dates, which entails issues in terms of availability/reliability for some biochemical, imaging or genetic tests.

Nevertheless, our study provides novel and unique insights into the complex topic of pseudoacromegaly and gives an overview about the spectrum of pseudoacromegaly conditions that may be encountered by endocrinologists, as we focused in cases presented with high suspicion for acromegaly.[71–75] Additionally, our study illustrates well the key role of adult and paediatric endocrinologists in the work-up and management of a pseudoacromegaly patient. We acknowledge that our series comprises patients who were selected based on exclusion of GH/IGF-1 excess, while a large proportion of published pseudoacromegaly cases have not had this assessment. Also, it is worth noting that we included only pseudoacromegaly cases where an underlying disease has been elucidated, which may lead to an overrepresentation of rare causes of pseudoacromegaly, while other etiologies of pseudoacromegaly, including individuals with pseudoacromegaly of no clear cause, or even normal subjects with physical acromegalic traits, are not represented. However, by including only pseudoacromegaly patients who presented with a strong suspicion for acromegaly and where the pseudoacromegaly diagnosis was established, we identified and characterized the pseudoacromegaly conditions more likely to be referred to the endocrine clinic, while at the same time, we prevented the risk of including pseudoacromegaly conditions with a low likelihood to masquerade as acromegaly,[1,2] less likely to be referred to endocrinologists, as well as patients with acromegaly with apparently normal GH secretion, inappropriate/discrepant assessment of the somatotroph axis, or with "burnt out" acromegaly.[54,76–78]

In summary, pseudoacromegaly is a challenging entity with pachydermoperiostosis and insulin-mediated pseudoacromegaly being the most often conditions mimicking acromegaly that may be encountered by adult and paediatric endocrinologists. Adequate assessment of the GH/IGF-1 axis by an endocrinologist is crucial to exclude acromegaly, and further work-up should be undertaken to diagnose the underlying pseudoacromegaly condition. Pituitary imaging is not indicated in pseudoacromegaly cases where the biochemical assessment of GH/IGF-1 axis is normal. Pituitary incidentalomas found in patients with pseudoacromegaly require careful judgement to prevent inappropriate pituitary surgery.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

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

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