Journal of the ASEAN Federation of Endocrine Societies

FEATURE ARTICLE

Malaysian Consensus Statement for the Diagnosis and Management of Acromegaly

Zanariah Hussein,[1] Mohamed Long Bidin,[2] Azmi Alias,[2] Muthukkumaran Thiagarajan,[2] Kartikasalwah Abdul Latif,[2] Jeyakantha Ratnasingam,[3] Wan Juani Wan Seman,[1] Azraai Nasruddin[1]

[1]*Hospital Putrajaya, Malaysia*
[2]*Hospital Kuala Lumpur, Malaysia*
[3]*University of Malaya, Kuala Lumpur, Malaysia*

Abstract

In Malaysia, acromegaly is under-recognised with only 10-15% of the expected number of cases from prevalence estimates, having been diagnosed and managed in established endocrine centres with access to multidisciplinary care. This is mainly due to lack of awareness and standardised approach in diagnosing this disease resulting in delay in diagnosis and management with suboptimal treatment outcomes. This first Malaysian consensus statement on the diagnosis and management of acromegaly addresses these issues and is based on current best practices and latest available evidence so as to reduce the disease burden on acromegaly patients managed in the Malaysian healthcare system.

Key words: acromegaly, consensus, Malaysia, growth hormone excess

INTRODUCTION

Acromegaly is an uncommon clinical syndrome resulting from excessive growth hormone (GH) production. In most cases, it arises from a GH secreting pituitary adenoma with resultant increased production of insulin-like growth factor-1 (IGF-1) from the liver. Both hormones exert characteristic changes and growth effects on major organ, skeletal and soft tissues. The resultant insulin resistant state, leads to predisposition of developing glucose intolerance, metabolic dysfunction and increased cardiovascular risk with associated co-morbidities such as hypertension, obstructive sleep apnoea (OSA) and arthritis. OSA in acromegaly is due to osseous and soft tissue changes which lead to narrowing and collapse of the upper airway during sleep. The pituitary tumour, typically a macroadenoma, can contribute to local mass effect with complications such as visual disturbance and hypopituitarism.

Main aims of treatment in acromegaly are to reduce and restore GH and IGF-1 levels to normal range, as this is associated with control of symptoms, prevention and control of complications, and reduction in morbidity and mortality. Treatment choices include surgical, medical and radiation therapy (RT) needing long-term multidisciplinary monitoring.

Currently there are no available guidelines addressing the diagnosis and management of patients with acromegaly in Malaysia. As the disease is chronic, associated with multiple co-morbidities and complications requiring multidisciplinary care, it is important to establish evidence-based guidelines to standardise screening, diagnosis, management and long-term follow-up of these patients. This manuscript presents the first Malaysian Consensus Statement for the Diagnosis and Management of Acromegaly in Malaysia.

METHODOLOGY

This consensus statement is based on latest best practice recommendations of the Endocrine Society[1] and American Association of Clinical Endocrinologists (AACE)[2] guidelines, and a comprehensive review of current medical literature. The recommendations were then developed with consensus building through face-to-face meetings by a multidisciplinary group of Malaysian specialists involved in the care of acromegaly patients consisting of endocrinologists, neurosurgeons, radiologists, radiation oncologists and laboratory specialists. The local recommendations were then carefully formulated taking into consideration the Malaysian healthcare system and the local availability and accessibility of diagnostic procedures and management options for patients with this disease. This was then circulated to a group of external reviewers in the same specialities and practicing within Malaysia for further review and feedback, which were taken into consideration resulting in these final recommendations.

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2019 by the JAFES
Received: March 27, 2019. Accepted: May 14, 2019.
Published online first: May 28, 2019.
https://doi.org/10.15605/jafes.034.01.03

Corresponding author: Zanariah Hussein, MRCP (UK)
Medical Department, Jalan P9, Presint 7,
62250 Putrajaya, Wilayah Persekutuan Putrajaya, Malaysia
Tel. No.: +603-8312 4200
Fax No.: +603-8888 0137
E-mail: zanariahh@hotmail.com
ORCiD: https://orcid.org/0000-0002-7367-2853

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/).

Epidemiology

Acromegaly is a rare disease with significant risk of mortality. Based on existing data from western countries, the prevalence of acromegaly is approximately 70-80 cases per million population (cpmp) and its incidence, 3-11 cpmp/year.[3-6] However, data from some Asian countries have approximated the prevalence of acromegaly at 28 cpmp and its incidence at 4 cpmp/year.[7] Males and females are equally affected by the disease.[3,4,7] The mean age of diagnosis is from mid-forties to early fifties[3,7-9] however, there is an average of 4-7 years of delay in confirming diagnosis from the onset of GH hypersecretion.[3,4,10]

There are at present very limited Malaysian epidemiological data available for acromegaly. From unpublished observational data of the Malaysian Acromegaly Registry, acromegaly appears to be seriously under-recognised and under-diagnosed in the country, with fewer than 150 patients being managed at established endocrine centres. However, from the case series collected, the ratio of male to female is similar with other countries.

The most common cause of acromegaly, accounting for >95% of cases is GH-secreting pituitary tumours arising from somatotroph cells.[1] The majority of the pituitary tumours (70%) are macroadenomas (≥1 cm in diameter) whilst the rest are microadenomas (<1 cm in diameter).[3] In the hands of high-volume pituitary surgeons, patients with microadenomas are expected to have 80-90% chance of surgical cure.[3] On the other hand, patients with macroadenoma are expected to have 40-50% chance of surgical cure. Achieving disease control in these patients with macroadenoma is challenging even with combination treatment of pituitary surgery, RT and medical therapy. These treatment options are notably costly, so a sensible and schematic selection of patients for specific modalities of treatment is paramount. It is important to note that individuals with uncontrolled disease have at least a 2-fold increase in mortality risk compared to the general population.[1,11-13] The most common cause of mortality in acromegaly is from cardiorespiratory diseases.

Clinical features

The most common complaints bringing patients with acromegaly to consult their primary care doctors, that lead to further tests to confirm diagnosis are headache and acral enlargement.[14] The latter feature usually comprises of lower jaw enlargement and protrusion (prognathism) with dental malocclusion, overbite and interdental separation[15] and, increasing ring and shoe size.[10,16]

Acromegaly is also associated with various co-morbidities. Data from the Malaysian Acromegaly Registry show that co-morbidities commonly encountered are diabetes mellitus, hypertension, cardiac diseases, OSA and multinodular goitre.

Other features that may be associated with acromegaly are visual field defects (typically bitemporal hemianopia), hyperprolactinemia, hypopituitarism (comprised of hypogonadism, hypothyroidism and hypocortisolism), colonic polyps, visceromegaly, carpal tunnel syndrome (CTS) , large joint pains, oily perspiration (mainly noted by hand examination) and multiple skin tags.[16,17]

Diagnosis

Clinical diagnosis

In the local context, if any clinician encounters a patient with acral enlargement of the face, hands or feet with two or more co-morbidities or features associated with acromegaly, biochemical screening is then indicated. The clinical features suggestive of Acromegaly include the presence or complaints of headache, diabetes mellitus, hypertension, heart disease of uncertain aetiology, OSA, colonic polyps, large joint pains, CTS, sweaty/oily hands or multiple skin tags.

In Malaysia, efforts have been carried out to educate primary care physicians regarding early recognition of clinical features of acromegaly. Regional level disease awareness talks by endocrinologists to primary care doctors have been carried out to highlight the disease and it's comorbidities and complications and emphasising the need for earlier diagnosis at the primary care level. Promotional educational material have been developed in the form of posters and video clips and distributed to all government primary care clinics. A screening algorithm will also soon be introduced to ease and facilitate the referral pathway of suspected cases of Acromegaly to receive prompt review by an endocrinologist at the nearest hospital.

Biochemical diagnosis

Biochemical screening should be performed promptly where clinically indicated and serum IGF-1 assessed if the test is available and accessible. In Malaysia, serum IGF-1 testing is limited and only available at endocrine laboratories at a single central government hospital, few university hospitals and private hospitals. Where the test is not accessible, referral should be made to an endocrinologist for biochemical screening and confirmation of acromegaly. Serum IGF-1 is measured as an initial screening test as it is the most sensitive and specific test for diagnosis. The levels should be interpreted using assay-specific age and gender matched reference ranges developed by the assay manufacturer. In Malaysia, different laboratories are using different assays which result in differences in the reference ranges. There are also various conditions that may elevate (e.g., puberty, pregnancy and hyperthyroidism) or lower (e.g., malnutrition, liver failure, renal failure, oral oestrogen use, untreated hypothyroidism and uncontrolled diabetes) serum IGF-1 levels. Interpretation of results will need careful consideration of the clinical context of the patient.[18,19]

An oral glucose tolerance test (OGTT) in patients with elevated IGF-1 that fails to suppress GH confirms diagnosis of acromegaly. At times it is justified to proceed simultaneously with an OGTT without waiting for IGF-1 levels in patients with a very high index of clinical suspicion to minimise diagnostic delay. The nadir GH level is seen between 60-120 minutes following an oral glucose load thus, GH measurements are recommended to be taken at 0, 60 and 120 minutes during the OGTT[2,20] and failure to supress GH levels to <1 mcg/L during OGTT (at 120 minutes) is considered diagnostic of acromegaly.[1]

There are instances however, where there may be discordance in IGF-1 and GH levels, i.e., elevated IGF-1 with nadir GH <1mcg/L during OGTT. With improvement in the sensitivity of modern GH assays, it has been established that in normal individuals, the nadir GH is <0.3 mcg/L.[21] Depending on the sensitivity and accuracy of the GH assay used, some authorities advocate using a cut-off of 0.4 mcg/L during an OGTT to diagnose acromegaly.[2] Therefore, when a highly sensitive GH assay is used in the context of an elevated serum IGF-1, a nadir GH above 0.4 mcg/L is consistent with a diagnosis of acromegaly. Discussion with a laboratory biochemist is required to establish sensitivity of GH assay in use.

Random GH or mean GH levels are not suitable or recommended to be used for making the initial diagnosis of acromegaly due to poor specificity.[1]

Imaging

Magnetic resonance imaging (MRI) of the pituitary (MR pituitary) with and without contrast is the neuroimaging investigation of choice in patients with acromegaly confirmed by biochemical diagnosis. All patients with likely exposure to contrast agents should have their serum creatinine and estimated glomerular filtration rate (eGFR) tested to identify individuals that are at potential risk of developing contrast induced nephrogenic systemic fibrosis. Patients with eGFR <30 ml/min/1.73m^2 should not have contrast administered.

MR pituitary is the preferred diagnostic imaging modality to evaluate sellar and parasellar tumours, offering high contrast and multiplanar thin cuts[22] which enable the evaluation of small soft tissue changes.

MR pituitary protocols should include pituitary sequences, 3 mm thick slices with Coronal T1WI /T2WI /T1 post-gadolinium and Sagittal T1WI /T1 post-gadolinium with or without a dynamic study. Optional added brain sequences include, T2WI axial and T1 axial post-contrast sequences. A dynamic MR pituitary may be useful particularly when functioning microadenomas are suspected as, it obtains images within seconds after administration of gadolinium.[23]

Computed tomography (CT) scan of the pituitary is only suggested in patients where MRI is contraindicated, as anatomical details are less defined.[2] Locally, this is already less commonly done. However, if necessary, CT should be done with use of contrast and must include multiplanar reformats.

Management

The management of acromegaly involves multimodal therapy.[1,2,24,25] Individualised treatment decisions should ideally be made following multidisciplinary team (MDT) discussions involving endocrinology, neurosurgery, neuroradiology, oncology, ophthalmology and pathology specialities. Hence, the management of acromegaly patients in Malaysia should be centred in major public, university and private hospitals with availability of specialists in these disciplines.

The main goals in acromegaly treatment[1,2] are tumour shrinkage, reduction of GH (<1 mcg/L) and normalisation of IGF-1,[26] resolution of clinical symptoms, improvement in co-morbidities and reduction in long-term mortality.

Surgery, is the recommended first line treatment[1,2] of acromegaly. Medical therapy with somatostatin receptor ligands (SRL) and dopamine agonists (DA) such as cabergoline are also available.

Locally, despite advancements in surgical techniques and medical therapy, RT[27] still has an important role as salvage therapy. Indications for RT include patients unfit for or who refuse surgery, residual or recurrent tumours not amenable to repeat surgery or failed medical therapy.[27,28]

Surgery

In Malaysia currently, most patients diagnosed with acromegaly, are recommended trans-sphenoidal surgery as the first line of treatment followed by medical therapy and RT, should surgery not be curative.[1,2,29] A well-coordinated multidisciplinary team approach in the surgical management of acromegaly can offer optimal treatment with better outcomes and lower morbidity.[1]

The goal of surgery is to achieve cure and to avoid life-long post-operative hormonal replacement therapy. Aggressive and complete removal of GH secreting tissue is therefore advocated whenever possible, whilst attempting to identify and preserve the remaining normal pituitary tissue.[2]

The ability to rapidly normalise GH and IGF-1 levels, compared to medical and RT, makes trans-sphenoidal surgery (TSS) the treatment of choice.[29,] For large and invasive tumours, debulking surgery is suggested to relieve compressive symptoms and to enhance response to medical therapy.[1,2] Therefore, it is also advocated in patients where surgical cure is not feasible due to tumour location or invasiveness. [29] Repeat surgery is recommended when there is elevated IGF-1 in the presence of an accessible residual or recurrent tumour.

Pre-operative evaluation should consist of imaging and management of co-morbidities. MRI is the recommended imaging modality of choice for pre-operative evaluation and surgical planning followed by dynamic contrast-enhanced multisection CT scan when MRI is contraindicated or not available. High resolution MRI with pituitary protocol helps in localising the tumour and visualising fine anatomic details surrounding the tumour and its neighbouring structures as well as presence of haemorrhage or tumour necrosis. MRI for Image Guided Surgery protocol is recommended for removal of macroadenoma with cavernous sinus invasion, destruction of sellar floor, poor pneumotisation of sphenoid sinus, repeated surgery and microadenoma with normal size sellar turcica.

On the other hand, computer assisted imaging navigation provides a pre-operative and intraoperative 3-dimensional (3-D) mapping of tumour margins in relation to surrounding tissues which, can be useful during the pre-operative planning. It serves as a guide to safe resection whilst preserving critical functions, ensuring patient safety and improving outcomes. Additionally, high resolution CT scan may be required in the presence of significant bony enlargements within the nasal cavity and skull

base to determine the necessity of an adjunct endonasal surgical procedure.

Selective adenomectomy via trans-sphenoidal-trans-nasal route should be the preferred surgical technique as it emphasises targeted and minimally invasive approaches. This is done by using either an operating endoscope or microscope for visualisation and microsurgical techniques.[1,2]

For tumours that are not visualised well on MRI, the possibility of an ectopic neuroendocrine tumour producing GHRH should be considered, even though very rare. For those undergoing transphenoidal surgery with unidentifiable tumour intraoperatively despite confirmative biochemical analysis, partial hypophysectomy may be considered. In failed remission, a more aggressive approach during repeat surgery may be required. Other alternative approaches can include conventional microscopic sublabial trans-septal approach and endoscopic assisted trans-nasal microsurgery.

For large tumours with significant extension to suprasellar, intraventricular, lateral, parasellar or fronto-temporal regions, cavernous sinus invasion or involvement of critical neurovascular structures, transcranial surgery is recommended. In large and invasive tumours, multiple approaches may be required.

Reconstruction of the sellar defect after tumour removal with vascularised mucoperiosteum-mucoperichondrium nasoseptal flap is recommended for large defects or in the presence of an intraoperative cerebrospinal fluid (CSF).

Additionally, Image Guided Surgery protocol is strongly recommended when normal anatomical landmarks of the nasal cavity and endonasal skull base are altered or destroyed by a large tumour or previous surgery.

Medical therapy

SRL is offered as secondary treatment in the presence of residual disease without mass effects after primary surgery.[1,2,25] As long-term indefinite use of SRL is heavily limited by its cost in the Malaysian setting, most patients are offered other definitive treatment options such as repeat surgery and/or RT. As such, the most common indication of SRL would be as bridging therapy while awaiting the effects of RT or to control co-morbidities while awaiting the second surgery.

SRL is also an option as primary medical therapy in macroadenomas with extrasellar extension particularly into the cavernous sinus, without mass effect or chiasmal compression where surgical cure is unlikely.[1,2] Other indications of SRL as primary therapy should be in patients who are poor surgical candidates (e.g., age and co-morbidity restrictions)[1,2] and those who refuse surgery. As a pre-operative treatment, SRL has limited use to those with severe pharyngeal thickness, sleep apnoea or heart failure to improve surgical outcomes.[1,30]

The two commonly used SRL in Malaysia are the intramuscular (IM) octreotide long-acting release (LAR) and subcutaneous (SC) lanreotide depot formulations that are administered four weekly. IM octreotide LAR is available in 20 mg and 30 mg doses and SC lanreotide is only available in 120 mg dose formulation. Most physicians in Malaysia do not use a test dose of short acting (SA) octreotide prior to commencing the long-acting formulation. In terms of efficacy, both octreotide LAR and lanreotide are similar[1,2,31] with an expected GH control to safe levels (<2.5 mcg/L) and/or IGF-1 normalisation in 34-55% of patients.[32-36] With SRL, a clinically relevant reduction in tumour volume (>20%) is seen in 53-63%[37,38] of patients.

SC lanreotide has an added benefit of convenience in a pre-filled ready to use pen that allows partner or self-injection[39] compared to IM octreotide LAR which requires reconstitution and administration by a healthcare professional. With improvement in clinical, biochemical parameters and reduction in tumour size, physicians may extend the dosing intervals up to 8-12 weekly for octreotide LAR and 6-8 weekly for SC lanreotide in order to improve cost effectiveness.[40,41] However, if SRL standard dosing does not achieve control, the frequency may be increased to every 3-weekly (for lanreotide 120 mg and octreotide 30 mg) for better disease control.[42,43] The main adverse events are abdominal cramps and diarrhoea that are usually temporary. However, more severe side effects such as formation of gall bladder sludge and stones require an abdominal ultrasound only if patients present with symptoms of gall bladder disease.[1]

Pasireotide LAR, a second generation SRL can be used in selected cases when octreotide LAR or lanreotide fail to control IGF-1, as data show better efficacy with this agent.[35,44,45] However, its use is limited by very high cost and to patients without poorly controlled glucose, as there is a high rate of worsening hyperglycaemia seen in up to 70% of treated patients.[35] Though pegvisomant, the GH receptor antagonist is the most effective medical therapy for acromegaly[46] it is currently unavailable in Malaysia.

DA is another option in medical therapy for acromegaly. It is mainly used for mild residual disease (IGF-1 <2 times upper limit of normal; ULN)[47] or when cost limits the use of SRL, and has the added benefit of being orally administered. DA is used regardless of prolactin co-secretion. Though accepted as a less effective form of treatment, these drugs may be used in Malaysia as bridging therapy as it is less costly in comparison to SRL. Cabergoline is the only DA that has been widely studied and recommended for use in acromegaly[47,48] with 30% of patients reaching normalised IGF-1 when used as a single agent. The dose of cabergoline is between 1.5-3.5 mg/week and patients should be warned of its side effects such as nausea, hypotension and headaches prior to initiating treatment. All patients on cabergoline should have an annual clinical cardiovascular examination to detect valvulopathy.[49] Echocardiogram (ECHO) should be reserved for patients with audible murmur, on cabergoline ≥3 mg/week for more than five years or equivalent cumulative dose, and those who maintain treatment after the age of 50 years.[49]

Combination treatment with SRL and DA is recommended in patients who have only partial control with SRL monotherapy[50,51] with 42-44% of patients uncontrolled on single therapy reaching normal IGF-1 levels with combination therapy.[2,50] Generally considered a weak agent, selective oestrogen receptor modulators (SERMs) or oral oestrogen[2,52] may be used in combination with

SRL and DA. This may be an option in patients with mild disease who cannot afford the use of SRL. However, this combination is not commonly practiced in Malaysia and experience is therefore limited.

Radiotherapy

Indications for intensity modulated radiotherapy (IMRT), fractionated stereotactic radiotherapy (FSRT) or stereotactic radiosurgery (SRS) are normally reserved for residual or recurrent tumour cases where risk of surgery is high or when patients refuse surgery. RT services including FRST are available in four out of five Ministry of Health, Malaysia centres. IMRT is available in all centres whilst SRS is offered in Kuala Lumpur General Hospital and the National Cancer Institute. Therefore, fractionated RT with 1.8-2 Gray (Gy) per day (up to a total dose of 50.4-54 Gy) is the recommended standard approach toward irradiating secreting pituitary adenomas. This results in tumour growth control in 80-90% and normalisation of GH/IGF-1 in 50-60% of patients at 10 years.[53] Rapid decrease in GH occurs in the first two years followed by progressive, slow decrease over 10-20 years.[54] Median onset of biochemical remission is between 7-10 years.[55] Hypopituitarism occurs in up to 60% of treated patients and its onset follows a similar time course as the development of remission. Optic neuropathy (1-5%), brain necrosis (<1%), cerebrovascular accident and second intracranial neoplasms (1-2%) are long-term side effects that should be followed up.[55] Fractionated RT should be delivered using 3-D conformal radiation technique with CT image acquisition[53] and is consistent with local practice. IMRT and FRST are preferred, as it significantly reduces dose of radiation to normal tissues and incidence of long-term toxicities.[53]

SRS is preferred[56] if appropriate equipment such as linear accelerator, gamma knife or Cyberknife, and trained personnel are available. Minimum distance of tumour to optic chiasm of 3 mm needs to be fulfilled for this approach to be possible.[53] A margin dose of 18-25 Gy is recommended. Though long-term tumour control rate of 80-90%, similar to fractionated RT, is achievable, its strength lies in earlier normalisation of GH/IGF-1 as early as 1.4 years (median 4.5 years).[55] Risk of long-term side effects are further reduced, even though hypopituitarism still remains common reaching up to 50% in some case series.[28,53]

As data is conflicting in different case series,[54,55] interruption of somatostatin analogue during RT should not be routinely adopted in our setting. Patients who have received RT should be monitored with GH/IGF-1 and hormonal profiles annually.[1]

Monitoring

GH and IGF-1 levels should be monitored to assess treatment efficacy and to detect persistent or recurrent disease. Regular assessment of possible development of hypopituitarism, co-morbidities and complications should be carried out.

Post-surgical monitoring

Monitoring patients post-surgery should include both biochemical and imaging studies. The recommendation for IGF-1 level and random GH measurements is at 12 weeks post-surgery.[1] Immediate post-operative measurement of GH is not recommended in the local context. GH value of <1 mcg/L at 12 weeks and a normal IGF-1 value (after age-dependent normalisation) by 3-6 months are consistent with surgical remission.[2] GH level <1 mcg/L indicates "control" and normalisation of mortality risk.[1,57] If the GH is >1 mcg/L, we suggest to measure nadir GH levels after an OGTT.[1]

Following a surgical cure, all patients should have at least an annual IGF-1 level with the addition of OGTT if there is any suspicion of recurrence clinically or based on IGF-1 levels.[2,57] Although most cases have concordant GH and IGF-1 levels, discordant levels can be seen in about 35% of patients with active acromegaly.[58] A repeat testing of GH and IGF-1 levels is suggested 3-4 months after a discrepant result.[59] However, there is no specific guideline on the management of patients with discordant GH and IGF-1 levels.

The first post-surgical MR pituitary should be done at least 3-4 months after the surgery[2,60-62] and subsequently based on disease activity.[2] In patients with pre-operative visual field defects, visual field testing should be done regularly post-surgery.[1]

As there is no available consensus on frequency of post-operative pituitary hormone assessment, based on current local practice, we recommend that it be performed at 3- and 6-months post-surgery and annually thereafter. Hypopituitarism is a significant complication of either continued tumour growth compromising normal pituitary function, or consequences of loss of pituitary function post-surgery or post-radiotherapy.

Monitoring patients receiving medical therapy

For patients who are on medical treatment with SRL or DA, it is recommended to monitor both GH and IGF-1 levels to assess response to treatment. GH and IGF-1 levels should ideally be monitored 4-6 weeks after any dose change.[2] It is also recommended to monitor adverse events associated with SRL such as gastrointestinal and metabolic disorders.

OGTT should not be used to monitor treatment response to SRL, as it is unreliable. Disease monitoring should be done using IGF-1 and random GH levels.[63]

Monitoring patients receiving radiotherapy

Patients receiving RT are at risk of developing hypopituitarism, radiation-induced secondary tumours and radionecrosis. The recommendation is for annual assessments to evaluate pituitary function for hypopituitarism and monitoring of GH and IGF-1 levels.[2,57] Visual acuity and visual field should be closely monitored by regular formal testing to assess any damage to the optic chiasm or optic nerves following RT.

Monitoring of co-morbidities

Cardiovascular and cerebrovascular events are the main causes of death in patients with acromegaly. Cardiovascular risk factors should be appropriately treated and monitored. Patients with symptoms of OSA should have an overnight polysomnography done. ECHO and electrocardiography (ECG) should be performed in patients with suspected cardiac disease. Screening for hypertension and diabetes should be regularly performed.

Patients should also be monitored for signs and symptoms of CTS and arthropathy whilst bone densitometry should be performed in patients with history of hypogonadism or fractures.[2] All patients should undergo colonoscopy once diagnosed with acromegaly[1,2] and repeated either every five years in patients with a colonic polyp at screening or with persistently elevated IGF-levels, or 10 years in those without any polyps at screening and controlled disease.[1] Ultrasound of the thyroid should be performed if there is palpable thyroid nodularity[1] in view of increased risk of thyroid cancer in acromegaly.[64]

CONCLUSION

There are significant challenges in the management of patients with acromegaly in Malaysia. There need to be better awareness of the condition among primary care doctors and other specialities due to the heterogeneity of GH-related morbidity presentation. There is a need for improved screening to identify patients and earlier referral to endocrinologists for confirmation of diagnosis and treatment initiation.

A multidisciplinary team should assess each newly diagnosed acromegaly patient to ensure individualised plan of treatment. Comprehensive care and follow-up should be accessible via a dedicated pituitary clinic led by an experienced endocrinologist, with access to neuroimaging and endocrine laboratory facilities that provide appropriate assays for prompt measurements of GH and IGF-1.

This consensus has been developed to standardise the management of this uncommon disease in Malaysia. A prompt and optimal resource allocation and utilisation for the management of acromegaly will enable patients to achieve a good quality of life with reduction of chronic complications and co-morbidities. Ultimately, this strategy will contribute to true cost savings and reduce this disease burden on the Malaysian healthcare system in the long-term.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

References

1. Katznelson L, Laws ER Jr, Melmed S, et al. Acromegaly: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933-51. PMID: 25356808. https://doi.org/10.1210/jc.2014-2700.
2. Katznelson L, Atkinson JL, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly--2011 update. Endocr Pract. 2011;17(Suppl 4):1-44. PMID:21846616.
3. Burton T, Le Nestour E, Neary M, Ludlam WH. Incidence and prevalence of acromegaly in a large US health plan database. Pituitary. 2016;19(3):262-7. PMID: 26792654. PMCID: PMC4858553. https://doi.org/10.1007/s11102-015-0701-2.
4. Broder MS, Chang E, Cherepanov D, Neary MP, Ludlam WH. Incidence and prevalence of acromegaly in the United States: A claims-based analysis. Endocr Pract. 2016;22(11):1327-35. PMID:27540880.
5. Dal J, Feldt-Rasmussen U, Andersen M, et al. Acromegaly incidence, prevalence, complications and long-term prognosis: A nationwide cohort study. Eur J Endocrinol. 2016;175(3):181-90. PMID: 27280374. https://doi.org/10.1530/EJE-16-0117.
6. Gatto F, Trifirò G, Lapi F, et al. Epidemiology of acromegaly in Italy: Analysis from a large longitudinal primary care database. Endocrine. 2018;61(3):533-41. PMID: 29797214. https://doi.org/10.1007/s12020-018-1630-4.
7. Kwon O, Song YD, Seong YK, Lee EJ, et al. Nationwide survey of acromegaly in South Korea. Clin Endocrinol (Oxf). 2013;78(4):577-85. PMID: 22909047. https://doi.org/10.1111/cen.12020.
8. Sesmilo G, Webb SM; for the Neuroendocrinology Group of the Spanish Society of Endocrinology and Nutrition. Twelve years of the Spanish acromegaly registry: A historical view of acromegaly management in Spain. Endocrinol Nutr. 2010;57(2):39-42. PMID: 20189894. https://doi.org/10.1016/j.endonu.2010.01.003.
9. Zarool-Hassan R, Conaglen HM, Conaglen JV, Elston MS. Symptoms and signs of acromegaly: An ongoing need to raise awareness among healthcare practitioners. J Prim Health Care. 2016;8(2):157-63. PMID: 27477558. https://doi.org/10.1071/HC15033 .
10. Hong JW, Ku CR, Kim SH, Lee EJ. Characteristics of acromegaly in Korea with a literature review. Endocrinol Metab (Seoul). 2013;28(3):164-8. PMID: 24396674. PMCID: PMC3811698. https://doi.org/10.3803/EnM.2013.28.3.164.
11. Sherlock M, Ayuk J, Tomlinson J, et al. c. MOrtality in patients with pituitary disease. Endocr Rev. 2010;31(3):301-42. PMID: 20086217. https://doi.org/ 10.1210/er.2009-0033.
12. Dekkers OM, Biermasz NR, Pereira AM, Romijn JA, Vandenbroucke JP. Mortality in acromegaly: A metaanalysis. J Clin Endocrinol Metab. 2008;93(1):61-7. PMID: 17971431. https://doi.org/10.1210/jc.2007-1191.
13. Holdaway IM, Bolland MJ, Gamble GD. A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. Eur J Endocrinol. 2008;159(2):89-95. PMID: 18524797. https://doi.org/10.1530/EJE-08-0267.
14. Nachtigall L, Delgado A, Swearingen B, Lee H, Zerikly R, Klibanski A. Changing patterns in diagnosis and therapy of acromegaly over two decades. J Clin Endocrinol Metab. 2008;93(6):2035-41. PMID: 18381584. https://doi.org/10.1210/jc.2007-2149.
15. Sesmilo G, Resmini E, Sambo M, et al. Prevalence of acromegaly in patients with symptoms of sleep apnea. PLoS ONE. 2017;12(9):e0183539. PMID: 28898247. PMCID: PMC5595301. https://doi.org/10.1371/journal.pone.0183539.
16. Melmed S. Acromegaly pathogenesis and treatment. J Clin Invest. 2009;119(11):3189-202. PMID: 19884662. PMCID: PMC2769196. https://doi.org/10.1172/JCI39375.
17. Lugo G, Pena L, Cordido F. Clinical manifestations and diagnosis of acromegaly. Int J Endocrinol. 2012;2012:540398. PMID: 22518126. PMCID: PMC3296170. https://doi.org/10.1155/2012/540398.
18. Ribeiro-Oliveira A Jr., Barkan A. The changing face of acromegaly -- advances in diagnosis and treatment. Nat Rev Endocrinol. 2012;8(10):605-11. PMID: 22733271. https://doi.org/10.1038/nrendo.2012.101.
19. Giustina A, Chanson P, Bronstein M, et al. A consensus on criteria for cure of acromegaly. J Clin Endocrinol Metab. 2010;95(7):3141-8. PMID: 20410227. https://doi.org/10.1210/jc.2009-2670.
20. Arafat AM, Möhlig M, Weickert MO, et al. Growth hormone response during oral glucose tolerance test: The impact assay method on the estimation of reference values in patients with acromegaly and in healthy controls, and the role of gender, age and body mass index. J Clin Endocrinol Metab. 2008;93(4):1254-62. PMID: 18171702. https://doi.org/10.1210/jc.2007-2084.
21. Cazabat L, Souberbielle JC, Chanson P. Dynamic tests for the diagnosis and assessment of treatment efficacy in acromegaly. Pituitary. 2008;11(2):129-39. PMID: 18418712. https://doi.org/10.1007/s11102-008-0113-7.
22. Rennert J, Doerfler A. Imaging of sellar and parasellar lesions. Clin Neurol Neurosurg. 2007;109(2):111-24. PMID: 17126479.
23. Tabarin A, Laurent F, Catargi B, et al. Comparative evaluation of conventional and dynamic magnetic resonance imaging of the pituitary gland for the diagnosis of Cushing's disease. Clin Endocrinol (Oxf). 1998;49(3):293-300. PMID: 9861318.
24. Melmed S, Casanueva FF, Klibanski A, et al. A consensus on the diagnosis and treatment of acromegaly complications. Pituitary. 2013;16(3):294-302. PMID: 22903574. PMCID: PMC3730092. https://doi.org/10.1007/s11102-012-0420-x.
25. Giustina A, Chanson P, Kleinberg D, et al. Expert consensus document: A consensus on the medical treatment of acromegaly. Nat Rev Endocrinol. 2014;10(4):243-8. PMID: 24566817. https://doi.org/10.1038/nrendo.2014.21.
26. Holdaway IM, Rajasoorya RC, Gamble GD. Factors influencing mortality in acromegaly. J Clin Endocrinol Metab. 2004;89(2):667-74. PMID: 14764779. https://doi.org/10.1210/jc.2003-031199.
27. Hannon MJ, Barkan AL, Drake WM. The role of radiotherapy in acromegaly. Neuroendocrinology. 2016;103(1):42-9. PMID: 26088716. https://doi.org/10.1159/000435776.
28. Marquez Y, Tuchman A, Zada G. Surgery and radiosurgery for acromegaly: A review of indications, operative techniques, outcomes and complications. Int J Endocrinol. 2012;2012:386401. PMID: 22518121. PMCID: PMC3303541. https://doi.org/10.1155/2012/386401.
29. Banerji D, Das NK, Sharma S, Jindal Y, Jain VK, Behari S. Surgical management of acromegaly: Long term functional outcome analysis and assessment of recurrent/residual disease. Asian J Neurosurg.

2016;11(3):261-7. PMID: 27366253. PMCID: PMC4849295. https://doi.org/10.4103/1793-5482.145354.
30. Lombardi G, Colao A, Marzullo P, et al. Improvement of left ventricular hypertrophy and arrhythmias after lanriotide-induced GH and IGF-I decrease in acromegaly: a prospective multi-center study. J Endocrinol Invest. 2002;25(11):971-6. PMID: 12553557. https://doi.org/10.1007/BF03344070.
31. Murray RD, Melmed S. A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly. J Clin Endocrinol Metab. 2008;93(8):2957-68. PMID: 18477663. https://doi.org/10.1210/jc.2008-0027.
32. Melmed S, Cook D, Schopohl J, Goth MI, Lam KS, Marek J. Rapid and sustained reduction of serum growth hormone and insulin-like growth factor-1 in patient with acromegaly receiving lanreotide Autogel ® therapy: A randomised, placebo-controlled multicentre study with a 52 week open extension. Pituitary. 2010;13(1):18-28. PMID: 19639415. PMCID: PMC2807598. https://doi.org/10.1007/s11102-009-0191-1.
33. Mercado M, Borges F, Bouterfa H, et al. A prospective, multicentre study to investigate the efficacy, safety and tolerability of octreotide LAR® (long-acting repeatable octreotide) in the primary therapy of patients with acromegaly. Clin Endocrinol (Oxf). 2007;66(6):859-68. PMID: 17465997. PMCID: PMC1974838. https://doi.org/10.1111/j.1365-2265.2007.02825.x.
34. Howlett TA, Willis D, Walker G, Wass JA, Trainer PJ; UK Acromegaly Register Study Group (UKAR-3). Control of growth hormone and IGF1 in patients with acromegaly in the UK: Responses to medical treatment with somatostatin analogues and dopamine agonists. Clin Endocrinol (Oxf). 2013;79(5):689-99. PMID: 23574573. https://doi.org/10.1111/cen.12207.
35. Melmed S, Bronstein MD, Chanson P, et al. A consensus statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol. 2018;14(9):552-61. PMID: 30050156. https://doi.org/10.1038/s41574-018-0058-5.
36. Carmichael JD, Bonert VS, Nuño M, Ly D, Melmed S. Acromegaly clinical trial methodology impact on reported biochemical efficacy rates of somatostatin receptor ligand treatments: a meta-analysis. J Clin Endocrinol Metab. 2014;99(5):1825-33. PMID: 24606084. PMCID: PMC4010703. https://doi.org/10.1210/jc.2013-3757.
37. Giustina A, Mazziotti G, Torri V, Spinello M, Floriani I, Melmed S. Meta-analysis on the effects of octreotide on tumor mass in acromegaly. PLoS ONE. 2012;7(5):e36411. PMID: 22574156. PMCID: PMC3344864. https://doi.org/10.1371/journal.pone.0036411.
38. Caron PJ, Bevan JS, Petersenn S, et al. Tumour shrinkage with lanreotide autogel 120 mg as primary therapy in acromegaly: Results of a prospective multicenter clinical trial. J Clin Endocrinol Metab. 2014;99(4):1282-90. PMID: 24423301. PMCID: PMC4009579. https://doi.org/10.1210/jc.2013-3318.
39. Bevan JS, Newell-Price J, Wass JA, et al. Home administration of lanreotide Autogel by patients with acromegaly, or their partners, is safe and effective. Clin Endocrinol (Oxf). 2008;68(3):343-9. PMID: 17892497. PMCID: PMC2268964. https://doi.org/10.1111/j.1365-2265.2007.03044.x.
40. Schopohl J, Strasburger CJ, Caird D, et al. Efficacy and acceptability of lanreotide Autogel® 120 mg at different dose intervals in patients with acromegaly previously treated with octreotide LAR. Exp Clin Endocrinol Diabetes. 2011;119(3):156-62. PMID: 21086246. https://doi.org/10.1055/s-0030-1267244.
41. Turner HE, Thornton-Jones VA, Wass JA. Systemic dose-extension of octreotide LAR: The importance of individual tailoring of treatment in patients with acromegaly. Clin Endcocrinol. 2004;61(2):224-31. PMID: 15272918. https://doi.org/10.1111/j.1365-2265.2004.02084.x.
42. Giustina A, Bonadonna S, Bugari G, et al. High-dose intramuscular octreotide in patients with acromegaly inadequately controlled on conventional somatostatin analogue therapy: A randomised controlled trial. Eur J Endocrinol. 2009;161(2):331-8. PMID: 19465485. https://doi.org/10.1530/EJE-09-0372.
43. Giustina A, Mazziotti G, Cannavo S, et al. High-dose and high-frequency lanreotide autogel in acromegaly: A randomised, multicenter study. J Clin Endocrinol Metab. 2017;102(7):2454-64. PMID: 28419317. https://doi.org/10.1210/jc.2017-00142.
44. Colao A, Bronstein MD, Freda P, et al. Pasireotide versus octreotide in acromegaly: A head-to-head superiority study. J Clin Endocrinol Metab. 2014;99(3):791-9. PMID: 24423324. PMCID: PMC3965714. https://doi.org/10.1210/jc.2013-2480.
45. Gadelha MR, Bronstein MD, Brue T, et al. Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): A randomised, phase 3 trial. Lancet Diabetes Endocrinol. 2014;2(11):875-84. PMID: 25260838. https://doi.org/10.1016/S2213-8587(14)70169-X.
46. van der Lely AJ, Hutson RK, Trainer PJ, et al. Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. Lancet. 2001;358(9295):1754-9. PMID: 11734231.
47. Abs R, Verhelst J, Maiter D, et al. Cabergoline in the treatment of acromegaly: A study in 64 patients. J Clin Endocrinol Metab. 1998;83(2):374-8. PMID: 9467544. https://doi.org/10.1210/jcem.83.2.4556.
48. Sandret L, Maison P, Chanson P. Place of cabergoline in acromegaly: A meta-analysis. J Clin Endocrinol Metab. 2011;96(5):1327-35. PMID: 21325455. https://doi.org/10.1210/jc.2010-2443.
49. Caputo C, Prior D, Inder WJ. The need for annual echocardiography to detect cabergoline-associated valvulopathy in patients with prolactinoma: a systemic review and additional clinical data. Lancet Diabetes Endocrinol. 2014;3(11):906-13. PMID: 25466526. https://doi.org/10.1016/S2213-8587(14)70212-8.
50. Cozzi R, Attanasio R, Lodrini S, Lasio G. Cabergoline addition to depot somatostatin analogues in resistant acromegalic patients: Efficacy and lack of predictive value of prolactin status. Clin Endocrinol (Oxf). 2004;61(2):209-15. PMID: 15272916. https://doi.org/10.1111/j.1365-2265.2004.02082.x.
51. Gatta B, Hau DH, Catargi B, Roger P, Tabarin A. Re-evaluation of the efficacy of the association of cabergoline to somatostatin analogues in acromegalic patients. Clin Endocrinol (Oxf). 2005;63(34):477-8. PMID: 16181243. https://doi.org/10.1111/j.1365-2265.2005.02329.x.
52. Dimaraki EV, Symons KV, Barkan AL. Raloxifene decreases serum IGF-I in male patients with acromegaly. Eur J Endocrinol. 2004;150(4):481-7. PMID: 15080777.
53. Minniti G, Scaringi C, Enrici RM. Radiation techniques for acromegaly. Radiat Oncol. 2011;6:167. https://doi.org/10.1186/1748-717X-6-167.
54. Castinetti F, Morange I, Dufour H, Regis J, Brue T. Radiotherapy and radiosurgery in acromegaly. Pituitary. 2009;12(1):3-10. PMID: 18175223. https://doi.org/10.1007/s11102-007-0078-y.
55. Rowland NC, Aghi MK. Radiation treatment strategies for acromegaly. Neurosurg Focus. 2010;29(4):E12. PMID: 20887122. https://doi.org/10.3171/2010.7.FOCUS10124.
56. Abu Dabrh AM, Asi N, Farah WH, et al. Radiotherapy versus radiosurgery in treating patients with acromegaly: A systemic reivew and meta-analysis. Endocr Pract. 2015;21(8):943-56. PMID: 26247235. https://doi.org/10.4158/EP14574.OR.
57. Silverstein JM. Need for improved monitoring in patients with acromegaly. Endocr Connect. 2015;4(4):R59-67. PMID: 26381160. PMCID: PMC4606206. https://doi.org/10.1530/EC-15-0064.
58. Alexopoulou O, Bex M, Abs R, T'Sjoen G, Velkeniers B, Maiter D. Divergence between growth hormone and insulin-like growth factor-1 concentrations in the follow-up of acromegaly. J Clin Endocrinol Metab. 2008;93(4):1324-30. PMID: 18230660. https://doi.org/10.1210/jc.2007-2104.
59. Freda PU. Monitoring of acromegaly: What should be performed when GH and IGF-1 levels are discrepant? Clin Endocrinol (Oxf). 2009;71(2):166-70. PMID: 19226264. PMCID: PMC3654652. https://doi.org/10.1111/j.1365-2265.2009.03556.x.
60. Zirkzee EJ, Corssmit EP, Biermasz NR, et al. Pituitary magnetic resonance imaging is not required in the postoperative follow-up of acromegalic patients with long-term biochemical cure after transsphenoidal surgery. J Clin Endocrinol Metab. 2004;89:4320-4. PMID: 15356027. https://doi.org/10.1210/jc.2003-032141.
61. Dina TS, Feaster SH, Laws E Jr, Davis DO. MR of the pituitary gland postsurgery: Serial MR studies following transsphenoidal resection. AJNR Am J Neuroradiol. 1993;14(3):763-9. PMID: 8517370.
62. Ciric I, Mikhael M, Stafford T, Lawson L, Garces R. Transsphenoidal microsurgery of pituitary macroadenomas with long-term follow-up results. J Neurosurg. 1983;59(3):395-401. PMID: 6886753. https://doi.org/10.3171/jns.1983.59.3.0395.
63. Carmichael JD, Bonert VS, Mirocha JM, Melmed S. The utility of oral glucose tolerance testing for diagnosis and assessment of treatment outcomes in 166 patients with acromegaly. J Clin Endocinol Metab. 2009;94(2):523-7. PMID: 19033371. https://doi.org/10.1210/jc.2008-1371.
64. Wolinski K, Czarnywojtek A, Ruchala M. Risk of thyroid nodular disease and thyroid cancer patients with acromegaly -- meta-analysis and systematic review. PLoS One. 2014;9(2):e88787. PMID: 24551163. PMCID: PMC3925168. https://doi.org/10.1371/journal.pone.0088787.

Authors are required to accomplish, sign and submit scanned copies of the JAFES Author Form consisting of: (1) Authorship Certification, that authors contributed substantially to the work, that the manuscript has been read and approved by all authors, and that the requirements for authorship have been met by each author; (2) the Author Declaration, that the article represents original material that is not being considered for publication or has not been published or accepted for publication elsewhere, that the article does not infringe or violate any copyrights or intellectual property rights, and that no references have been made to predatory/suspected predatory journals; (3) the Author Contribution Disclosure, which lists the specific contributions of authors; and (4) the Author Publishing Agreement which retains author copyright, grants publishing and distribution rights to JAFES, and allows JAFES to apply and enforce an Attribution-Non-Commercial Creative Commons user license. Authors are also required to accomplish, sign, and submit the signed ICMJE form for Disclosure of Potential Conflicts of Interest. For original articles, authors are required to submit a scanned copy of the Ethics Review Approval of their research as well as registration in trial registries as appropriate. For manuscripts reporting data from studies involving animals, authors are required to submit a scanned copy of the Institutional Animal Care and Use Committee approval. For Case Reports or Series, and Images in Endocrinology, consent forms, are required for the publication of information about patients; otherwise, appropriate ethical clearance has been obtained from the institutional review board. Articles and any other material published in the JAFES represent the work of the author(s) and should not be construed to reflect the opinions of the Editors or the Publisher.