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Acromegaly management in the Nordic countries: A Delphi consensus survey

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Abstract

Objective: Acromegaly is associated with increased morbidity and mortality if left untreated. The therapeutic options include surgery, medical treatment, and radiotherapy. Several guidelines and recommendations on treatment algorithms and follow-up exist. However, not all recommendations are strictly evidence-based. To evaluate consensus on the treatment and follow-up of patients with acromegaly in the Nordic countries.

Methods: A Delphi process was used to map the landscape of acromegaly management in Denmark, Sweden, Norway, Finland, and Iceland. An expert panel developed 37 statements on the treatment and follow-up of patients with

For affiliations refer to page 272.

Mai C. Arlien-Søborg and Jakob Dal are shared first authorship.

acromegaly. Dedicated endocrinologists ($n = 47$) from the Nordic countries were invited to rate their extent of agreement with the statements, using a Likert-type scale (1–7). Consensus was defined as ≥80% of panelists rating their agreement as ≥5 or ≤3 on the Likert-type scale.

Results: Consensus was reached in 41% (15/37) of the statements. Panelists agreed that pituitary surgery remains first line treatment. There was general agreement to recommend first-generation somatostatin analog (SSA) treatment after failed surgery and to consider repeat surgery. In addition, there was agreement to recommend combination therapy with first-generation SSA and pegvisomant as second- or third-line treatment. In more than 50% of the statements, consensus was not achieved. Considerable disagreement existed regarding pegvisomant monotherapy, and treatment with pasireotide and dopamine agonists.

Conclusion: This consensus exploration study on the management of patients with acromegaly in the Nordic countries revealed a relatively large degree of disagreement among experts, which mirrors the complexity of the disease and the shortage of evidence-based data.

KEYWORDS

acromegaly, Delphi, dopamine agonist, growth hormone, growth hormone receptor antagonist, insulin-like growth factor i, somatostatin

1 | INTRODUCTION

Acromegaly is a disease characterized by growth hormone (GH) hypersecretion in most cases from a benign pituitary adenoma, which causes disproportionate and excessive growth of the skeleton, soft tissues, and internal organs. The disease is associated with comorbidities and metabolic complications, including arterial hypertension, cardiomyopathy, diabetes, sleep apnea, arthropathy, vertebral fractures and increased mortality.[1,2]

The treatment options include surgery, pharmacological treatment, and radiotherapy.[3,4] Pituitary surgery, preferably via the transsphenoidal route, remains a cornerstone in the treatment algorithm as the best opportunity for biochemical remission. However, disease control with surgery is only obtained in 50–60% depending on adenoma size and invasiveness of surrounding structures, particularly the cavernous sinus.[5,6] Medical treatment with a first-generation somatostatin analog (SSA) is recommended when surgery fails or is contraindicated and provides adequate control in 30–50% in addition to adenoma shrinkage in a subset of patients.[7] The GH receptor antagonist pegvisomant is often used in patients, who fail to achieve biochemical control with first-generation SSA, and normalizes Insulin-like growth factor I (IGF-I) levels in a dose-dependent manner.[8] Moreover, pegvisomant is frequently used in combination with a first-generation SSA.[9,10] Pasireotide LAR, a second-generation SSA, can provide disease control and adenoma shrinkage in patients who fail to respond sufficiently to first-generation SSA[11,12] and may alleviate headache.[13] Clinically significant hyperglycemia, however, is a frequent side effect of pasireotide.[14] The effect of dopamine agonists is usually moderate and unpredictable but may be used as an add-on in treatment resistant patients or in patients with mild disease.[4] Finally, focused radiotherapy remains an option, which according to current guidelines is restricted to patients who remain uncontrolled after surgery and/or medical therapy.[3,4]

Taken together, most patients are amenable to disease control, but it frequently demands a personalized and multimodal treatment.[7,15] Thus, even the most comprehensive treatment guidelines and consensus statements fail to cover all cases and not all recommendations can be strictly evidence-based for this rare disease. Consequently, several questions remain controversial, such as the role of preoperative SSA treatment, the risk-benefit of repeat surgery, the use of pegvisomant as primary treatment, and the position of pasireotide in the treatment algorithm. Moreover, external factors such as the organization of the health care system and health insurance coverage play an important role. In this regard, the Nordic countries, which include Denmark, Sweden, Norway, Finland, and Iceland are relatively homogenous and provide its inhabitants access to a tax-funded health care system. This prompted us to compare real life clinical practice of acromegaly treatment in these countries. We used the Delphi survey technique[16] to measure consensus as well as disagreement among clinical experts on the treatment of acromegaly. This process is interactive and iterative, during which anonymized opinions feedback to the same expert panel in a series of rounds.

2 | MATERIALS AND METHODS

A scientific committee of five experienced endocrinologists developed the study objectives and an online survey containing 42 statements focusing on the treatment and follow-up of acromegaly. Forty-seven endocrinologists with at least 5 years of experience in the treatment of acromegaly from 23 centers, Denmark ($n = 14$), Sweden ($n = 13$), Norway ($n = 5$), Finland ($n = 14$), and Iceland ($n = 1$), were invited to participate.

The survey consisted of three Delphi rounds. In the first round, the survey was anonymously answered with the possibility to comment on each statement and to suggest new ones. For each statement, the participants were asked to rate their agreement or disagreement on a Likert-type scale as follows: (1) strong disagreement, (2) disagreement, (3) some disagreement, (4) neutral, (5) some agreement, (6) agreement (7) strong agreement. Consensus was defined as ≥80% of panelists rating their agreement as ≥5 (indicating agreement) or ≤3 (indicating disagreement) on the Likert-type scale.

Aggregated and anonymized data from the first round were sent to all participants before a physical consensus meeting was held. Based on the issues raised, the scientific committee rephrased eleven statements, deleted eight statements, and added three new statements. The final online Delphi survey consisted of 37 statements, which were used in round two and three. The statements focused on (1) primary treatment of acromegaly ($n = 4$), (2) preoperative treatment with SSA ($n = 3$), (3) second-line treatment ($n = 5$), (4) second- and third-line medical treatment ($n = 14$), (5) treatment of acromegaly in relation to pregnancy ($n = 7$), (6) long-term follow-up after disease control with surgery only ($n = 4$). In the second round, the participants were again asked to rate their agreement with the 37 statements using the Likert-type scale. Aggregated and anonymized data from the second round were sent to the participants before the third round.

3 | RESULTS

Forty-seven endocrinologists from the Nordic countries participated in the survey (67% women; on average 18 (range: 1–40) years of experience). The endocrinologists from Denmark, Sweden, Norway, and Iceland answered rounds 1–3. The endocrinologists from Finland answered the third round only.

3.1 | First Delphi round

Consensus was achieved in 33% (14/42) of all statements.

As regards *Primary treatment*, there was consensus to recommend pituitary surgery as first choice of treatment (statement 1).

Panelists did not reach consensus on statements regarding *Preoperative treatment with SSA*.

There was agreement to consider repeat surgery, first-generation SSA treatment after failed surgery and combination therapy with first-generation SSA and pegvisomant as *second and third line treatment* reached consensus in 45% of the statements. However, the panel did not reach consensus on the therapeutic roles of pegvisomant monotherapy, pasireotide or dopamine agonists, respectively.

Topics focusing on the *Treatment of acromegaly in relation to pregnancy* reached consensus in one-third of the statements. Panelists agreed that pituitary surgery is first choice treatment also in patients seeking pregnancy and recommended postponement of treatment in newly diagnosed and pregnant women with mild symptoms and signs of acromegaly. It was also agreed to pause medical treatment during pregnancy.

Consensus was not reached concerning *Long-term follow-up after disease control*.

3.2 | Second and third Delphi round

After the feedback from the first round, the statements were modified where after the consensus rate increased to 41% (15/37). The distribution of panelists' agreement with each statement from the second round was provided to all Delphi panel members in the third round. Panelists reached the same degree of consensus in the third round. The proportion of Delphi panelists that indicated some or complete agreement/disagreement with each statement (≥5 or ≤3 on a Likert-type scale) is shown for the third Delphi round in Table 1.

Consensus on *Primary treatment* increased after one statement was rephrased from 'I consider surgery first choice treatment in all eligible patients regardless of tumor size and location' to 'I consider surgery first choice treatment in all eligible patients including curative and debulking surgery' (statement 1).

Panelists still did not reach consensus regarding *Preoperative treatment with SSA* (statement 5–7).

Consensus on *Second line treatment* including repeat-surgery (statement 11) and postsurgical SSA treatment (statement 9-10) remained high.

Panelists reached agreement in one fifth of statements regarding *Second and third line medical treatment* (statement 13 + 15 + 26). Disagreement remained on the use of pegvisomant monotherapy, pasireotide, and dopamine agonists (statement 14 + 16-25).

As regards *Acromegaly in relation to pregnancy*, one statement was rephrased to 'I recommend to initiate/restart treatment with 1st generation SSA in a pregnant woman who has marked symptoms and/or tumor growth', which panelists agreed upon (statement 30). Panelists also achieved consensus on a new statement recommending first-generation SSA treatment until conception for women with acromegaly seeking pregnancy, who are ineligible for surgery (statement 31).

Panelists achieved consensus on one statement about *Long-term follow-up after disease control*, which was added after the consensus

TABLE 1 Proportion of panelists indicating some or complete agreement/disagreement (rating ≥ 5 or ≤3 on a Likert-type scale) with topics pertaining to the treatment and follow-up of patients with acromegaly.

No.	Statement	
About primary treatment		
1	I consider surgery first choice treatment in all eligible patients including curative and debulking surgery.	90% agreement
2	I consider surgery first choice treatment mainly for adenomas where complete resection is realistic.	75% agreement
3	I consider surgery first choice treatment for any adenoma abutting the visual pathway.	95% agreement
4	I consider that first choice treatment of an adenoma with no visual pathway involvement and with low probability of complete resection is somatostatin analogues (SSA).	51% agreement
Preoperative treatment with SSA (before pituitary surgery)		
5	I consider not recommending presurgical SSA treatment, as I do not find compelling evidence for a better treatment outcome.	74% agreement
6	I consider the use of presurgical SSA treatment only in macroadenomas to increase the probability of postsurgical disease control.	56% agreement
7	I consider the use of presurgical medical treatment to lower disease activity and thereby reduce the risk of complications to surgery.	44% disagreement
Second line treatment		
8	I consider watchful waiting rather than initiation of medical treatment in an asymptomatic patient with marginally elevated GH/IGF-I postsurgery and without significant tumor remnant or disease-specific co-morbidity	51% agreement
9	In a patient with overt and significant persistent disease, I recommend 1st generation SSA regardless of any pituitary tumour remnant.	97% agreement
10	I recommend 1st generation SSA treatment in the presence of overt and significant persistent disease and an un-resectable tumor remnant postsurgery.	97% agreement
11	I consider repeat-surgery in the presence of overt and significant persistent disease with a potentially resectable tumor remnant after first line pituitary surgery.	95% agreement
12	I consider partial biochemical resistance to SSA when IGF-I does not reach normal values despite maximal dosing.	95% agreement
Second and third line medical treatment		
13	In patients with acromegaly, who are partially resistant to SSA treatment at maximum doses, I preferentially combine SSA with pegvisomant.	95% agreement
14	In patients with acromegaly, who are partially resistant to SSA treatment at maximum doses, I preferentially switch to pegvisomant monotherapy and monitor tumor size	67% disagreement
15	As regards pegvisomant treatment, I recommend to initiate with daily or twice weekly injections and to increase the dose until normalization of IGF-I levels are achieved.	97% agreement
16	I consider a large suprasellar tumor remnant a relative contraindication for pegvisomant mono-therapy.	54% disagreement
17	In patients with acromegaly with clinical significant growth of a residual tumor after surgery, who partially respond to 1st generation SSA treatment at maximum doses, I preferentially switch to pasireotide.	67% agreement
18	I consider treatment-resistance to 1st generation SSA and severe headache as a relative indication for a trial with pasireotide.	79% agreement
19	I consider known diabetes mellitus a relative contraindication for pasireotide treatment.	62% agreement
20	I consider discontinuing pasireotide treatment in all patients who develop diabetes mellitus on the drug.	64% disagreement
21	I recommend discontinuation of pasireotide if a patient develops diabetes mellitus which is not controlled by lifestyle modifications and/or metformin.	46% agreement
22	I consider that the efficacy of DA treatment in acromegaly is too low to justify a trial of DA as mono-therapy.	62% agreement
23	I consider that treatment of acromegaly with DA should be restricted to patients who have mild GH/IGF-I elevations.	74% agreement
24	I consider treatment of acromegaly with a dopamine agonist (DA) only to reduce the symptoms of hyperprolactinemia	54% disagreement
25	I consider treatment of acromegaly with a dopamine agonist (DA) only in the presence of hyperprolactinemia.	54% agreement
26	I take histological results after pituitary surgery into account when making decisions about further treatment.	90% agreement

TABLE 1 (Continued)

No.	Statement	
Treatment of acromegaly in relation to pregnancy		
27	I recommend surgery as first-line therapy in women with newly diagnosed acromegaly seeking pregnancy.	100% agreement
28	I recommend postponing acromegaly treatment in a newly diagnosed and pregnant woman with mild symptoms and signs until after delivery.	97% agreement
29	I usually recommend stopping medical treatment once pregnancy is established.	97% agreement
30	I recommend to initiate/restart treatment with 1st generation SSA in a pregnant woman who has marked symptoms and/or tumor growth.	85% agreement
31	I recommend 1st generation SSA treatment until conception for women with acromegaly seeking pregnancy, who have an indication for medical treatment and are ineligible for surgery.	92% agreement
32	I recommend discontinuing 1st generation SSA and pegvisomant treatment approximately 2 months before attempts to conceive, with use of short-acting octreotide where necessary until conception.	51% disagreement
33	I consider to advise against breastfeeding in women who need medical therapy after parturition.	55% agreement
Long-term follow-up after disease control		
34	I consider recommending life-long follow-up in patients controlled by medical treatment.	97% agreement
35	I consider recommending follow-up for 5 years in patients who have been biochemically controlled by surgery-only and do not require treatment for pituitary insufficiency.	72% disagreement
36	I consider recommending follow-up for 10 years in patients who have been biochemically controlled by surgery-only and do not require treatment for pituitary insufficiency.	64% agreement
37	I consider recommending life-long follow-up for patients who are biochemically controlled by surgery-only and do not require treatment for pituitary insufficiency.	56% agreement

Note: Results from the third round in the Delphi process.

meeting, recommending life-long follow-up in patients controlled by medical treatment (statement 34).

3.3 | Country-specific consensus

Country-specific consensus in the third round is shown in Table 2. Two of the five participating endocrinologists from Norway answered the third round. Panelists from Denmark, Sweden, Finland and Iceland agreed on surgery as first choice in *all* eligible patients (statement 1). However, the majority also considered first-generation SSA as first choice in patients with low probability of complete resection (statement 4). A large suprasellar tumor remnant was considered a relative contraindication for pegvisomant monotherapy only among panelists from Finland (statement 16). Panelists from Norway, Finland, and Iceland reached consensus on treatment with pasireotide in patients who fail to respond sufficiently to first-generation SSA and/or complain about severe headache (statement 17, 18). In addition, Finland, and Iceland agreed that the efficacy of DA treatment in acromegaly is too low to justify a trial of DA as monotherapy and if so, it should be restricted to patients with mild GH/IGF-I elevations, which endocrinologist from Sweden also supported.

Panelists from all countries agreed about the need for life-long follow-up in patients controlled by medical treatment.

4 | DISCUSSION

In the present study using the Delphi method, 47 endocrinologists from the Nordic countries achieved consensus on 41% of statements concerning the treatment and follow-up of acromegaly. Overall, there was agreement to recommend pituitary surgery as first line treatment. There was wide agreement to recommend first-generation SSA treatment after failed surgery and to consider repeat surgery. Panelists also agreed to recommend combination therapy with first-generation SSA and pegvisomant as second- or third-line treatment. Notably, considerable disagreement prevailed regarding pegvisomant monotherapy, and the therapeutic role of both pasireotide and dopamine agonists (Figure 1).

Although most panelists agreed on surgery as the first choice, some also considered first line therapy with first-generation SSA in case of low probability for surgical cure, which resonates well with existing recommendations.[4] Agreement was achieved about first-generation SSA as second line treatment in case of significant persistent disease regardless of any pituitary tumor remnant. Further, consensus was achieved on repeating surgery in the presence of clinically significant persistent disease in patients with a potentially resectable residual after initial surgery, which is in line with a current consensus statement.[4]

The panel favored pegvisomant as add-on to first-generation SSA treatment rather than as mono therapy. According to current

TABLE 2 Country- specific consensus for Denmark, Sweden, Norway, Finland, and Iceland during the third round in the Delphi process.

No.	Statement	Denmark (*n* = 14)	Sweden (*n* = 13)	Finland (*n* = 14)	Norway (*n* = 2)	Iceland (*n* = 1)
About primary treatment						
1	I consider surgery first choice treatment in all eligible patients including curative and debulking surgery.	100% agreement	92% agreement	90% agreement	100% disagreement	100% agreement
2	I consider surgery first choice treatment mainly for adenomas where complete resection is realistic.	85% agreement	54% disagreement	100% agreement	100% agreement	100% agreement
3	I consider surgery first choice treatment for any adenoma abutting the visual pathway.	100% agreement	100% agreement	100% agreement	100% disagreement	100% agreement
4	I consider that first choice treatment of an adenoma with no visual pathway involvement and with low probability of complete resection is somatostatin analogues (SSA).	70% agreement	77% disagreement	60% agreement	100% agreement	100% agreement
Preoperative treatment with SSA (before pituitary surgery)						
5	I consider not recommending presurgical SSA treatment, as I do not find compelling evidence for a better treatment outcome.	69% agreement	85% agreement	80% agreement	100% disagreement	100% agreement
6	I consider the use of presurgical SSA treatment only in macroadenomas to increase the probability of postsurgical disease control.	61% agreement	46% agreement	70% agreement	50% agreement	100% agreement
7	I consider the use of presurgical medical treatment to lower disease activity and thereby reduce the risk of complications to surgery.	61% disagreement	47% agreement	60% disagreement	100% agreement	100% disagreement
Second line treatment						
8	I consider watchful waiting rather than initiation of medical treatment in an asymptomatic patient with marginally elevated GH/IGF-I postsurgery and without significant tumor remnant or disease-specific comorbidity	54% disagreement	62% agreement	60% agreement	100% agreement	100% disagreement
9	In a patient with overt and significant persistent disease, I recommend 1st generation SSA regardless of any pituitary tumour remnant.	100% agreement	100% agreement	100% agreement	50% agreement	100% agreement
10	I recommend 1st generation SSA treatment in the presence of overt and significant persistent disease and an unresectable tumor remnant postsurgery.	100% agreement	100% agreement	100% agreement	50% agreement	100% agreement
11	I consider repeat-surgery in the presence of overt and significant persistent disease with a potentially resectable tumor remnant after first line pituitary surgery.	84% agreement	100% agreement	100% agreement	100% agreement	100% agreement
12	I consider partial biochemical resistance to SSA when IGF-I does not reach normal values despite maximal dosing.	100% agreement	100% agreement	90% agreement	50% agreement	100% agreement
Second and third line medical treatment						
13	In patients with acromegaly, who are partially resistant to SSA treatment at maximum doses, I preferentially combine SSA with pegvisomant.	100% agreement	92% agreement	90% agreement	100% agreement	100% agreement
14	In patients with acromegaly, who are partially resistant to SSA treatment at maximum doses, I preferentially switch to pegvisomant monotherapy and monitor tumor size	77% disagreement	61% disagreement	60% disagreement	50% disagreement	100% disagreement

TABLE 2 (Continued)

No.	Statement	Denmark (*n* = 14)	Sweden (*n* = 13)	Finland (*n* = 14)	Norway (*n* = 2)	Iceland (*n* = 1)
15	As regards pegvisomant treatment, I recommend to initiate with daily or twice weekly injections and to increase the dose until normalization of IGF-I levels are achieved.	100% agreement	100% agreement	90% agreement	100% agreement	100% agreement
16	I consider a large suprasellar tumor remnant a relative contraindication for pegvisomant mono-therapy.	85% disagreement	61% disagreement	90% agreement	100% disagreement	100% disagreement
17	In patients with acromegaly with clinical significant growth of a residual tumor after surgery, who partially respond to 1st generation SSA treatment at maximum doses, I preferentially switch to pasireotide.	46% agreement	69% agreement	80% agreement	100% agreement	100% agreement
18	I consider treatment-resistance to 1st generation SSA and severe headache as a relative indication for a trial with pasireotide.	69% agreement	77% agreement	90% agreement	100% agreement	100% agreement
19	I consider known diabetes mellitus a relative contraindication for pasireotide treatment.	54% agreement	70% agreement	60% agreement	50% agreement	100% agreement
20	I consider discontinuing pasireotide treatment in all patients who develop diabetes mellitus on the drug.	46% agreement	62% disagreement	70% disagreement	100% disagreement	100% disagreement
21	I recommend discontinuation of pasireotide if a patient develops diabetes mellitus which is not controlled by lifestyle modifications and/or metformin.	46% disagreement	54% agreement	50% agreement	100% disagreement	100% disagreement
22	I consider that the efficacy of DA treatment in acromegaly is too low to justify a trial of DA as mono-therapy.	69% agreement	54% disagreement	80% agreement	50% agreement	100% disagreement
23	I consider that treatment of acromegaly with DA should be restricted to patients who have mild GH/IGF-I elevations.	66% agreement	84% agreement	80% agreement	50% agreement	100% agreement
24	I consider treatment of acromegaly with a dopamine agonist (DA) only to reduce the symptoms of hyperprolactinemia	54% disagreement	54% disagreement	50% disagreement	50% disagreement	100% disagreement
25	I consider treatment of acromegaly with a dopamine agonist (DA) only in the presence of hyperprolactinemia.	77% agreement	61% disagreement	50% agreement	50% agreement	100% disagreement
26	I take histological results after pituitary surgery into account when making decisions about further treatment.	84% agreement	87% agreement	100% agreement	100% agreement	100% agreement
Treatment of acromegaly in relation to pregnancy						
27	I recommend surgery as first-line therapy in women with newly diagnosed acromegaly seeking pregnancy.	100% agreement	100% agreement	100% agreement	100% agreement	100% agreement
28	I recommend postponing acromegaly treatment in a newly diagnosed and pregnant woman with mild symptoms and signs until after delivery.	100% agreement	100% agreement	90% agreement	100% agreement	100% agreement
29	I usually recommend stopping medical treatment once pregnancy is established.	100% agreement	100% agreement	90% agreement	100% agreement	100% agreement
30	I recommend to initiate/restart treatment with 1st generation SSA in a pregnant woman who has marked symptoms and/or tumor growth.	85% agreement	92% agreement	70% agreement	100% agreement	100% agreement

(Continues)

TABLE 2 (Continued)

No.	Statement	Denmark (*n* = 14)	Sweden (*n* = 13)	Finland (*n* = 14)	Norway (*n* = 2)	Iceland (*n* = 1)
31	I recommend 1st generation SSA treatment until conception for women with acromegaly seeking pregnancy, who have an indication for medical treatment and are ineligible for surgery.	92% agreement	92% agreement	90% agreement	100% agreement	100% agreement
32	I recommend discontinuing 1st generation SSA and pegvisomant treatment approximately 2 months before attempts to conceive, with use of short-acting octreotide where necessary until conception.	53% disagreement	39% agreement	60% disagreement	100% disagreement	100% disagreement
33	I consider to advise against breastfeeding in women who need medical therapy after parturition.	54% agreement	69% agreement	50% agreement	100% disagreement	100% agreement
Long-term follow-up after disease control						
34	I consider recommending life-long follow-up in patients controlled by medical treatment.	92% agreement	100% agreement	100% agreement	100% agreement	100% agreement
35	I consider recommending follow-up for 5 years in patients who have been biochemically controlled by surgery-only and do not require treatment for pituitary insufficiency.	92% disagreement	77% disagreement	50% disagreement	50% disagreement	100% disagreement
36	I consider recommending follow-up for 10 years in patients who have been biochemically controlled by surgery-only and do not require treatment for pituitary insufficiency.	54% agreement	62% agreement	80% agreement	50% agreement	100% agreement
37	I consider recommending life-long follow-up for patients who are biochemically controlled by surgery-only and do not require treatment for pituitary insufficiency.	69% agreement	55% agreement	60% disagreement	100% agreement	100% agreement

Note: Two of the five panelists from Norway answered the third round. Only one panelist from Iceland participated in the consensus survey.

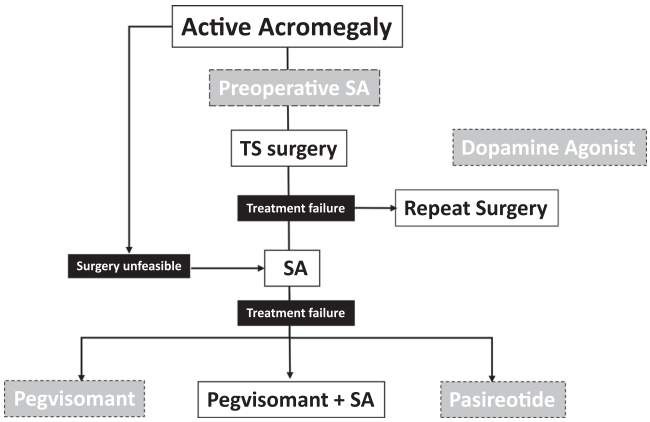

FIGURE 1 Consensus and controversies on the management and follow-up of acromegalybased on the Nordic Delphi consensus survey. White boxes indicate consensus, whereas grey boxes indicate lack of consensus. SA, First-generation somatostatin analogues; TS surgery, Transsphenoidal surgery.

guidelines combination therapy with pegvisomant and first-generation SSA can be considered in patients not controlled by SSA as monotherapy [3,4,17–19] as combination therapy has proven efficacious and safe in several investigator-initiated trials [9,10,20,21] and may also be cost-effective.[9,22,23] Still, it is not a licensed treatment modality.

Lack of consensus remained as regards the role of debulking pituitary surgery in cases with a low likelihood of complete resection. Similarly, the value of preoperative SSA treatment was questioned by the panel. This treatment has been tested in five randomized clinical trials[24–28] and subjected to several meta-analyses.[29–32] Current consensus statements only recommend preoperative SSA treatment in individual cases where the likelihood of surgical cure is considered low.[4,17,33]

Consensus was not reached regarding the management of asymptomatic patients with marginally elevated GH/IGF-I postsurgery in the absence of a significant tumor remnant or disease-specific comorbidity. This is noteworthy, considering the increasing incidence of pituitary incidentalomas including some with mildly increased GH/IGF-I levels.[34,35]

Pasireotide LAR, which is a second-generation SSA with a stronger and broader affinity to somatostatin receptors including subtype 5, has proven more efficacious than first generation-SSA in patients with inadequately controlled acromegaly.[11] In addition, pasireotide LAR may be favorable when tumor volume and headache are relevant issues.[11,12] In the present survey, 79% of the panel recommended to initiate treatment with pasireotide in patients with treatment-resistance to first-generation SSA and severe headache. It is well known that pasireotide may induce hyperglycemia due to suppression of insulin and glucagon-like peptide 1 (GLP1) secretion wherefore it is recommended only to be considered in patients with normal glucose tolerance.[13,14] In the survey, panelists did not agree whether a history of diabetes mellitus is a relative contraindication for pasireotide and whether it should be discontinued if the patient develops diabetes mellitus. Current guidelines recommend that first-line treatment in the occurrence of mild diabetes after pasireotide should be a Dipeptidyl Peptidase 4 inhibitor or a GLP1 analogue.[13,36]

The usefulness of DA treatment in patients with acromegaly did not reach consensus. The role of DA is limited by its relatively modest effect and should primarily be considered in patients with mild disease activity as an add-on treatment independent of concomitant hyperprolactinemia.[3,4,37]

Acromegaly is a rare disorder in which the average age of the female patient at the time of diagnosis is 44 years, wherefore pregnancies are relatively rare.[38] According to a nation-wide study, the frequency of pregnancy in patients with acromegaly is significantly reduced compared to age-matched healthy females.[39] The panel's view on the approach to pregnancy in acromegaly was generally in accordance with a recently published guideline[40] as regards treatment indications and modalities.[40–43] Lack of consensus persisted regarding breastfeeding in women receiving medical therapy after parturition even though recent guidelines recommend avoiding the use SSA and pegvisomant in this situation.[40]

Though panelist agreed on life-long follow-up in patients controlled by medical treatment, the follow-up of patients controlled by surgery-only without pituitary insufficiency seemed controversial and perhaps driven by country-specific guidelines and practice.

In the present survey, consensus on treatment of acromegaly within the Nordic countries was quite homogeneous, which may reflect the relatively similar organization of a tax-funded health care systems including unfettered access to all inhabitants. Certain country-specific differences, however, appeared including a preference in Finland for both pasireotide and dopamine agonists. The role of radiotherapy in acromegaly treatment was not included in the current statements since it was considered that this modality is indicated only in the rare cases where control of tumor mass is otherwise unattainable.[3,4] This standpoint is, however, not necessarily uniformly shared.

Certain limitations of this study merit attention. Our selection of experts may have been biased, but our aim was to include every specialist who manage acromegaly patients on a regular basis. Moreover, despite efforts to provide unambiguous statements they still leave room for individual interpretation. As an example, it may appear contradictory that a vast majority of the panel consider surgery first choice treatment in all patients and, at the same time, more than half of the panel also consider SSA first choice in a patient with no visual pathway involvement and a low probability of complete resection. Certainly, the sum of statements are unlikely to encompass every combination of treatment and follow-up of acromegaly.

Finally, the threshold of 80% for consensus is arbitrary albeit used in previous consensus-building surveys.[44]

In conclusion, this survey reflects the management of acromegaly in specialized centers in the Nordic countries. A relatively large degree of disagreement existed among the experts, which probably reflects the complexity of the disease and a shortage of evidence-based data. While awaiting the latter, personalized treatment, clinical

acumen and continuous discussions of treatment guidelines seem the best way to minimize noise and bias.

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CONFLICT OF INTEREST STATEMENT

Jens Otto Lunde Jørgensen and Jakob Dal have received unrestricted research grants and lecture fees from Pfizer and IPSEN. Mai C. Arlien-Søborg has received lecture fees from Pfizer. Daniel Olsson has served as a consultant for Ipsen, Pfizer, Novo Nordisk, and Sandoz; has received research grants from Sandoz and Pfizer; and is an employee at AstraZeneca as of 30 August 2021. This work was supported by an unrestricted research grant from Pfizer. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data set generated and analysed during the current study is available from the corresponding author on request.

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