Achalasia and acromegaly: Co-incidence of these diseases or a new syndrome?

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Background. Acromegaly is a disorder associated with hypersecretion of growth hormone, most usually caused by a pituitary adenoma. Dysmotility of the gastrointestinal tract has been reported in acromegalic patients. Achalasia is a disorder characterized by aperistalsis of the oesophagus with incomplete lower oesophageal sphincter relaxation and whose aetiology remains unknown. Mutations in some genes have previously been associated with the development of acromegaly or achalasia. The study aims were to analyse mutations in selected genes in a woman having both of these diseases, to identify their aetiological factors, and to suggest explanations for the co-incidence of acromegaly and achalasia.

Methods and Results. A female patient with acromegaly, achalasia, and a multinodular thyroid gland with hyperplastic colloid nodules underwent successful treatment of achalasia via laparoscopic Heller myotomy, a thyroidectomy was performed, and the pituitary macroadenoma was surgically excised via transnasal endoscopic extirpation. Germline DNA from the leukocytes was analysed by sequencing methods for a panel of genes. No pathogenic mutation in *AAAS, AIP, MEN1, CDKN1B, PRKAR1A, SDHB, GPR101*, and *GNAS* genes was found in germline DNA. The somatic mutation c.601C>T/p.R201C in the *GNAS* gene was identified in DNA extracted from a tissue sample of the pituitary macroadenoma.

Conclusions. We here describe the first case report to our knowledge of a patient with both acromegaly and achalasia. Association of acromegaly and soft muscle tissue hypertrophy may contribute to achalasia's development. If one of these diagnoses is determined, the other also should be considered along with increased risk of oesophageal and colorectal malignancy.

Key words: acromegaly, pituitary tumour, achalasia, autoimmune syndrome, gene, mutation, *AAAS, GPR101, GNAS*

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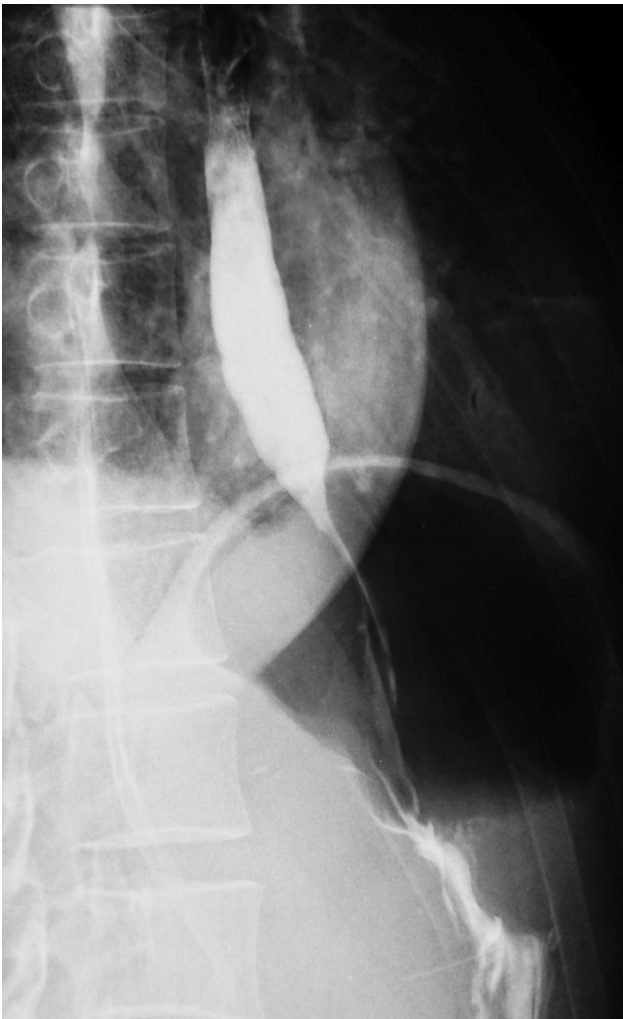Corresponding author: Lumir Kunovsky, e-mail: lumir.kunovsky@gmail.com

BACKGROUND

Acromegaly is a rare disease with incidence of approximately 3–5 persons per 1,000,000 (ref.[1-3]). This disorder is characterized by hypersecretion of growth hormone (GH), which is usually caused by a pituitary adenoma[2,4]. This leads to overgrowth of almost all tissues in the body, most especially of acral and soft tissues, and to visceromegaly[5]. Multisystemic complications develop in acromegalic patients due to high GH and insulin-like growth factor-1 (IGF-1) levels, and these include joint pain, diabetes mellitus, hypertension, heart and respiratory failure, as well as disorders of the gastrointestinal (GI) system[2,3]. GI manifestations associated with acromegaly include adenomatous polyps, colon carcinoma, dolichocolon, and dysmotility (prolonged bowel transit time and impaired relaxation of the lower oesophageal sphincter [LES]) (ref.[4]).

Acromegaly is associated with decreased survival rate[6]. Acromegalic patients experience mortality due to cardiovascular disease in 60% of cases, respiratory disorders in

25% of cases, and neoplasms in 15% of cases (ref.[3,7]). This survival rate can be improved by successful surgical and adjunctive therapy[3].

Although acromegaly occurs sporadically in 95% of all cases, almost 50% of childhood-onset cases have an identifiable genetic background, most commonly in the form of mutations in the genes encoding aryl hydrocarbon receptor interacting protein (*AIP*) or G-protein coupled receptor 101 (*GPR101*) (ref.[8]). In addition, mutations in genes such as multiple endocrine neoplasia type 1 (*MEN1*); cyclin-dependent kinase inhibitor 1B (*CDKN1B*); protein kinase A regulatory subunit type I alpha (*PRKAR1A*); genes of the succinate dehydrogenase family A, B, C, and D (*SDHx*); and the adenylate cyclase stimulatory protein alpha subunit (*GNAS*) also have been associated with acromegaly/gigantism[8].

Achalasia is an oesophageal motility disease characterized by aperistalsis of the oesophagus and impaired LES relaxation[9,10]. This disorder is caused by a degeneration of the myenteric plexus, but the aetiology of this degeneration remains unclear[11]. It is assumed that the plexus degeneration arises from a genetic predisposition caused by a viral infection and/or autoimmune process[9,11]. The incidence of this disease varies worldwide from 0.27 to 1.63 per 100,000 (ref.[12-17]).

The diagnosis is based on clinical symptoms, endoscopy, high-resolution oesophageal manometry (HRM), and/or swallow radiography. Treatment can be conservative, endoscopic, or surgical[11,18].

Achalasia can develop independently or as a part of Allgrove (Triple A) syndrome (i.e., adrenal insufficiency, achalasia, and alacrimia) (ref.[19]). In the latter case, association with mutations in the *AAAS* gene has been identified[20].

The aims of this study were to analyse the genes associated with acromegaly and achalasia in a woman with both of these diseases, to find their aetiopathogenetic factors, and to suggest some explanations for the co-incidence of acromegaly and achalasia.

CASE PRESENTATION

We present a female whose history consists solely of recurrent superficial venous thrombosis of the lower extremities. No hypercoagulation syndrome was noted. In the family history there was no oesophageal disease or acromegaly. The patient has a monozygotic twin. At 30 years of age (in 2008), a multinodular thyroid gland with hyperplastic colloid nodules was identified, resulting 1 year later in a total thyroidectomy (preoperative values of thyroid gland hormones: thyroid stimulating hormone 1.07 mU/L, thyroxine 12.86 pmol/L).

In 2009 (at 31 years), an investigation for oesophageal dysmotility was performed due to dysphagia. Achalasia was identified by manometry with characteristic findings (Fig. 1). Treatment was started with balloon dilation of the oesophagus, but the effect was only temporary. The control swallow radiograph can be seen in Fig. 2. A laparoscopic Heller myotomy (LHM) with Nissen–Rossetti fundoplication was performed. After this procedure, the patient recovered without any signs of dysphagia.

In 2016 (at 38 years of age), acromegaly was suspected because the typical acromegalic changes of the face (acral growth) as well as of the lower and upper extremities were observed. The patient started to experience severe headaches. Her foot size had grown 5 cm in 7 years, she was not able to put a ring on her finger, and changes in

Fig. 1. HRM showing a typical view of achalasia type II – simultaneous contraction and non-relaxing LES during swallowing.

Fig. 2. The patient underwent sequential balloon dilations without treatment response. Fluoroscopy with barium revealed mild dilatation of the oesophagus with distal smooth, short-segment tapering.

Fig. 3a, 3b. Contrast-enhanced MRI - T1WI. Sagittal section (a), coronal section (b) showing a non-enhanced pituitary mass 14 × 10 × 9 mm in size. The optic chiasm was not affected by the lesion.

the patient's voice also occurred. Laboratory tests gave reasons for suspicion of acromegaly (GH 48 mU/L, reference range 0−24 mU/L; IGF-1 725 µg/L, reference range 109−284 µg/L). The diagnosis of acromegaly was confirmed by serum GH concentrations assessed during an oral glucose tolerance test (GH 48 mU/L at beginning of test, 28 mU/L after 1 h of glucose application, 22 mU/L after 2 h. The test was positive due to inadequate suppression of GH after application of 75 g of glucose. Magnetic resonance imaging (MRI) revealed a macroadenoma of the non-enhanced pituitary gland 14 × 10 × 9 mm in size (Fig. 3a, 3b). The optic chiasm was not affected by the lesion. The patient was referred to neurosurgery and transnasal endoscopic extirpation of the adenoma was performed. The histopathology of the adenoma of the pituitary gland can be seen in Fig. 4a and 4b. The patient

was discharged 8 days after surgery. The control MRI showed a small residual amount of adenoma tissue, which was successfully treated by gamma knife radiosurgery. Subsequently, the levels of GH and IGF-1 normalized (hormone levels after surgery GH 7 mU/L, IGF-1 345 µg/L; after radiotherapy GH 15 mU/L, IGF-1 189 µg/L; 1 year after radiosurgery GH 8 mU/L, IGF-1 178 µg/L). We also performed a colonoscopy, with normal findings. An echocardiography showed normal heart function without signs of cardiomyopathy or valve dysfunction.

Table 1. Sequences of the specific primers used for PCR amplification of all 16 exons of the *AAAS* gene (NM_015665).

Location of exons (NM_015665)	Forward primer	Reverse primer
1..286 287...414	5′-GTGACCCAGGAAACCCTTT-3′	5′-AGAAGCTTTGGAGGTCTGTC-3′
415...470 471...562	5′-AAGGATAGGAATGAGGGCAGA-3′	5′-AAGCTGACCCACATTTTCCTC-3′
563...609 610...708 709...852	5′-AACTCTCAGGCCAAGGTAAG-3′	5′-CCAGTGTGTCCTGTGTCTATC-3′
853...973 974...1098 1099...1159 1160...1250	5′-TGACCACCCCAAATACTGAA-3′	5′-TTCTGACTCCACATCCTCTGT-3′
1251...1344 1345...1412 1413...1494 1495...1579 1580...1837	5′-CAACTCCCTGGAAAAGACAGA-3′	5′-CTTGCAAGAACCTCTCTGCT-3′

Table 2. Common polymorphisms in the genes associated with acromegaly found in the patient.

Gene	Variant cDNA	Variant protein	RefSeq accession	dbSNP	Hetero/ homozygous	MAF in EU population (%)	Method
MEN1	c.1621A>G	p.T541A	NM_000244	rs2959656	homozygous	99.0	NGS panel
MEN1	c.1314T>C	p.H438H	NM_000244	rs540012	homozygous	100.0	NGS panel
AIP	c.682C>A	p.Q228K	NM_003977	rs641081	homozygous	100.0	NGS panel
AIP	c.920A>G	p.Q307R	NM_003977	rs4930199	homozygous	100.0	NGS panel
CDKN1B	c.326T>G	p.V109G	NM_004064	rs2066827	heterozygous	24.3	NGS panel
PRKAR1A	c.998G>A	p.S333N	NM_002734	rs9789047	heterozygous	20.6	NGS panel
PRKAR1A	c.349-5dupT	-	NM_002734	rs3841514	heterozygous	24.7	NGS panel
PRKAR1A	c.770-24G>A	-	NM_002734	rs2302230	homozygous	68.0	NGS panel
PRKAR1A	c.892-34G>T	-	NM_002734	rs2302231	homozygous	67.8	NGS panel
SDHB	c.201-36G>T	-	NM_003000	rs1022580	homozygous	97.2	NGS panel
SDHB	c.18C>A	p.A6A	NM_003000	rs2746462	homozygous	97.2	NGS panel
GPR101	c.370G>T	p.V124L	NM_054021	rs1190736	homozygous	38.0	Sanger sequencing

Minor allele frequency (MAF) refers to the frequency at which the second most common allele occurs in a given population.

GENETIC ANALYSIS

Germline DNA was isolated from leukocytes of peripheral blood by a standard protocol (phenol–chloroform method).

An original protocol was created for identifying mutations in the *AAAS* gene associated with achalasia. Five pairs of specific polymerase chain reaction (PCR) primers were designed to amplify all 16 exons of the *AAAS* gene (NM_015665) (Table 1). The PCRs were performed using RED*Taq*® DNA polymerase (VWR, Radnor, PA, USA) in a 20 µL reaction volume. The conditions for PCR were as follow: 95 °C for the 2.5 min activation/denaturation step, followed by 40 cycles of 95 °C for 20 s, 60 °C for 20 s, 72 °C for 60 s, with a final extension for 5 min. Amplicons were purified by *Exo*I-FastAP (Thermo Fisher Scientific, Waltham, MA, USA). The mixtures were incubated at 37 °C for 15 min and at 85 °C for 15 min to inactivate the enzymes, followed by sequencing with a BigDye Terminator v.3.1 (Applied Biosystems, Foster City, CA, USA). Sequencing reactions were purified by EDTA/ethanol precipitation, resuspended in 15 µL Hi-Di Formamide (Applied Biosystems), then sequenced on an automated ABI 3500 Genetic Analyzer (Applied Biosystems). Finally, sequences were compared using BioEdit v.7.0.9.0 (ref.[21]) with a standard sequence NM_015665 of the *AAAS* gene obtained from the GenBank database.

There were two differences between the patient's sequence and the standard sequence NM_015665 of the *AAAS* gene. First, the patient was heterozygous (AT) in position 195 (counting according to the translated sequence). Second, the T base of the C855T single nucleotide polymorphism (SNP), known as rs1546808, was recorded on both strands (Supplementary data 1).

For identification of mutations in genes associated with acromegaly/gigantism in the patient, an NGS-based panel targeting 345 genes was used. This panel is customized and primarily designed for detecting mutations in
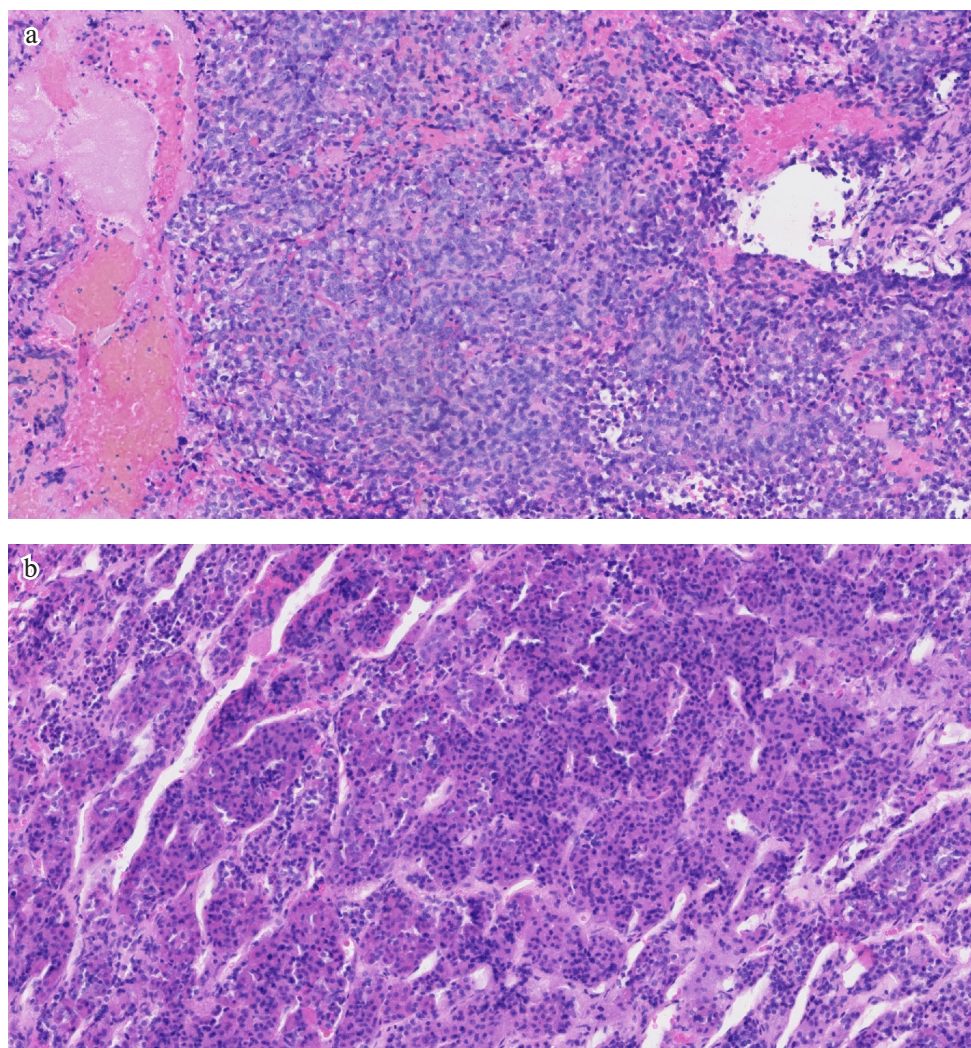
Fig. 4a, 4b. Histopathology of the adenoma of the pituitary gland. A tumour consisting of trabeculae of polygonal cells with uniform, round to oval nuclei with smooth chromatin and amphophilic cytoplasm. No mitoses or necrosis present. Haematoxylin-eosin staining (200×).

genes associated with a predisposition towards various cancers, but it includes five genes that have been found to be mutated also in patients with acromegaly: *AIP*, *MEN1*, *CDKN1B*, *PRKAR1A*, and *SDHB* (ref.[8]). The patient's DNA extracted from the leukocytes was used as input material for the assay, followed by the preparation of sequencing libraries using SureSelectXT HS Target Enrichment System (Agilent, Santa Clara, CA, USA) according to the manufacturer's protocol and sequencing on a NextSeq 500 device (Illumina, San Diego, CA, USA). In the bioinformatic analysis, sequencing reads in fastq format were mapped to the human reference genome GRCh37 with the bwa mem algorithm. PCR duplicates were marked in the resulting alignments with the Fgbio toolkit, which can utilize unique molecular identifiers included in the library. The quality of the final alignments was checked in respect to region coverage and depth and was used to assess germline variants. To minimize false negative calls, three different tools were used for germline variant calling (i.e., GATK HaplotypeCaller, VarDict, and Strelka2) and resulting variants were merged. Merged variants were annotated using the VEP annotation tool, which includes

PolyPhen and SIFT scores for variant structural impact and reports co-located variants from several databases (snpDB, COSMIC, HGMD, NHLBI_ESP, and ClinVar).

Variants were filtered manually. Examination using this NGS-based panel revealed only common polymorphisms in the genes of interest in our patient (reported in Table 2).

Because no pathogenic mutation was found using the NGS panel, we decided to take a closer look at the remaining genes that have been related to acromegaly: *GPR101* and *GNAS*.

Amplification and sequencing primers were designed (primer sequences and PCR conditions are available in Supplementary data 2) for the whole coding region of the *GPR101* gene and the most common mutations in codons R201 and Q227 of the *GNAS* gene.

DNA extracted from the formalin-fixed paraffin-embedded (FFPE) tissue sample of the pituitary macroadenoma and of the thyroid gland was used for identifying somatic mutations in the *GNAS* gene.

Sequencing was performed on an ABI 3500 Genetic Analyzer device (Applied Biosystems) and sequences
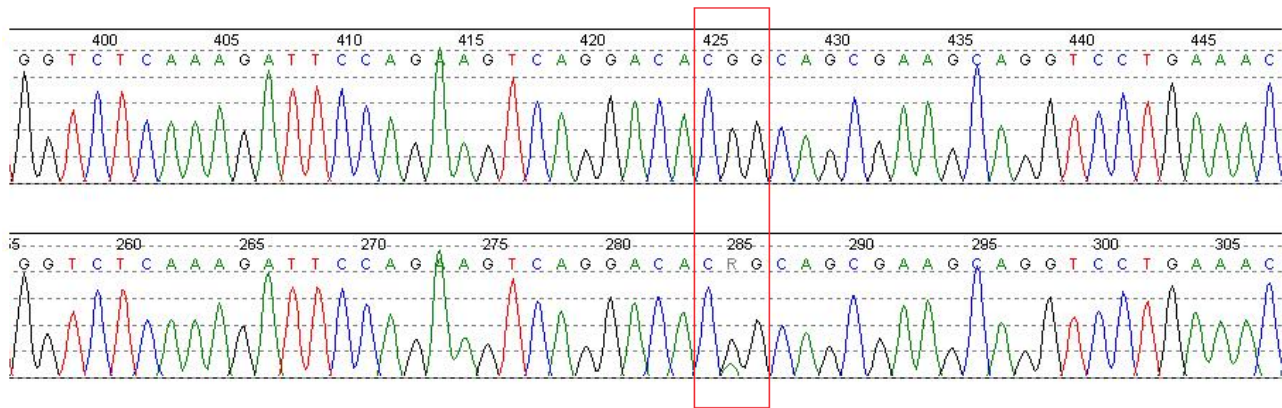
Fig. 5. Part of the *GNAS* gene sequence – reference sequence NM_000516 (upper row), patient sequence with the c.601C>T/p.R201C mutation (lower row). The red square is a codon.

were analysed using the Mutation surveyor V4.0.9 software (SoftGenetics, State College, PA, USA).

The common polymorphism c.370G>T/p.V124L (NM_054021, rs1190736; see Table 2) was found using Sanger sequencing, while sequencing of the *GNAS* gene revealed the somatic mutation c.601C>T/p.R201C (NM_000516, rs11554273; Fig. 5) in tissue of the pituitary macroadenoma only but not in that of the thyroid gland. Peripheral blood samples were obtained from the patient's monozygotic twin, mother, and father. DNA from leukocytes was extracted and the *GNAS* gene was analysed. No pathogenic mutation was found in this gene within the germline DNA of the patient's relatives.

DISCUSSION AND CONCLUSION

The diagnosis of achalasia is based on clinical symptoms (dysphagia, regurgitation, retrosternal pain, vomiting, and weight loss), endoscopy, HRM, and/or swallow radiography. Treatment can be conservative (botulinum toxin, pneumatic dilation, or medical therapy), endoscopic (peroral endoscopic myotomy [POEM]), or surgical (LHM) (ref.[11,18]). The best long-term results in therapy are achieved by pneumatic dilation or LHM (ref.[18,22]). Long-term follow-up studies to evaluate the effectiveness of POEM are needed[23,24]. The main limitation of POEM may be its non-association with any anti-reflux procedure, which is in contrast to LHM (ref.[24]). Our patient achieved excellent postoperative results with LHM and the dysphagia disappeared.

The clinical manifestations of acromegaly usually develop slowly and the diagnosis is often determined late (from 4 years to more than 10 years after onset) (ref.[3]). So it is possible also in our patient that the acromegaly could already have started even before the diagnosis of achalasia. The average onset of the disease is at 49 years, with no difference by gender[25]. Because of the increased morbidity and mortality in acromegalic patients, early diagnosis of the disease is critical[6]. Making a diagnosis generally starts with a clinical suspicion (most typically acral growth and changes, as well as increased shoe and/or ring size). A diagnosis of acromegaly is confirmed, however, by high levels of GH and IGF-1 (ref.[2,3]).

Due to the excess of GH and IGF-1, soft tissue hypertrophy involving the GI organs occurs in acromegalic patients[1]. This results in an enlargement of the GI organs. For example, dolichocolon is often observed in patients with acromegaly. George et al.[5] reported the case of an acromegalic patient with megaduodenum, where the destruction of neurons within the plexuses was mentioned as the possible aetiological cause.

Higher prevalence of colorectal neoplasm, prolonged bowel transit time, and dysmotility of the entire GI tract (including the oesophagus) have been described. Baldy-Waligorska et al.[26] stated that long-lasting uncontrolled acromegaly significantly increased the risk of malignant neoplasms. Higher prevalence of colorectal neoplasm in acromegalic patients has been reported in many studies[1,3,27]. Because of an increased risk of colorectal neoplasms, more frequent endoscopic screening is recommended[27].

Prolonged exposure to high levels of GH and IGF-1 also affects the heart muscle. Dilation and hypertrophy of the heart (dilated cardiomyopathy) can develop[28].

Oesophageal dysmotility and impaired LES relaxation in acromegalic patients have been described previously[4,29]. Some theories of motility disorders have been associated with low levels of nitric oxide (as the main neurotransmitter in the GI tract causing smooth muscle relaxation). Another theory of oesophageal motility dysfunction considers alterations in GI hormones (ghrelin and somatostatin) and GH levels[4].

An association between dilation and hypertrophy of soft tissue and muscle tissue (oesophageal dysmotility, prolonged bowel transit time, dolichocolon, megaduodenum, and dilated cardiomyopathy) in achalasia aetiology should be considered. Hypertrophy of the soft tissue possibly causes the destruction of neuron plexuses, which can be one of the possible aetiologies of achalasia.

A co-occurrence of achalasia and oesophageal cancer has also been reported[23]. A relationship between food stasis, chronic inflammation, and a potentially increased risk of carcinoma development has also been described[30,31].

Based on these reports, a thorough endoscopic surveillance was required for our patient having co-occurrence of acromegaly and achalasia.

Some authors have reported an increased incidence of achalasia with autoimmune thyropathy[32]. This strengthens the theory of achalasia's having an autoimmune disease aetiology. In our case, the thyroid gland of the patient had also been treated. Nevertheless, no autoimmune thyroid disorder was revealed.

A possible association of achalasia and polyglandular autoimmune syndrome type 2 (autoimmune Addison's disease in combination with autoimmune thyroid disease and/or type 1 diabetes mellitus) is also described in the literature[10,33]. Moreover, there are several reports associating megaesophagus with adrenocortical insufficiency and other autoimmune endocrine diseases in dogs[34,35]. Fritzen et al.[36] in 1996 even described a human with megaesophagus and autoimmune adrenal failure as a feature of autoimmune polyglandular syndrome type 2. In addition to these findings, dysphagia and vomiting are also characteristic in untreated Addison patients, but they usually resolve after hormone substitution[33,36]. It nevertheless remains unclear whether low cortisol levels could possibly play a role in the development of lower oesophagus dysmotility or achalasia. Moreover, our patient had normal cortisol levels.

Because of the possibility that our patient with achalasia might be suffering from Allgrove (Triple A) syndrome, the *AAAS* gene was analysed. This gene encoding the ALADIN protein (WD-repeat protein) (ref.[20]) is located on chromosome 12 and is strongly associated with Allgrove syndrome[37]. In our patient, however, we found no clinical signs for this syndrome (the patient did not suffer from alacrimia or adrenal insufficiency), nor did we find the typical mutations to confirm the presence of this syndrome. We found a novel mutation A195T in exon 2 leading to the synonymous substitution (Thr65Thr). There was also a difference between the patient's and the standard sequence in position 855 (Phe285Phe). The T allele of SNP rs1546808 occurs with high frequency in the European Caucasian population (99.5%, https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1546808), however, and therefore these findings are not significant in relation to this syndrome.

In addition, we found no "causal" mutations in genes previously associated with acromegaly (i.e., *MEN1, AIP, CDKN1B, PRKAR1A, SDHB, GPR101*) and only common polymorphisms were detected in these genes in our patient. Activating mutations in the *GNAS* gene, with a frequency of about 40%, are the most common somatic mutations in acromegaly. Mutation c.601C>T/p.R201C in the *GNAS* gene leads to a loss of GTPase activity of the G-stimulatory protein alpha subunit while leaving adenyl cyclase stimulatory activity intact. The result of constitutive activation and increased intracellular cAMP levels could probably lead to somatotroph hyperplasia/adenoma and GH hypersecretion[38]. Genetic examination proved that our patient had sporadic acromegaly with no evidence for family-based acromegaly. Further, we suppose the co-occurrence of acromegaly with the previously diagnosed achalasia, but the aetiopathogenesis of this state is unclear.

Co-incidence of acromegaly and McCune–Albright syndrome (MAS) has been described in the literature. Acromegaly affects around 20–30% of MAS patients[39]. MAS includes the triad of poly/monostotic fibrous dysplasia, café-au-lait spots, and hyperfunctioning endocrinopathies (precocious puberty) (ref.[40]). In our patient, we found no café-au-lait spots, fibrous dysplasia of the bones, or precocious puberty.

CONCLUSION

In conclusion, acromegaly, with its typical overproduction of GH, affects all systems of the human body. Gastrointestinal dysmotility in acromegalic patients (i.e., impaired relaxation of the LES) has been previously described. We report the first co-occurrence of acromegaly and achalasia, and we suggest the association of acromegaly and soft muscle tissue hypertrophy as one of the factors contributing to achalasia development. If one of these two diagnoses is determined, therefore, presence of the other should be considered. Moreover, an increased risk of malignancy (oesophageal and colorectal) should also be considered. More studies are needed to clarify the aetiology and association of these two diseases.

ABBREVIATIONS

GH, Growth hormone; GI, Gastrointestinal; HRM, High-resolution oesophageal manometry; IGF-1, Insulin-like growth factor-1; LES, Lower oesophageal sphincter; LHM, Laparoscopic Heller myotomy; MAS, McCune–Albright syndrome; POEM, Peroral endoscopic myotomy; SNP, Single nucleotide polymorphism.

Author contributions: JD: writing, main author, conception and design of the work, literature search; LK: consultant, writing, text editor, conception and design of the work, literature search, figures; RK, KS, PJ, TN, KM, TA, FM, ZK, and JV: consultants, text editors, conception and design of the work, figures, literature search; DS: histopathological examination; MZ, JL, HPN, OS: text editors, genetic analyses; LIH: consultant and text editor; PBL:

design of genetic analysis, literature search, text editor. All authors made critical revisions and gave their final approval for publishing.

Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

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Supplemental Material:
The online version of this article (doi: 10.5507/bp.2021.040) offers supplemental material.