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THE PSYCHIATRIC ASPECTS (DEPRESSION & ANXIETY) IN PATIENTS WITH ACROMEGALY: A STUDY OF INFLUENCING FACTORS

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ABSTRACT

Background: Acromegaly is a chronic illness in the setting of excessive levels of GH and IGF-1 leading to coarse physical features and requires assessment for surgical and non-surgical management with management of associated comorbidities. the disease features and chronicity have negative influences on quality of life from psychiatric point of view in addition to biochemical aspects. **Aim of study:** To assess the rate of depression and anxiety in acromegaly patients with correlation to age, gender, duration of disease, hypophysectomy, Octreotide use, deep xray therapy and response to all treatments modalities. **Methods:** This was a cross sectional study done at the national diabetes center in Baghdad, Iraq. during a period of ten months from November 2020 to August 2021.it included 80 known Acromegalic adults treated with either surgical or non-surgical methods or both . a questionnaire was utilized to obtain demographic & clinical data .HAM –A scale was used to assess Anxiety while BDI II was used to assess depression. **Results:** In this study, 45% of cases had mild anxiety, 16.3% had moderate anxiety and 2.5% had severe anxiety. The prevalence of moderate to severe anxiety was significantly higher with duration of disease > 10 years (53.8 %, p=0.015), those with abnormal GH level (52.2 %, p= 0.001) and those with associated diabetes (52%, p=0.002). regarding depression, 36.3% of patients were in mild depression, 18.8 % were in moderate depression And 2.5 % were in severe depression. moderate to severe depression was significantly higher among acromegalic patients who had diabetes (40%, p=0.011), no significant association (p> 0.05) was found between depression and other demographic and clinical characteristics. **Conclusion:** Longer duration of Acromegaly and failure of GH suppression down to the previously specified target increases the chance of anxiety in Acromegaly patients. Coexistent diabetes mellitus increases the chance of depression in addition to its impact on Anxiety.

KEYWORDS: Acromegaly, Depression, Anxiety, Iraq.

1. INTRODUCTION

1.1 Acromegaly

1.1.1 Defintion & Epidemiology

Historically a French neurologist in 1886 suggested that (Acromegaly) would be the term to describe hypertrophy of the Face and Extremities.[1] Through following years it was established that it is resulting from superfluous growth hormone secretion mostly due to adenoma in the pituitary gland.[2] The Acromegaly prevalence is approximately between 28-137 cases per million. Yearly incidence is reported to have risen from 3-4 to10 cases per million according to the results of modern surveys conducted in Europe.[3,4,5]

1.1.2 Pathophysiology of acromegaly

Acromegaly manifests by increased GH and IGF-I with Consequently clinical features of hypersomatotropism.[6] Acromegaly is linked to adenoma in the pituitary gland in almost 95% of patients. In 5% of cases excessive GH is released from non-pituitary origin.[7] The prevailing sequel of excessive growth hormone is the increased synthesized IGF-1 from hepatocytes.

The impact of IGF-1 (Also known as somatomedin) is the emergence of features of Acromegaly in various systems.[8] Following the time the growth plates have fused, IGF-1 influence the acral growth spurt as swollen hands andfeet and coarsening of facial features. Somatic cell proliferation in Acromegaly is initiated by a bond **to IGF receptor.**[10]

1.1.3 Clinical features

Manifestation of acromegaly may take many years to be obvious which may delay diagnosis. Usually the

earliest sign of increased GH is wide-spaced teeth. Other clinical features include enlarged tongue, prognathism, broadened nose, swollen distal extremities, increased sweating, arthralgia, headache.[6] Other diseases linked to acromegaly include DM, hypertension, Obstructive sleep apnea, hypertrophic cardiomyopathy, colon polyps and colon ca and others.[10]

1.1.4 Diagnosis

Laboratory investigations of Acromegaly begin with IGF-1 assay as a screening tool that may warrant later confirming the diagnosis with OGTT.[11] Pituitary MRI is advised in assessment of pituitary adenoma.[12]

1.1.5 Management of AcromegalySurgical operation

Excision of the pituitary gland tumor is the initial therapy of choice in most Acromegalic patients.[13] three months after surgery, pituitary MRI must be done to exclude presence of remaining tumor tissue. Acromegalic subjects must be assessed for tumor effect and followed up to avoid hypopituitarism postoperatively; Pharmacotherapy must be given only to patients with ongoing disease.[14,15]

Pharmacotherapy

Somatostatin analogs

Lanreotide, octreotide both can decrease GH & IGF-1 release by bindingto somatostatin receptor.[16]

GH receptor blocker

Pegvisomant can aid in symptomatic relief but not in reduction of GHlevel.[17]

Dopamine receptor agonist

Cabergoline and Bromocriptine often used as an addition to somatostatinanalogue.[18]

Radiation therapy

Stereotactic gamma knife therapy is Advised in patients whom levels of GH weren't corrected by surgical approach.[19]

1.2 Depression

1.2.1 Definitions

Depression can imply[20,21]

- A mood state described as sadness, despair, anxiety, emptiness or hopelessness, absence of feelings or being tearful. Depressed mood can be normal and occasional an adaptive reaction to loss, lack of success. Depressed mood may be a symptom of a psychopathological syndrome or another medical disease.

- A syndrome group of symptoms and signs that may involve depressed mood. (For example major depression syndrome, minor depression ,dysthymia whichis persistent depressive syndrome).

- Mental disease that is a separate clinical entity. For instance the syndrome of major depression can take place in unipolar major depression, bipolar, schizophrenia, substance/medication-induced depressive disorder, depressive disorder due to another medical condition.

1.2.2 Assessment for depression

Subjects who are assessed for depression are asked about present illness history, current and past medical diseases, family and socioeconomic history. Assessment also involves mental status examination, physical examination and focused lab test. It is also important to assess suicidal thoughts.[22]

A clinical examination, complete blood Picture, biochemical and thyroid function, rapid reagin test, general urine exam, pregnancy test and urine toxicology screen can be helpful when there is suspicion of medical disease.[23] One recommended method of screening is to assess all patient routinely and patients who had a score that's not beneath the threshold would be subjects for further evaluation according to the US Preventive services task force. without screening only 50% of major depression patients would be identified.[24]

Unless directly questioned About their mood Patients don't report symptoms of depression. Reasons may include being afraid of stigmatization thoughts that isn't real pathology but a personal fault or or being concerned about being referred to the psychiatrist and using pharmacological treatments.[25]

1.2.3 Screening instruments for depression

Include patient health questionnaire 2 & 9 (PHQ2 and PHQ9) and WHO-5 and Beck depression inventory for primary care comprised of 7 items is originated from Beck 21 items inventory that is beneficial for assessment of responding to therapy. The threshold of 4 points in Beck depression inventory for primary care had 97 percent sensitivity and 99 percent specificity for identification of major depression.[24,26]

1.2.4 Diagnosis of depression

The depressive disorders consists of[27,28]

- Unipolar major depression
- Episodes of major depression must include at least 5 depressive symptoms, involving depressed mood or loss of interest, for at least 2 consecutive weeks
- Persistent depressive disorder Also known as dysthymiais diagnosed in cases having 3 or more depressive symptoms for at least 2consecutive years; at least one symptom must be depressed mood
- Disruptive mood deregulation disorder
- Premenstrual dysphoric disorder
- Substance/medication induced depressive disorder
- Depressive disorder attributable another medical condition
- Other specified depressive disorder (eg, minor depression)
- Unspecified depressive disorder.

1.2.5 Depressive disorder due to another medical condition

Defined as mood disturbance that manifests as a continuing irritable or depressed mood, or reduced interest or pleasure in majority of activities.[20]

With patient history, clinical examination, or laboratory investigations suggest that the disturbance of mood is attributable to A separate medical illness (For example adrenal insufficiency, hypercortisolism, hypothyroidism, obstructive sleep apnea, stroke, SLE, or vitamin b12 deficiency).[27] also, the mood disturbance causes remarkable distress that it interferes with psychosocial interactions.[29]

For the most, the mood disturbance happens in the first month of the other medical disease. Some patients suffer depressive symptoms before the onset of the other medical illness.[30]

The differential diagnosis of unipolar depressive disorders includes general medical disorders, sadness, burnout, adjustment disorder with depressed mood, attention hyperactivity disorder, bipolar disorder, borderline personality disorder, complicated grief, delirium, schizophrenia, and schizo-affective disorder.[28]

1.2.6 Referral to a psychiatrist

Referral to a mental health specialist is indicated for patients In whom the diagnosis of depression or its commodities is uncertain; patients with severe depression, depression not responding to initial therapy, and psychotic or catatonic depression; or depression that is part of bipolar disorder.[24]

1.2.7 Depression and Acromegaly

Depression is common in patients of acromegaly and affects their reduced quality of life.[31] In these patients, the hormonal disturbance and the physical features caused by acromegaly may take part in the pathophysiology of depression. Although attention to the endocrine system's role in the pathophysiology of depression is mounting, it has primarily focused on the hypothalami-pituitary-adrenal axes. The role of growth hormone in the pathophysiology of depression, however, has not been sufficiently studied.[32]

Remission criteria of acromegaly are built on normalization of growth hormone and insulin like growth factor levels. Although, there is an established reduction in Quality of Life that is questioned to be present despite of biochemical control of disease. Psycho-pathological variables are candidate modifiable factors to correlate acromegaly, to a reduced health-related quality of life. On the one hand, acromegaly is reported to be associated with depressive symptoms. On the other hand, there is a clear connection between psychopathology and perceived quality of patients' lives.[33]

1.3 Anxiety disorders

1.3.1 Definition and epidemiology

Anxiety disorders describe illnesses that presents with manifestations of overwhelming anxiety and fear and changes of behavior. These encompass separation anxiety disorder, selective mutism, specific phobia, agoraphobia, social phobia, generalized anxiety disorder & substance/medication – induced anxiety disorder & anxiety attributable to another medical condition.[20] In American population, anxiety disorders are considered the most common among Psychiatric illnesses.[34] Social phobia is the most common among anxiety disorders. It presents in young population and could predispose later to depressive disorder and substance abuse. Generalized anxiety disorder is likely the most common anxiety disorder among the older adult population.[35,36]

Late-onset GAD is often linked with predisposing factors: Female gender, Poor socioeconomic status, Recent adverse life events, Chronic organic disease (Respiratory, cardiovascular, metabolic), Chronic mental disorder (for example depression), loss of a parent or separation, Low affective support during childhood, psychological disorders in the family.[37]

1.3.2 Pathophysiology

In the central nervous system (CNS), the significant mediators of the clinical features of anxiety disorders seem to be Noradrenalinedopamine, serotonin, and gamma-aminobutyric acid (GABA). Other neurotransmitters and peptides, such as corticotropin-releasing factor, may be incorporated. Peripherally, sympathetic nervous system, causes many of the clinical features.[38,39]

1.3.3 Clinical presentations of anxiety disorders

- Patients with generalized anxiety disorder complain of worry and anxiety with a minimum of 3 of the following symptoms (Restlessness, easy fatigability, poor concentration, irritability, muscle tension, sleep disturbance) for a minimum of 6 months.[40]

- A patient with social anxiety disorder will complain of a significant andconstant fear of social events that interfere with his/her functions.

- A patient with a specific phobia may complain of Fear of (Being trapped or fear of heights, fear of needles or other specific phobia).[37,41]

- A patient with Panic disorder will report recurrent panic attacks or a minimumof 1 attack with ensuing 1 month of fear of a recurring event.

Panic attack is a startling bout of extreme fear or discomfort associated with four or more of the following symptoms (palpitations, diaphoresis, trembling, dyspnea, sensation of checking, chest pain, nausea or abdominal discomfort, dizziness, chills, parasthesias, derealization,

fear of losing control, fear of death).[20]

1.3.4 Assessment of generalized anxiety disorder

Includes a thorough enquiry of symptoms suggestive of generalized anxiety disorder and symptoms suggestive of related or unrelated medical or psychiatric illness, which take in substance use disorder.[40] Individuals who present with symptoms of anxiety and a possible underlying physical illness must by clinically examined & investigated to exclude organic causes of anxiety. Laboratory investigations must contain complete blood picture, biochemical profile, thyroid function studies, urinalysis, electrocardiogram (Insubjects over 40 years of age with chest pain or palpitations), or urine or serum toxicology screen.[43]

1.3.5 Screening instruments of GAD

The Hamilton Anxiety Scale (HAM-A) is still the worldwide most acquainted clinician-rated scale in cases of clinical anxiety, The GAD seven- item (GAD-7) scale is a screening tool for GAD in primary care. The Penn State Worry Questionnaire is beneficial in evaluation of increased worrying.[44]

1.3.6 Diagnosis

Generalized anxiety disorder is diagnosed in a person with increased anxiety and worry that manifest more days than not for a minimum of 6 months. The worry impact a number of events or activities (like job or learning performance) and is related with 3 or more of (Irritability, muscle tension, restlessness, or sleep disturbance). The anxiety, worry or physical symptoms cause clinical distress in social, work, or other important personal activities.[45]

1.3.7 Referral to psychiatrist

Referral to specialist is important especially in patients of anxiety with-co-occurrence of substance use disorder or major depressive disorder, suicidal ideation)- interference with occupation, education, daily functions.[46]

1.3.8 Anxiety and Acromegaly

Patients with acromegaly display more anxiety-associated personality traits compared with the healthy population, potentially due to the pituitary adenoma and consequently the growth hormone disturbance and the comorbidities.[32]

Psycho-pathological variables are candidate modifiable factors to correlate acromegaly, to a reduced health-related quality of life. On the one hand, acromegaly is reported to be associated with anxiety symptoms. On the other hand, there is a clear connection between psychopathology and perceived quality of patients' lives.[33]

Aim of study

To assess the rate of depression and anxiety in Acromegaly patients With correlation to age, gender, duration of disease, hypophysectomy, octreotide use, deep x-ray therapy and response to all treatment modalities.

2. PATIENTS AND METHODS

2.1 Study design, Setting and Data collection time

This was a cross sectional study done at the national diabetes Center in Baghdad during a period of ten months from November 2020 to August 2021.

2.2 study Patients and Sample size

The study included 80 known Acromegalic adults who visited national diabetes center in Baghdad treated with either surgical or non- surgical methods or both, the data was obtained from patients records kept in the archives unit of the national diabetes center in Baghdad.

2.3 Exclusion criteria

- Previously Diagnosed depression
- Previously Diagnosed anxiety.

2.4 Data collection tools

A questionnaire was utilized to obtain the required information. It was formulated to gather the following data

- Age and gender.
- Age of diagnosis and duration of disease.
- Diabetes mellitus or not
- Hypertension or not
- Octreotide use and cumulative dose and response
- Hypophysectomy or not
- Gamma knife radiation therapy or not
- Hamilton anxiety scale

With Interpretation of scoring number of HAM-A scale
0-7 = No anxiety
8-14 = Mild anxiety
15- 23 = Moderate anxiety
>23 = Severe anxiety

- Beck depression inventory II

With Interpretation of scoring number of BDI II
0-9 = no depression
10-18 = mild depression
19-29 = moderate depression
30-63 = severe depression

2.5 Ethical Considerations and Official permission

Subject Names were hidden and instead identification codes were used. All information secret in a password secured laptop and information collected exclusively for the purpose of research.

Permissions were granted for initiating this research by

1. The Council of Arab Board of Medical Specialization.
2. Agreement of Iraqi national diabetes center.

2.6 Statistical analysis

The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean,

standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent t-test (two tailed) was used to compare the continuous variables accordingly. Chi square test was used to assess the association between provisional diagnosis and certain information, while fisher exact test was used instead when the expected frequency was less than 5.

A level of P – value less than 0.05 was considered significant.

3. RESULTS

A total of 80 acromegalic patients were recruited for this study. All of them were treated with either surgical or non- surgical methods or both.

3.1 Demographic and Clinical characteristics

Patients' age ranged from 23 to 71 years with a mean of 45.9 years and standard deviation of ± 12.17 years, and 51.2% were found in the age group of (30 – 49) years (table 3.1).

Regarding gender, proportion of males was higher than females (61.2% versus 38.8%) with male to female ratio of 1.58:1. Concerning chronic medical conditions, hypertension and diabetes were reported in 22 cases (27.5%) and 25 cases (31.2%), respectively. The most frequent duration of acromegaly was (3 – 6) years, reported in 30 (37.5%). Regarding the management of acromegaly, 73 patients (91.2%) were treated with octreotide, 39 (38.8%) were operated onwith pituitary surgery, while 8 (10%) underwent the radiation therapy.

After treatment, no change in the size of pituitary adenoma was noted in 35 cases (43.8%); macro to microadenoma in 28 (35%); and the remaining 17 (21.2%) were with normal size. Normal levels of IGF1 and GH were reported among 56 (70%) and 57 (71.3%) of the recruited patients, respectively (Table3.1).

Table 3.1: Distribution of acromegalic patients bydemographic and clinical characteristics.

Variable	No. (n= 80)	Percentage (%)
Gender		
Male	49	61.2
Female	31	38.8
History of HPT		
Yes	22	27.5
No	58	72.5
History of DM		
Yes	25	31.2
No	55	68.8
Duration of Disease (Years)		
< 3	10	12.5
3 – 6	30	37.5
7 – 10	27	33.8
> 10	13	16.2
Octreotide Use		
Yes	73	91.2
No	7	8.8
Pituitary Surgery		
Yes	39	48.8
No	41	51.2
Radiation Therapy		
Yes	8	10.0
No	72	90.0
Size of Pituitary Adenoma		
Normal	17	21.2
Macro to Micro	28	35.0
No Change	35	43.8
IGF1		
Normal	56	70.0
Abnormal	24	30.0
GH		
Normal	57	71.3
Abnormal	23	28.7

3.2 Results of hamilton anxiety rating scale (HAM-A)

According to the results of HAM-A scale, the highest percentage of score zero (83.8%) was to somatic (sensory) symptoms, the highest percentage of score one (21.3%) was to intellectual and GIT symptoms, while 28 patients (35%) scored two in regards to tension symptoms, and 4 patients (5%) scored three in regards to anxious mood symptoms (Table 3.2).

Table 3.2: Distribution of acromegalic patients according to results of HAM-Ascale.

HAM-A Items	Results			
	Score 0 no. (%)	Score 1 no. (%)	Score 2 no. (%)	Score 3 no. (%)
1. Anxious mood	48 (60.0)	15 (18.8)	13 (16.2)	4 (5.0)
2. Tension	38 (47.5)	13 (16.2)	28 (35.0)	1 (1.3)
3. Fears	63 (78.8)	14 (17.5)	3 (3.8)	0 (0)
4. Insomnia	55 (68.8)	16 (20.0)	8 (10.0)	1 (1.3)
5. Intellectual	58 (72.5)	17 (21.3)	5 (6.2)	0 (0)
6. Depressed mood	58 (72.5)	9 (11.3)	12 (15.0)	1 (1.3)
7. Somatic (muscular)	66 (82.5)	14 (17.5)	0 (0)	0 (0)
8. Somatic (sensory)	67 (83.8)	13 (16.2)	0 (0)	0 (0)
9. Cardiovascular symptoms	64 (80.0)	14 (17.5)	2 (2.5)	0 (0)
10. Respiratory symptoms	61 (76.3)	13 (16.2)	6 (7.5)	0 (0)
11. Gastrointestinal symptoms	53 (66.3)	17 (21.3)	8 (10.0)	2 (2.5)
12. Genitourinary symptoms	56 (70.0)	14 (17.5)	10 (12.5)	0 (0)
13. Autonomic symptoms	57 (71.3)	15 (18.8)	8 (10.0)	0 (0)
14. Behavior at interview	64 (80.0)	14 (17.5)	2 (2.5)	0 (0)

3.3 Severity of anxiety

Out of the 80 acromegalic patients, 36 (45%) had mild anxiety, 13 (16.3%) had moderate anxiety, 2 (2.5%) had severe anxiety, while the remaining 29 (36.2%) had no anxiety (Figure 3.2).

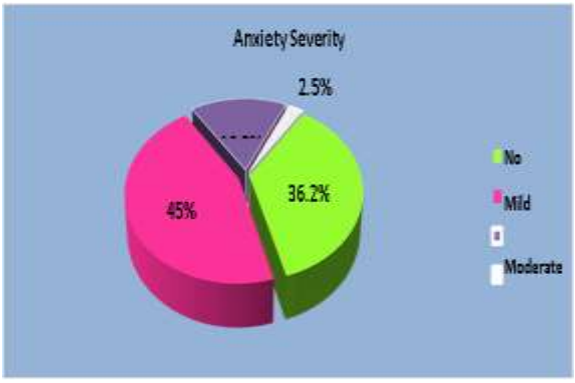

Figure 3.1: Distribution of the study patients by degree of anxietyaccording to HAM-A scale.

The distribution of acromegalic patients by results of HAM-A scale and certain socio-demographic and clinical characteristics showed that there was a statistically significant association between anxiety and diabetes, duration of disease, and GH level. The prevalence of moderate to severe anxiety was significantly higher among acromegalic patients who had diabetes (52%, P= 0.002), patients with duration of > 10 years (53.8%, P= 0.015), and those with abnormal GH level (52.2%, P= 0.001). Other demographic and clinical characteristic revealed no significant association (P > 0.05) with anxiety (Table 3.3).

Table 3.3: Distribution of acromegalic patients by results of HAM-A Scale and Certain Demographic and Clinical characteristics.

Demographic andClinical Characteristics	Anxiety According to HAM-A			Total (%) n= 80	P- Value
	Mild (%) n= 36	Moderate to Severe (%) n= 15	No Anxiety(%) n= 29		
Age (Years)					
< 30	2 (28.6)	1 (14.3)	4 (57.1)	7 (8.8)	**0.301**
30 - 49	22 (53.7)	5 (12.2)	14 (34.1)	41 (51.2)	

50 - 64	11 (44.0)	6 (24.0)	8 (32.0)	25 (31.2)	
≥ 65	1 (14.3)	3 (42.9)	3 (42.9)	7 (8.8)	
Gender					
Male	22 (44.9)	7 (14.3)	20 (40.8)	49 (61.2)	**0.355**
Female	14 (45.2)	8 (25.8)	9 (29.0)	31 (38.8)	
History of HPT					
Yes	9 (40.9)	6 (27.3)	7 (31.8)	22 (27.5)	**0.484**
No	27 (46.6)	9 (15.5)	22 (37.9)	58 (72.5)	
History of DM					
Yes	10 (40.0)	13 (52.0)	2 (8.0)	25 (31.2)	**0.002**
No	26 (47.3)	2 (3.6)	27 (49.1)	55 (68.8)	
Duration of Acromegaly (Years)					
< 3	4 (40.0)	1 (10.0)	5 (50.0)	10 (12.5)	
3 - 6	15 (50.0)	1 (3.3)	14 (46.7)	30 (37.5)	
7 - 10	14 (51.9)	6 (22.2)	7 (25.9)	27 (33.8)	
> 10	3 (23.1)	7 (53.8)	3 (23.1)	13 (16.2)	**0.015**
Octreotide Use					
Yes	33 (45.2)	15 (20.5)	25 (34.2)	73 (91.2)	**0.305**
No	3 (42.9)	0 (0)	4 (57.1)	7 (8.8)	
Pituitary Surgery					
Yes	19 (48.7)	8 (20.5)	12 (30.8)	39 (48.8)	**0.609**
No	17 (41.5)	7 (17.1)	17 (41.5)	41 (51.2)	
Radiation Therapy					
Yes	4 (50.0)	2 (25.0)	2 (25.0)	8 (10.0)	**0.762**
No	32 (44.4)	13 (18.1)	27 (37.5)	72 (90.0)	
Size of Adenoma					
Normal	8 (47.1)	4 (23.5)	5 (29.4)	17(21.2)	**0.367**
Macro to Micro	15 (53.6)	6 (21.4)	7 (25.0)	28(35.0)	
No Change	13 (37.1)	5 (14.3)	17 (48.6)	35(43.8)	
IGF1					
Normal	29 (51.8)	8 (14.3)	19 (33.9)	56 (70.0)	**0.124**
Abnormal	7 (29.2)	7 (29.2)	10 (41.7)	24 (30.0)	
GH					
Normal	29 (50.9)	3 (5.3)	25 (43.9)	57 (71.3)	**0.001**
Abnormal	7 (30.4)	12 (52.2)	4 (17.4)	23 (28.7)	

3.4 Results of Beck Depression Inventory (BDI II) scale

According to the results of BDI scale, the higher scoring of study patients was as follows: all of the 80 acromegalic patients scored zero regarding suicidal ideas; 31 (38.8%) scored one regarding loss of energy; 15 (18.8%) scored two regarding change in appetite, while only two patients (2.5%) had score three concerning insomnia (Table 3.4).

Table 3.4: Distribution of acromegalic patients according toresults of BDI II scale.

BDI II Items	Results			
	Score 0 no. (%)	Score 1 no. (%)	Score 2 no. (%)	Score 3 no. (%)
1. Sadness	56 (70.0)	17 (21.3)	7 (8.8)	0 (0)
2. Pessimism	64 (80.0)	15 (18.8)	1 (1.3)	0 (0)
3. Sense of failure	69 (86.2)	11 (13.8)	0 (0)	0 (0)
4. Loss of pleasure	60 (75.0)	18 (22.5)	2 (2.5)	0 (0)
5. Guilt	71 (88.7)	9 (11.3)	0 (0)	0 (0)
6. Expectation of punishment	67 (83.8)	10 (12.5)	3 (3.7)	0 (0)
7. Self-dislike	63 (78.7)	15 (18.8)	2 (2.5)	0 (0)
8. Self-accusations	57 (71.3)	19 (23.7)	4 (5.0)	0 (0)
9. Suicidal ideas	80 (100.0)	0 (0)	0 (0)	0 (0)
10. Crying	64 (80.0)	16 (20.0)	0 (0)	0 (0)
11. Agitation	50 (62.5)	22 (27.5)	8 (10.0)	0 (0)
12. Loss of interest	68 (85.0)	9 (11.3)	3 (3.7)	0 (0)

13. Indecisiveness	62 (77.5)	14 (17.5)	4 (5.0)	0 (0)
14. Worthlessness	79 (98.8)	1 (1.3)	0 (0.0)	0 (0)
15. Loss of energy	44 (55.0)	31 (38.8)	5 (6.2)	0 (0)
16. change in sleep pattern	48 (60.0)	18 (22.5)	12 (15.0)	2 (2.5)
17. Irritability	52 (65.0)	15 (18.8)	13 (16.2)	0 (0)
18. Change in appetite	49 (61.2)	16 (20.0)	15 (18.8)	0 (0)
19. Concentration difficulty	58 (72.5)	12 (15.0)	10 (12.5)	0 (0)
20. Tiredness	54 (67.5)	14 (17.5)	11 (13.7)	1 (1.3)
21. Loss of libido	62 (77.5)	10 (12.5)	8 (10.0)	0 (0)

3.5 Severity of depression

Depending on the results of BDI II scale, 29 patients (36.3%) were in mild depression, 15 (18.8%) in moderate depression, 2 (2.5%) in severe depression, while the other 34 (42.5%) had no depression (Figure 3.2).

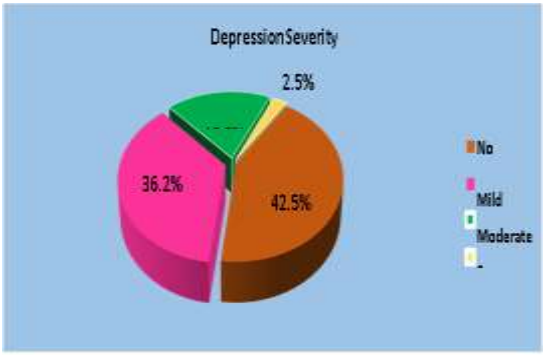

Figure 3.2: Distribution of the study patients by degree of depression according to BDI scale.

The distribution of acromegalic patients by results of BDI scale and certain socio-demographic and clinical characteristics revealed that there was a statistically significant association between depression and diabetes. Moderate to severe depression was significantly higher among acromegalic patients who had diabetes (40%, P= 0.011). No significant association (P > 0.05) was found between depression and other demographic and clinical characteristic (Table 3.5).

Table 3.5: Distribution of acromegalic patients by results of BDI Scale and Certain Demographic and Clinical characteristics.

Demographic and Clinical Characteristics	Depression According to BDI			Total (%) n= 80	P- Value
	Mild(%) n= 29	Moderate to Severe (%) n= 17	No Depression (%) n= 34		
Age (Years)					
< 30	0 (0)	1 (14.3)	6 (85.7)	7(8.8)	**0.123**
30 - 49	18 (43.9)	6 (14.6)	17 (41.5)	41(51.3)	
50 - 64	9 (36)	7 (28)	9 (36)	25(31.3)	
≥ 65	2 (28.6)	3 (42.9)	2 (28.6)	7(8.8)	
Gender					
Male	16 (32.7)	8 (16.3)	25 (51)	49 (61.2)	**0.132**
Female	13 (41.9)	9 (29)	9 (29)	31 (38.8)	
History of HPT					
Yes	7 (31.8)	8 (36.4)	7 (31.8)	22 (27.5)	**0.120**
No	22 (37.9)	9 (15.5)	27 (46.6)	58 (72.5)	
History of DM					
Yes	9 (36)	10 (40.0)	6 (24)	25 (31.2)	**0.011**
No	20 (36.4)	7 (12.7)	28 (50.9)	55 (68.8)	
Duration of Acromegaly (Years)					
< 3	5 (50)	0 (0)	5 (50)	10(12.5)	**0.128**
3 - 6	9 (30)	4 (13.3)	17 (56.7)	30(37.5)	
7 - 10	9 (33.3)	9 (33.3)	9 (33.3)	27(33.8)	
> 10	6 (46.2)	4 (30.8)	3 (23.1)	13(16.2)	

Octreotide Use					
Yes	27 (37)	17 (23.3)	29 (39.7)	73 (91.2)	**0.195**
No	2 (28.6)	0 (0)	5 (71.4)	7 (8.8)	
Pituitary Surgery					
Yes	15 (38.5)	9 (23.1)	15 (38.5)	39 (48.8)	**0.773**
No	14 (34.1)	8 (19.5)	19 (46.3)	41 (51.2)	
Radiation Therapy					
Yes	3 (37.5)	2 (25)	3 (37.5)	8 (10)	**0.944**
No	26 (36.1)	15 (20.8)	31 (43.1)	72 (90)	
Size of Adenoma					
Normal	7 (41.2)	4 (23.5)	6 (35.3)	17(21.2)	**0.721**
Macro to Micro	11 (39.3)	7 (25)	10 (35.7)	28(35)	
No Change	11 (31.4)	6 (17.1)	18 (51.4)	35(43.8)	
IGF1					
Normal according to age	21 (37.5)	10 (17.9)	25 (44.6)	56 (70)	**0.524**
Abnormal	8 (33.3)	7 (29.2)	9 (37.5)	24 (30)	
GH					
Normal(<1ng/ml)	21 (36.8)	9 (15.8)	27 (47.4)	57 (71.3)	**0.142**
Abnormal	8(34.8)	8(34.8)	7(30.4)	23(28.7)	

4. DISCUSSION

The main quest in this study is to determine the occurrence of anxiety and depression in a sample of Acromegaly patients.

Hamilton Anxiety scale and Beck depression inventory II are useful tools in previous research trials to detect features of Anxiety and Depressionrespectively.

In this study, anxiety by Hamilton scale was found in 63.8% of enrolled subjects. Depression by Beck depression inventory was found in 57.5% of cases. It is unclear whether these findings were due to Acromegaly, its associated comorbidities or its treatment.

4.1 Rate of anxiety in acromegaly patients

According to (table 3.2) 18.8% of patients scored 1 in anxious mood symptoms, 16.2% scored 2 & 5% of patients scored 3 by HAM-A scale. anxious mood symptoms include worries, anticipation of the worst, fearful anticipation and irritability. This finding differ from Jitske Tiemensma et al. study in which 4.6% of patients reported anxiousness.[74]

With regard to tension symptoms 35% of patients scored 2, 16.2% scored 1 while 1.3% scored 3. while in Lina Lasaite et al. study 21% of Acromegalic patients reported tension symptoms.[74]

Insomnia on the other hand was recorded to be score 1 in 20%, score 2 in 10% and score 1.3% score 3, insomnia in total was 31.3% of patients while S Cannavo et al. study demonstrated 18% of cases had insomnia & suggested association with obstructive sleep apnea and restless leg syndrome with hypothesized role of somatostatinergic and dopaminergic mechanisms of acromegaly-associated sleep disturbance.[74]

Intellectual aspect of HAM-A scale include difficulty in concentration and poor memory which combined received score 1 in 21.3% of patients and score 2 in 6.2% of patients.

With the sum of intellectual difficulties found in 27.5 % of this study patients supporting the idea of Emilia Solomon et al. study which reported 33% difficult concentration and poor memory in 24% of that study.[05]

With Leon-carrion et al. study conclusion of short and long term memory to be impaired with prefrontal and temporal cortices decreased activity and Sievers c et al. study claim that lower memory scores in association with long untreated disease duration.[01,05]

Somatic (Muscular) including (Pain and twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscle tone) score 0 in 82.5% and score 1 in 17.5% of patients similar to Fuchtbauer L et al. study which report muscular symptoms in 15% of Acromegalic patients in that with wooodhouse L J et al. study suggest that GH excess has greater effects on gas exchange and aerobic performance than on skeletal muscle mass and function.[05,07]

Somatic (Sensory) symptoms on the other hand include (Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation) score 0 in 83.8 % of patients by HAM-A Scale and score 1 in 16.2 % of patients similarly in kuan E et al. study in which 20% of Acromegalic patients reported tinnitus, in Aydin K et al. study hypertrophy of mastoid bone in 3 patients observed to suggest need for further research to confirm association of Acromegaly related soft tissue expansion and hearing problems.

Cardiovascular symptoms including (Tachycardia,

palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.) according to HAM-A scale with 80% of patients reporting no symptom (score 0), 17.5% of patients reporting score 1 and 2.5 % of patients reporting score 2. (The sum of 20% of patients in this study report cardiovascular symptoms according to HAM-A scale (In Maria fleseriu et al. study it's stated that it is controversial weather GH excess has deleterious impact on the heart or weather cardiovascular symptoms results from frequently observed increased prevalence of associated risk factors, and it's reported that concentric biventricular hypertrophy occurs in 20% of young Acromegalic patients.[05]

Regarding gastrointestinal symptoms, 21.3 % of patients scored 1 by HAM-A scale, 10% of patients scored 2 & 2.5% scored 3. (The sum of patients in this study who reported GIT symptoms was 33.8 %), while Inayet N et al. study in which 78% of patients had GIT symptom Though different sample size, duration of disease, drugs used with its duration are the major determinant of the differences observed among the studies.[04]

-in this study 45% of enrolled subjects had mild anxiety, 16.3 % had moderate anxiety while 2.5% had severe anxiety, 36.2 % of patients had no anxiety. These findings differ from Sievers C et al. study in which anxiety was present in 13.6 % of Acromegaly patients while Conaglen H et al. study in which 37 % of acromegaly patients with different in the sample size of the above studies.[04]

according to table 3.3 there is a significant statistical association between anxiety and duration of disease , 40 % of patients with less than 3 years had mild anxiety and 10 % of them had moderate to severe anxiety while in patients with 3-6 years of Acromegaly 50% had mild Anxiety and 3.3% had moderate to severe Anxiety, in 7-10 years of Acromegaly group 51.9% had mild Anxiety and 22.2% had moderate to severe Anxiety and for those with more than 10 years of Acromegaly 23% had mild Anxiety and 53.8 % had moderate to severe Anxiety. These finding support the idea of Gerontouko E L et al. study that in which 56% of chronic disease patients experienced some form of anxiety though both studies differ in sample size and screening tools used.[09]

It's also statistically significant that among patients with failure to suppress GH in this study 30.4% had mild anxiety and 52.2 % of them had moderate to severe anxiety. Auer M et al. study suggested that the axis of GHRH-GH- IGF-1 may impose permanent alteration in hippocampus which is widely associated with miscellaneous psychiatric dysfunction such as Anxiety. There is also significant statistic association between patients with history of diabetes mellitus and Anxiety, among these patients, 40% had mild anxiety and 52% had moderate to severe anxiety.[55]

4.2 Rate of depression in acromegaly patients

- According to table 3.4 all of the 80 Acromegaly patients in this study scored zero regarding suicidal ideations by BDI II scale , this finding is supported by the idea of the study by de Sousa A that report lack of suicidal thoughts (51).Regarding loss of energy 38.8% of patients scored 1 while 6.2% of patients scored 2 according to BDI II, this finding support the idea of Oliveira B et al. study in which acromegaly patients had 38.9 % less energetic compared to the non-acromegalic population.[55]

- In table 3.4 we also see that 20% of patients scored 1 and 18.8% of patients scored 2 regarding change in appetite which Reyes-Vidal C et al. study claim that in patient with Acromegaly experience change in ghrelin in correlation with fall in GH levels and with change in insulin resistance and also suggest that this effect occurs after hypophysectomy.[55]

The sleep pattern changes question by BDI II scale showed 22.5% of patients who scored 1, 15% of them scored 2 while 2.5% scored 3. Turan O et al. study showed Sleep associated apnoea in 62.9% of acromegalic subjects it's suggested that higher prevalence of sleep breathing disorder leads to a negative effect on quality of life of acromegaly patients.[57]

Zhang Y et al. study claimed that sleep quality was reduced in acromegalic patients in comparison with healthy controls (35 % of acromegalic patients had poor sleep quality with 5 % of control subjects had poor sleep quality in that study).[50]

In this study, 36.3% of patients had mild depression, 18.8% had moderate depression and 2.5% had severe depression. Similar to the idea of Malicki A et al. study in which depression rates among acromegalic patients were higher than healthy subjects .and Iris Crespo et al. study which used the BDI II scale to show that acromegalic subjects had more depressive symptoms than controls, same study suggested an association between anxiety and depression with performance in memory and decision making and suggested that emotional support may improve cognitive function.[55]

According to table 3.5 statistical significance association was found between diabetes and depression, among enrolled subjects with DM 36% of patients had mild depression while 40% had moderate to severe depression. The sum of patients from mild to severe depression is 76%.

4.3 Clinical information

In this study, the most frequent duration of Acromegaly was (3-6) years, reported in 37.5% of cases. Non-identical results noticed in Geraedts V J et al. study in which the most frequent duration of Acromegaly was 10 years.

In this study 91.2% of cases were treated with Octreotide, 48. 8% of cases were operated on with pituitary surgery and 10% of cases underwent radiation therapy. In 2020 Algahtany M et al. study, in which all of the acromegalic subjects enrolled underwent surgery, suggests that improvement in growth hormone level after surgery for acromegaly moderately correlate with improvement in depression score ($r = 52$ $p < 0.01$). On the other hand all patients in M Ruchala et al. study received octreotide and that study showed that respondent patient on octreotide reported good quality of life and had good interpersonal relations.

In this study hypertension was present in 27.5% of cases. This finding support the idea of the study by Puglisi S et al. which concluded hypertension to be present in 33.6% of Acromegalic patients in the study with unclear pathogenesis.

31.2% of patients enrolled in this study had diabetes mellitus which support the study of Petrussian P et al. in which 27.5% of cases had DM and among explanation suggested to that were impaired glucose homeostasis and insulin resistance in Acromegaly.

4.4 General characterstics

In this study, mean and standard deviation of age was 45.9 ± 12.7 years, ranging from 23 to 71 years with the highest proportion of subjects enrolled (51.2%) were between 30 and 49 years of age With regard to sex, male predominance recognized (61.2% were males versus 38.8% were females) with male to female ratio of 1.66:1. Different findings noticed in Dal J et al. study in 2020 in which the mean age of subjects enrolled was 47.2 with female predominance 53.3%. similar to Burton T et al. study conducted in 2016 in which the mean age was 41 and 52% of them were females.

Also in 2016 female predominance was observed in sardella et al. study in which females were 58.5% of 200 acromegalic patients .variations observed can be accounted for by dissimilarity of the sample size in each study with the demographic & hormonal variability that could have given difference in genderof patients.

Strength & Limitation

- This study has strength in that it provides new information to expand onthe subject that has yet to be thoroughly investigated.
- The sample size was comparatively smaller than other studies Which is a limiting factor for rare conditions such as acromegaly. lack of interest to partake in a detailed questionnaire is another limitation.

5. CONCLUSION AND RECOMMENDATION

5.1 Conclusion

1. Longer duration of Acromegaly and failure of GH suppression down to the previously specified target increases the chance of anxiety in Acromegaly patients though have no significant association with depression.
2. Coexistence of diabetes mellitus in Acromegaly subjects increases the chance of depression in addition to its impact on Anxiety.

5.2 Recommendation

1. Screen anxiety related symptoms in acromegalic subjects with non-suppressed GH level and those with long duration of the disease and Refer patients with positive symptoms for psychiatric management.
2. Conduct a similar study in a larger sample size.
3. Conduct a study of anxiety and depression in Diabetic patients.

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