Current Research in

# General Internal Medicine

Editor

Özden YILDIRIM AKAN

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Health Sciences

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# PREFACE

In internal medicine practice, there may be situations that can be missed or overlooked. In this book section, we have compiled these important diseases that we encounter in the clinic. Adrenal incidentalomas, evaluation of hirsutism in premenopausal women, ankylosing spondylitis, uremic and hepatic encephalopathy, suicidal behavior in the geriatric age, atopic dermatitis in childhood and a view of depression from the perspective of the enteric peptides topics are summarized in the light of current literature. We think that it will make a great contribution to clinicians and that they will benefit from this book in their daily practice.

**Asst. Prof. Dr. Özden YILDIRIM AKAN**

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# CHAPTER I

# ADRENAL INCIDENTALOMAS

**Elif GÜNEŞ**

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## 1. Introduction

Adrenal masses are usually detected incidentally in imaging studies performed for different health problems without any suspicion of adrenal disease.(1,2) Therefore, these lesions are defined as "adrenal incidentalomas". It should be emphasized here that a lesion detected in the adrenal gland must be at least 1 cm in size in order to be called an incidentaloma. (2) Since the 1970s, its prevalence has increased and AI has become a global health problem, thanks to increased hospital admissions and increased use of diagnostic imaging techniques. In recent studies, the incidence is reported to be between 4.2% and 7.3%, reaching 10% in elderly polpulation.(3,4) Although the etiology of adrenal incidentalomas varies according to studies and inclusion criteria, 80% are benign adrenal adenomas and 75% of masses do not produce hormones. The most common hyperfunctionality is autonomic cortisol secretion. When pheochromocytoma is considered separately, the incidence is around 7%. Primary adrenocortical cancer and adrenal metastases account for 12% of cases. (1) The distribution of patients presenting with incidental adrenal mass is shown in Table 1.

The majority of incidental adrenal masses are non-malignant and do not produce any hormones. However, if they are malignant in character or if there is a hormone-producing lesion that significantly affects human health, such as pheochromocytoma, primary hyperaldsteronism, and Cushing's syndrome, treatment is inevitable. When an incidental adrenal mass is encountered, it is

first necessary to differentiate whether this adrenal mass is benign or malignant. After this critical assessment, it is necessary to check whether it is functional.(2)

**2. Assesment of Malignancy Risk**

***2.1. Benign adrenal masses: homogeneous and ≤10 HU on unenhanced CT, irrespective of size***

**Table 1:** Prevalence of AIs by etiology and functional status

| | Prevalence |
|---|---|
| According to etiology causes | |
| Adrenocortical adenoma | 80%-85% |
| Malignant adrenal metastases | 3%-7% |
| Myelolipoma | 3%-6% |
| Cyst and pseudocyst | 1% |
| Ganglioneuroma | 1% |
| Hemorrhage | <1% |
| Schwannoma | <1% |
| Adrenocortical carcinoma | 0.4%-4% |
| In terms of functionality | |
| Nonfunctioning adenoma | 40%-70% |
| Mild autonomous cortisol secretion | 20%-50% |
| Primary aldosteronism | 2%-5% |
| Pheochromocytoma | 1%-5% |
| Overt Cushing's syndrome | 1%-4% |

Modified from Fassnacht M. et al. (2), AIs: adrenal incidentalomas.

Non-contrast CT is recommended as the first imaging modality in all adrenal incidentalomas. A benign adrenal mass is homogeneous and lipid-rich on non-contrast CT, with Hounsfield units (HU) ≤ 10.In this case, no other imaging modality is needed. In previous guidelines, the size of adrenal incidentalomas was additionally considered when evaluating benign adrenal masses and the above recommendations were given for adrenal incidentalomas measuring <4 cm. In the 2023 ESE guideline, the size criterion (< 4 cm) was removed and no additional imaging follow-up is now recommended for homogeneous adrenal masses ≤10 HU, aiming to reduce unnecessary follow-up and socio-economic cost.(2)

### *2.2. Nonfunctioning adrenal tumors with 11 to 20 HU on unenhanced CT and a size < 4 cm*

If non-contrast CT shows a homogeneous adrenal mass, if the tumor size is < 4 cm but the unenhanced HU is between 11 and 20, additional imaging is recommended immediately, even in the absence of hormone excess. However, the choice of imaging is left to the physician.(2) If the adrenal mass is homogeneous and the patient does not have an accompanying extra-adrenal malignancy, more than 90% of lesions with a HU value below 20 are benign.(5,6) These patients can be followed up 12 months later with CT or MRI for characterization of the adrenal mass, depending on the physician's preference.(2)

### *2.3. Indeterminate adrenal masses*

When adrenal masses are ≥4 cm, heterogeneous or have a HU > 20 on non-contrast CT image, there is a possibility that the lesion is malignant. The management of these masses requires a multidisciplinary approach. It is clear that most cases will require surgery.(2) However, it is possible that in some patients, as a result of a multidisciplinary meeting, additional imaging is recommended as an option. Before surgery, additional imaging, including thoracic CT, should be completed. FDG-PET/CT may even be planned. If a follow-up decision is made for these patients, a new imaging should be performed within 6-12 months.(2) Evaluating adrenal masses well from the very beginning and making the right decision will save unnecessary follow-up and cost.

If a patient chooses not to undergo adrenalectomy, or if the multidisciplinary team decides to do so, surgical treatment is recommended if there is a significant increase in mass size in the evaluation of adrenal incidentaloma after 6 or 12 months. According to our previous knowledge, an increase in mass size of >1 cm is defined as a significant increase.(7) While according to the latest guideline, a significant increase, that is, an increase in size indicating malignancy, is defined as an increase in maximum tumor diameter >20% and ≥5 mm.(2) Growths below this defined critical increase can be followed up with additional imaging and surgical treatment can be decided. Obviously, there is no standard follow-up protocol from this stage.

In the clinical pathway, some masses do not fall into the defined standard categories, e.g. an adrenal mass <4cm in diameter but HU>20 was measured. Or mass size ≥ 4 cm and The HU was measured 11-20. These examples can be expanded. It is recommended that each of these cases be approached on a patient-by-patient basis with decisions made at a multidisciplinary team meeting.(2)

In an individual with adrenal incidentaloma, adrenal biopsy is not recommended for diagnostic purposes unless there is a history of non-adrenal malignancy or metastasis is suspected.(2)

Measurement of sex steroids and steroidogenesis precursors is recommended in patients whose imaging or hormone profile is suspicious for malignancy.(1,2)

### 3. Assessment for hormone excess

As with any disease, all patients with adrenal incidentaloma should undergo a careful clinical examination from the first visit for signs and symptoms of possible hormone secretions.

#### *3.1. Remarks on terminology*

The term adrenal incidentaloma can be used in a much broader sense than defined above. Therefore, if the adrenal mass produces hormones, the term "functioning adrenal tumor." is preferred.(2)

In the 2016 European Society of Endocrinology (ESE) guidelines, 1-mg overnight dexamethasone suppression test (DST) results are categorized as follows: cortisol levels of 1.8 μg/dL or less are normal, levels between 1.9 and 5.0 μg/dL are possible autonomous cortisol secretion, and levels exceeding 5.0 μg/dL are autonomous cortisol secretion.(1)

The 2023 ESE guideline defines cases in which serum cortisol levels exceed 1.8 μg/dL after 1-mg DST as mild autonomous cortisol secretion (MACS), without further classification according to the degree of post-dexamethasone cortisol levels. Furthermore, the 2023 ESE guideline recommends testing for adrenocorticotropic hormone (ACTH) independence by demonstrating suppressed or low-normal morning plasma ACTH levels and recommends repeat DST to confirm MACS.(2)

#### *3.2. Initially hormonal evaluation*

Detailed clinical evaluation for symptoms should be performed for concomitant hormonal hypersecretions.

It is recommended that all patients with adrenal incidentaloma should receive 1 mg DST overnight to exclude Cushing's Syndrome and MACS. However, the latest guideline has made an important correction to this recommendation: fragile patients with limited life expectancy and patients over 65 years of age may not receive 1 mg DST because of the reduced clinical relevance of MACS even if it is present.(8,9)

Although previous guidelines recommended measuring plasma free or urinary fractionated metanephrines in all patients with adrenal incidentalomas to exclude pheochromocytoma, recent studies have shown that adrenal incidentalomas with HU ≤10 on non-contrast CT are very unlikely to be pheochromocytomas.(10) In light of these data, the latest guideline does not recommend measuring plasma free or urinary fractionated metanephrines in patients with adrenal incidentalomas with ≤10 HU on non-contrast CT imaging. (2) In a patient evaluated for an incidental adrenal mass with HU>10 on non-contrast CT, the first functional disease to be ruled out is pheochromocytoma. Screening tests for pheochromocytoma should be performed in patients with incidentaloma, whether or not they have hypertension and whether or not they have additional symptoms. The most appropriate screening test for pheochromocytoma is fractionated metanephrines in a 24-hour urine sample. The sensitivity of this test to diagnose pheochromocytoma is 95-100%. Urinary fractionated metanephrines must be normal to exclude pheochromocytoma in a patient. To diagnose pheochromocytoma, fractionated metanephrines, whether in plasma or urine, must be at least 3 times higher than the upper limit of the laboratory reference range.(11)

In patients with hypertension or unexplained hypokalemia, plasma aldosterone/renin ratio is recommended as a screening test for primary hyperaldesteronism.(1,2) If this ratio is above 20, confirmatory tests should be performed. If the test is to be performed on an outpatient basis, it is important not to restrict salt intake before the test. The test should be performed in the morning and at least half an hour should have passed since the patient got out of bed and the patient should have sat for at least 15 minutes before the blood test is performed. Patients' antihypertensive treatments should also be reviewed before the test. Diuretic treatments such as Spironolactone, Epleronon should be interrupted for at least 4 weeks before the test.(12)

### *3.3. Mild autonomous cortisol secretion (MACS)*

According to the latest guidelines, cases with serum cortisol levels exceeding 1.8 µg/dL after 1-mg DST are defined as MACS without further stratification according to the degree of cortisol level. In patients with MACS, a thorough clinical evaluation should be performed to look for clear signs of possible Cushing's syndrome.(2) Furthermore, recent studies have shown that MACS is associated with an increased prevalence of cardiometabolic diseases such as diabetes mellitus and dyslipidemia.(13,14) Current guidelines recommend a multidisciplinary team approach to decision-making in patients

with MACS, as there is no clear consensus on conservative or surgical treatment options, and no randomized controlled trials comparing conservative and surgical treatment outcomes. In making these decisions, the patient's age, general conditions, presence of comorbidities attributable to hypercortisolemia and patient preference should be considered.

### *3.4. Follow-up hormonal evaluation*

Up to 28% of non-functional adrenal incidentalomas may develop MACS in the following years. Therefore, different previous guidelines recommended hormonal testing once a year for at least four years.(15) The previous ESE guidelines did not recommend re-evaluation for hyperfunctionality if the adrenal incidentaloma was confirmed to be non-functional, unless the patient developed new symptoms or clinical signs.(1) The latest guideline, in line with this recommendation, states that a single initial hormonal evaluation test is sufficient, based on the fact that the incidence of overt Cushing's syndrome in patients with MACS is <1%.(2)

## 4. Surgicial Treatment

For patients with an indication for surgery, current guidelines recommend that a high-volume adrenal surgeon perform adrenalectomy.(1,2)

As a standard approach, adrenalectomy is recommended for all patients with adrenal incidentalomas with clinically significant hormone excess. In patients with MACS, surgical treatment can be planned when necessary, according to comorbidities and individual factors.

Surgical treatment is not recommended in patients with asymptomatic, nonfunctional and unilateral adrenal incidentalomas if the masses have obvious benign features. To clarify what we mean by these benign features, the first is that the imaging findings indicate a benign tumor, and the second is that it is not a hyperfunctioning mass.Regardless of its size, adrenalectomy is not routinely indicated if it has the above-mentioned characteristics of a benign mass. However, individualized approaches are preferred in patients with symptoms of mass effect or in the presence of a myelipoma that is increasing in size.(2)

For adrenal incidentalomas that meet the criteria for benign adrenal mass or cause hormone excess, if surgery is indicated, minimally invasive surgery is recommended primarily for patients with a mass <6 cm. If a unilateral adrenal mass is suspicious for malignancy but ≤6 cm in diameter and there is no evidence of local invasion, minimally invasive surgery by a high-volume surgeon is

recommended for this group of patients.If a mass suspicious for malignancy is accompanied by signs of local invasion, then open adrenalectomy by a high-volume adrenal surgeon is recommended.(2)

Perioperative stress dose glucocorticoid administration is recommended for all MACS patients scheduled for surgery. In addition, these patients should be followed by an endocrinologist until the hypothalamic-pituitary-adrenal axis recovers.

## 5. Special Circumstances

### *5.1. Patients with bilateral adrenal incidentalomas*

Patients with bilateral adrenal incidentalomas like unilateral adrenal incidentalomas, they should be subjected to clinical, radiologic and hormonal evaluations.

### *5.2. Adrenal incidentalomas in young patients*

Patients under 40 years of age and pregnant women are at higher risk of malignancy and hormone excess. In this group of patients, adrenal incidentalomas should be urgently differentiated as malignant or benign and hormonal hypersecretion should be evaluated.(2)

## 6. Conclusion

The first step in the assessment of malignancy risk in adrenal incidentalomas focuses on homogeneity and HU values regardless of the size of the mass.In the current guideline, the results of 1mg DST are no longer graded according to cortisol level and MACS is recommended as a general definition.The diagnosis and management of MACS focuses on ACTH-independence, age of the patients, comorbidities attributable to excess cortisol and other factors. The management of adrenal incidentalomas requires a multidisciplinary team approach.

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# CHAPTER II

# EVALUATION OF HIRSUTISM IN PREMENOPAUSAL WOMEN

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## 1. Introduction

Hirsutism is one of the most common causes of presentation to endocrinology clinics.(1) On the other hand, hirsutism is the most common clinical sign of hyperandrogenism.(1) The most common cause of hyperandrogenemia in the premenopausal age group is polycystic ovarian syndrome (PCOS); other causes include idiopathic hirsutism, classical and non-classical congenital adrenal hyperplasia (NCCAH), benign adrenal or ovarian androgen-secreting tumours (ASTMs) and, less commonly, malignant adrenal or ovarian ASTMs.(1) However, it would not be accurate to define all individuals with hirsutism as pathological. The Ferriman Gallway (FG) score has been developed to assess hirsutism.(2) An FG score of >8 in Caucasian American women and >9-10 in Middle Eastern women is considered pathological.(1,3) The FG scoring system is a useful test, but it is not sufficient and limits the population that can be studied. The variability of the FG score, which is considered pathological, according to race and the fact that different aetiological causes lead to similar clinical status can be listed as weaknesses.

Hypertrichosis should not be confused with hirsutism. Hypertrichosis usually occurs in areas outside the hormonal effect area of hyperandrogenemia, such as the forearm and leg area below the knee, and can sometimes increase with hyperandrogenemia.(1,3,4) Hypertrichosis is most common in people with a genetic predisposition and is caused by medication.(1,3,4)

Although clinical findings are helpful in determining the aetiological causes, reliable laboratory tests are needed to suspect benign or malignant ASETM.

## 2. Definition

### *2.1 Hisutism*

Hirsutism is generally defined as excessive growth of terminal hair in females, similar to males.(1,3) Bozdağ (5) and colleagues (et al) found the prevalence of hirsutism in their study to be 13% (8-20%).

### *2.2 Idiopathic hirsutism*

It is defined as a condition in which there are no clinical signs and symptoms of hyperandrogenemia.

### *2.3 Local hair growth*

This is unwanted hair growth in a localised area. Usually the FG score is within normal limits.(1)

### *2.4 Patient-relevant hirsutism*

Increased hair growth in the androgen effect zone independent of the FG score, which disturbs and stresses the patient.(1)

### *2.5 Hyperandrogenaemia*

Reflects increased androgen production or increased androgen activity.

### *2.6 Oligomenorrhoea*

Oligomenorrhoea is defined as less than 8 menstrual cycles in 12 months in the last one year.(1)

## 3. Etiological causes

A significant proportion of patients with premenopausal hyperandrogenemia are those with polycystic ovary syndrome (PCOS).(5,6) The most common cause after PCOS is idiopathic hirsutism.(5,6) Other non-malignant causes of hirsutism include hyperprolactinaemia (HP), Cushing's syndrome (CS) due to pituitary or adrenal adenoma, classical and NKCAH, adrenocortical carcinoma and ovarian ASTMs.(1) ASTMs are one of the most serious causes

of hyperandrogenemia and therefore their exclusion is very critical. In this differentiation, an increase in clinical findings in the last 6 months or 1 year is helpful. Although clinical findings are helpful, reliable laboratory tests are needed for differential diagnosis.

**4. Clinical findings**

Clinical findings may vary considerably depending on the aetiology. Hyperandrogenemia and oligomenorrhoea are absent in a significant proportion of women with premenopausal hirsutism (PHC) and these patients are classified as having idiopathic hirsutism.(1) Clinical findings other than hirsutism are not observed in this group of patients. The rate of onset and progression of clinical findings is important. A clinical finding that occurs suddenly in the last 6 months or 1 year and has a progressive course should alert the clinician to ASTMs. In addition, male pattern hair loss, increased acne and the presence of virilism findings (increase in muscle mass, coarsening of the voice, clitoromegaly, etc.) are very important in terms of aetiology. CS may be considered a rarer cause, in which case physical examination findings of CS should be sought (striae, moon face, buffalo hump, easy bruising, etc.). Patients with HP may also have galactorrhoea.

**5. Laboratory findings**

Laboratory testing is recommended in individuals with an FG score > 8 and in individuals with an FG score < 8 who have clinical signs and symptoms of hyperandrogenemia.(1) Laboratory testing is not recommended in individuals with an FG score <8 without clinical signs and symptoms of hyperandrogenemia (Figure 1).(1) Basic laboratory tests should include total testosterone (TT) and dehydroepiandrosterone sulphate (DHEAS). Follicle stimulating hormone (FSH), luteinising hormone (LH), estradiol (E2) and 17-OH-progesterone (17-OH-P) should be measured in the follicular phase to determine the aetiological causes. An FSH/LH ratio <1 is important in PCOS. In addition, a Synacthen stimulation test should be performed in patients with basal 17-OH-P levels >2.0 ng/mL in the follicular phase, and a 17-OH-P level >10 ng/mL after stimulation is diagnostic for NKCAH.(7) Free testosterone (FT) should be ordered in patients who have a high FG score as a clinical finding or who have progressive features but normal TT levels (Figure 1).(1) Patients with clinical signs and symptoms suggestive of CS should be screened with a cortisol level after suppression with 1 mg dexamethasone, and a level >1.8 µg/dL should be

considered pathological.(8) It should be noted that patients with mild HP may present only with oligomenorrhoea and hirsutism, and HP should be confirmed by looking at macro-PRL (mPRL) levels in patients with mildly elevated PRL levels and performing serial PRL measurements if necessary.

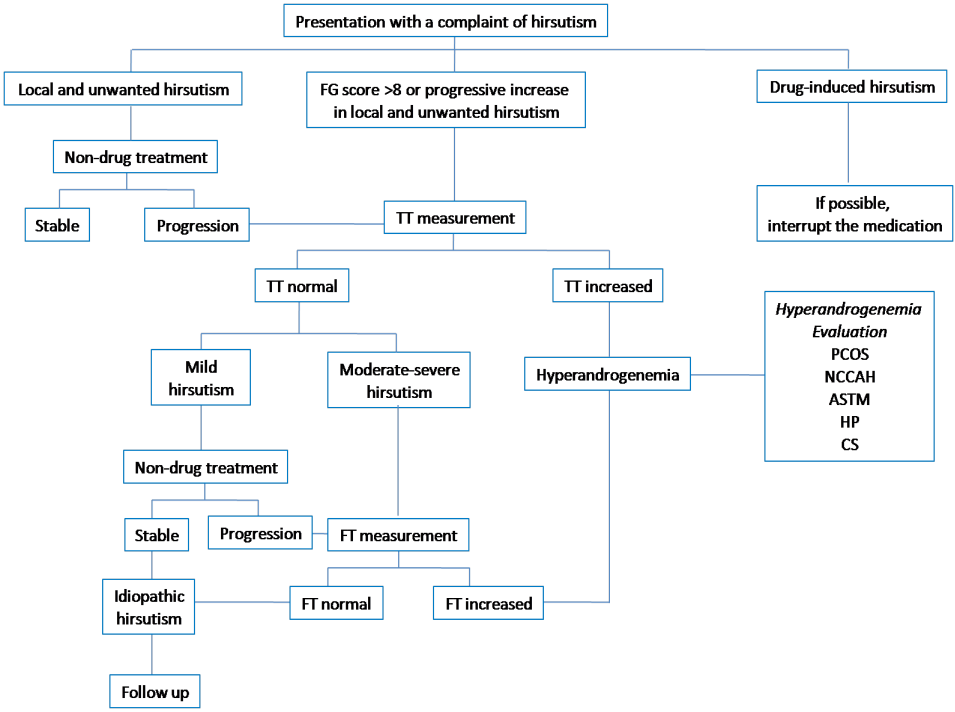
### 6. Diagnostic approach

Those without clinical signs and symptoms of hyperandrogenemia are defined as having idiopathic hirsutism. The Roterdam 2004 criteria are commonly used to diagnose PCOS.(9) Accordingly, the presence of 2 out of 3 criteria is considered compatible with PCOS. The criteria can be listed as follows: 1. oligomenorrhoea and/or anovulation, 2. clinical and/or biochemical symptoms of hyperandrogenism, 3. polycystic ovaries on ultrasonography (US). (9) The NIH and AE-PCOS Society criteria are also used.(10,11) Idiopathic hirsutism and PCOS account for approximately 95% of patients with hirsutism. The diagnostic approach in an individual with hirsutism is shown in Figure 1.

The third most common cause of hirsutism is NCCAH, the frequency of which varies between 2.4% and 7.1% in our country.(6,12) In patients with 17-OH-P levels >2.0 ng/mL in the follicular phase, 17-OH-P levels >10 ng/mL after synacthene stimulation test are diagnostic for NCCAH.(7) The frequency of HP has been reported to be 1.45% in patients with hirsutism.(6)

The remaining 1% are ASTMs, which are rare but should not be neglected. (6) The main difficulty is the lack of a specific laboratory test to make the diagnosis. An FG score >8 or >10 in Middle Easterners is considered pathological. One of the biggest difficulties here is that individuals presenting with hirsutism have already had photoepilation and are seeking treatment because it has failed. This raises the question of how accurate the calculated FG score is. The situation is further complicated by the fact that TT kits use different units of measurement such as ng/mL, ng/dL or nmol/L. Unfortunately, there are not enough studies in this area on which values for TT indicate ASTMs. Waggoner et al. determined the sensitivity and specificity of values above 8.67 nmol/l (2.3-fold increase) to be 100% and 98%, respectively, in predicting ASTMs using kits with an upper limit of TT of 3.0 nmol/L.(13) Other methods have also been developed for the diagnosis of ASTMs in individuals with hirsutism; Khaltsas et al. re-evaluated TT levels after a 48-hour low-dose dexamethasone suppression test (LDDST) in patients with hirsutism who had high TT levels and a defined androgen suppression ratio (ASR).(14) They found the sensitivity and specificity of an ASR of 40% or less from baseline to be 100% and 88%, respectively, in indicating an ASTM-derived aetiology.

**Figure 1:** Clinical evaluation of premenopausal women with hirsutism.




Modified from Martin KA (1). FG: Ferriman Gallway; TT: total testosterone; FT: free testosterone; PCOS: polycystic ovary syndrome; NCCAH: non-classical congenital adrenal hyperplasia; ASTMs: androgen-secreting tumours; HP: hyperprolactinaemia; CS: Cushing's syndrome.

They found the sensitivity and specificity of an ASR of 40% or less from baseline to be 100% and 88%, respectively, in indicating an ASTM-derived aetiology.(14) "The Turkish Society of Endocrinology and Metabolism Guidelines for the Diagnosis and Management of Adrenal and Gonadal Diseases'' specified the level of increase for TT as greater than 150 ng/dL and emphasised that approximately 2.8-fold increases (for women aged 21-49 years ng/dL normal limits of the kits; 13.84-53.35 ng/dL) should be taken seriously, but did not refer to the study on which these data were based.(15) In our study, when the cut-off value for the increase (in folds) according to the upper limit of normal (ULN) was 2.0-fold, the sensitivity was 100% and the specificity was 99.5% for kits with a normal limit of 0.34-1.97 nmol/L for TT levels,

When the cut-off was set at 2.4-fold, the sensitivity and specificity were 100% and 100%, respectively.(6) Thus, a 2.0-fold increase in TT (in nmol/L) should be taken seriously. In the same study, we found a sensitivity of 80% and a specificity of 100% for excluding ASTMs when the ASR was 49% and above after LDDST in patients with a 2.0-fold increase.(6) In conclusion, a 2-fold increase in basal TT (nmol/dL) should be taken seriously and investigated, and ASR after DDST seems to be a useful parameter for further investigation.

Individuals with a 2.0-fold increase in baseline TT (in nmol/L) and less than 49% suppression by LDDST should be investigated by magnetic resonance imaging (MRI) or computed tomography (CT). Although the diagnostic performance of MRI and CT is close, MRI has a slight advantage, but its cost varies by region, so the choice of method should be made on a patient-by-patient basis. Selective angiography should be considered in individuals with negative imaging but TT levels increased 2.0-fold or more and less than 49% suppression by LDDST.

In patients with a 1.0-2.0-fold increase in baseline TT (in nmol/L), the choice of imaging modality should be based on the presence of LDDST suppression or on the progression of clinical findings and laboratory parameters during follow-up.

Patients with less than a 1.0-fold increase in baseline TT (in nmol/L) should be followed and a decision should be made according to the progression of clinical findings and laboratory parameters during follow-up.

## 6. Treatment

Treatment of hirsutism depends on the aetiological cause. In patients with idiopathic hirsutism, photoepilation or electrolysis is used before medical treatment. In PCOS patients with oligomenorrhoea, oral contraceptives (OCS) may be more beneficial in treating both oligomenorrhoea and hirsutism. The use of OCS does not preclude photoepilation or electrolysis.

### *6.1 Non-drug treatments*

The most commonly used non-drug methods are photoepilation and electrolysis. Both methods are painful to some extent. There is no superiority of one method over the other.(1)

### *6.2 Medical treatment*

As one of the most common causes of hirsutism is PCOS, the combination of oligomenorrhoea and hirsutism is a very common clinical picture. In this case, the use of OCS may be an appropriate option for both symptoms. (1) Hyperandrogenemia itself is associated with an increased risk of venous thromboembolism (VTE). The use of OCS may lead to an increased risk of VTE with age (particularly in those aged 39 years and over). In this age group, obesity should be assessed or additional risk factors such as smoking should be considered.(1)

Anti-androgen therapy may be started in patients who do not respond adequately after 6 months of OCS treatment. The agents commonly used for anti-androgen therapy are flutamide, aldactone and cyproterone acetate. In women of childbearing age, the desire to become pregnant should be considered and should not be started in those planning to become pregnant. It should be started in those who are not planning a pregnancy, because antiandrogens have teratogenic effects.(1)

For the treatment of hirsutism in patients with NCCAH, OCS should be considered initially, and if the desired effect is not achieved after 6 months of use, the addition of an antiandrogen should be considered.(1) Steroid suppression is not recommended for hirsutism in patients with NCCAH (1). In NCCAH, androgen suppression therapy with steroids is used to treat infertility with prednisolone or methylprednisolone.(1) Dexamethasone is not recommended for the treatment of infertility because it cannot be inactivated by 11-b-hydroxysteroid dehydrogenase type 2.(1)

Patients with HP should be treated with dopamine agonists. However, hirsutism alone is not an indication for treatment in the absence of oligomenorrhoea and galactorrhoea in patients with HP.

### *6.3 Surgical management*

Surgical removal of adenomas of adrenal or ovarian origin is necessary. ASTMs of adrenal origin are usually malignant.(12) They may secrete more than one hormone (simultaneous CS). Androgen-secreting neoplasms of ovarian origin should also be surgically removed.

The primary treatment for CS of adrenal or pituitary origin is surgery.

## 7. Conclusion

Hirsutism is one of the most common causes of presentation to adult endocrinology outpatient clinics. The three most common causes of hirsutism are PCOS, idiopathic and NCCAH. PCOS and idiopathic hirsutism account for 95% of all presentations. ASTM-induced hirsutism accounts for approximately 1% of all presentations and can have important consequences if missed. A clinical finding that has progressed in the last 6 months or 1 year should alert the clinician. TT and FT should be requested in patients with FG score >8 and progressive disease during follow-up. The aetiological cause should be investigated in patients with hyperandrogenemia. When determining the aetiological cause, increases in TT (nmol/dL) of 2.0 or more compared to ULN from baseline should be seriously considered, and selective venous sampling should be considered in the absence of pathology on imaging, especially in patients with ASR <49. The primary treatment option in patients without oligomenorrhoea is non-drug treatment, and OCS should be considered in patients with oligomenorrhoea or in those who do not have the desired response to 6 months of non-drug treatment. Again, anti-androgen therapy may be tried in patients who are not planning to become pregnant, if the desired response is not achieved after 6 months of OCS treatment. Anti-androgen therapy is contraindicated in patients planning to become pregnant. Surgical removal of ASTMs of adrenal or ovarian origin is necessary.

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# CHAPTER III

# ANKYLOSING SPONDYLITIS

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## 1. Introduction

Ankylosing spondylitis (AS) is a major subtype of rheumatic disease that shares numerous features with spondyloarthritis. It may involve the axial skeleton, peripheral joints, and entheses, as well as extra-articular involvement like uveitis and inflammatory bowel disease. AS is characterized by radiographic sacroiliitis and inflammatory back pain. Over time, inflammation of the sacroiliac joint and spine may cause ankylosis of the bones. (1)

### *2. Epidemiology*

The prevalence of AS varies considerably among ethnic populations. It has been reported that the prevalence is 23.8/10,000 in Europe, 16.7/10,000 in Asia, 31.9/10,000 in North America, and 7.4/10,000 in Africa. (2) The prevalence of AS among people aged 20 and above in Turkey is 0.49% (0.54% in males and 0.44% in females), whereas the prevalence of spondyloarthritis (SpA) is 1.05%. (3)

AS is more frequent in young adult males, with males having a threefold higher frequency than females. (4)

The prevalence of AS in the general population is similar to the prevalence of human leukocyte antigen (HLA) B27. (5) HLA-B27 is present in around 90% of white AS patients, but it is present in approximately 50% of black AS patients. (1) The prevalence of HLA-B27 in the healthy population in Turkey is found to be 8%. (6)

## 3. Pathogenesis

While the exact etiology of AS is still not fully understood, genetic and environmental factors play important roles in its pathogenesis.

***3.1. Genetic Factors:*** A positive family history of AS is a significant risk factor for the development of the disease. In the general population, only about 1-2% of HLA-B27-positive adults will develop AS over their lifetime, but the risk increases to approximately 10% in first-degree relatives of AS patients. If a close relative of an AS patient is also HLA-B27 positive, this risk further rises to around 20%. (7)

It is estimated that HLA-B27 in the major histocompatibility complex (MHC) class I region contributes to genetic susceptibility in AS by approximately 25%. Genes related to cytokine pathways, such as endoplasmic reticulum aminopeptidase 1 (ERAP1) and the interleukin (IL) 17/23 pathway, which interact with HLA-B27 and are involved in intracellular antigen processing outside of the MHC locus, have less contribution to genetic susceptibility. (8) HLA-B27 is highly polymorphic, with more than 100 subtypes identified, varying in prevalence among different ethnic origins. The most common subtypes of HLA-B27 reported in AS are HLA-B2705 (Caucasian population), HLA-B2704 (Chinese population), and HLA-B2702 (Mediterranean population). (9)

Regarding the contribution of HLA-B27 to the pathogenesis of AS, there are three major hypotheses:

1. Arthritogenic Peptide: Self-peptides that resemble microbial peptides can bind to HLA-B27 and become targets of auto-reactive CD8+ cytotoxic T cells, resulting in chronic inflammation. (10)

2. Heavy Chain Homodimers: On the cell surface, HLA-B27 can form heavy chain homodimers. These HLA-B27 homodimers can induce the release of cytokines such as IL-17 and tumor necrosis factor (TNF).

3. HLA-B27 can readily misfold in the endoplasmic reticulum, resulting in an unfolded protein response and autophagy. This can activate pro-inflammatory T helper 17 cells and result in the release of inflammatory cytokines such as IL-23. (11)

### *3.2. Environmental Factors*

***3.2.1. Mechanical Stress:*** Rapid stress response generated in anatomical regions exposed to mechanical overload, such as the axial skeleton and entheses, can lead to local prostaglandin E2 production, vasodilation, and activation of the

IL-23/IL-17 axis. Inflammation in entheses is followed by a mesenchymal tissue response and new bone formation. (12)

***3.2.2. Microbiota:*** Subclinical gut inflammation has been observed in 60% of SpA patients, and more severe disease resembling inflammatory bowel disease has been described in 7% of cases. (13, 14) Increased gut permeability has been observed in AS patients and their first-degree relatives. (15)

## 4. Clinical Manifestations

The clinical presentations of AS may be categorized into two main categories: musculoskeletal and extra-articular manifestations.

### *4.1. Musculoskeletal Manifestations:*

***4.1.1. Inflammatory Back Pain and Morning Stiffness:*** The presence of inflammatory back pain (IBP) is a prominent clinical manifestation observed in individuals diagnosed with axial spondyloarthritis. (16) This type of pain is suggestive of inflammation existing in the sacroiliac joints and spine. IBP is usually differentiated by a gradual initiation, persisting for a duration over 3 months, and is related to chronic pain in the back or gluteal region. Frequently, individuals have a prolonged duration of morning stiffness over 30 minutes, which exhibits a favorable response to non-steroidal anti-inflammatory drugs (NSAIDs). (17)

***4.1.2. Dactylitis:*** Dactylitis, a condition characterized by inflammation and swelling of the fingers and toes, has been found to occur in around 6% of individuals diagnosed with AS. (18)

***4.1.3. Peripheral Arthriti***s: Approximately 30% of individuals diagnosed with AS manifest peripheral arthritis. (18) Peripheral arthritis in AS typically exhibits asymmetrical and oligoarticular involvement, mostly involving the lower extremities. (19) The extra-axial joints that are most frequently affected are the ankle (39.5%), hip (36.1%), knee (29.3%), shoulder (19%), and sternoclavicular (14.3%) joints. (20)

***4.1.4. Entehsitis:*** Enthesitis, the inflammatory condition affecting the areas where tendons, ligaments, fascia, or joint capsules attach to bone, is a distinguishing hallmark of AS and other SpAs. (21) Enthesitis is observed in roughly 30% of individuals. (18) Enthesitis commonly affects many anatomical regions, including the manubriosternal and costochondral joints, lateral epicondyle, iliac crests, spinal spinous processes, Achilles tendon, and plantar fascia. (22)

***4.2. Extra-Articular Manifestations:***

***4.2.1. Anterior Uveitis:*** Acute anterior uveitis, which is the acute inflammation of the front segment of the eye, is the most prevalent extra-articular manifestation in AS patients, occurring in approximately 20-30% of patients. It has no correlation with the severity of joint diseases. Typically, it manifests as unilateral ocular pain, redness, photophobia, increased tearing up, and vision blurring. (23)

***4.2.2. Psoriasis:*** Psoriasis is present in approximately 10% of AS patients. (18)

***4.2.3. Gastrointestinal Manifestations:*** Up to 46% of AS patients exhibit microscopic bowel inflammation. In approximately 30% of cases, there is acute inflammation, which is predominantly localized in the ileum (50% in the ileum, 23.3% in the colon, and 26.7% in both the ileum and colon). Microscopic bowel inflammation has been linked to a young age, short duration of symptoms, progressive disease, male gender, and high disease activity. (24) In approximately 5% of patients with bowel inflammation, clinically overt inflammatory bowel disease may develop. (18)

***4.2.4. Pulmonary Manifestations***: Apical lobe fibrosis is the most prevalent lung parenchymal abnormality and a late complication of the disease. It can be unilateral or bilateral and can be complicated by bullous or cavity formations. It is observed in approximately 7% of patients, and its prevalence rises with the duration of the disease. (25)

Reduced chest wall expansion and decreased spinal mobility are associated with restrictive lung disease. (26)

***4.2.5. Cardiac Manifestations***: AS patients may develop aortitis and aortic regurgitation, conduction defects, valvular regurgitation, as well as myocardial and pericardial involvement. (27)

Aortic valve disease is observed in 4% of patients in the early stages of the disease (<15 years), while it is seen in 10% of patients in the late stages (>30 years). (28)

***4.2.6. Renal Manifestations:*** Amyloidosis, IgA nephropathy, and NSAID-associated nephropathy can develop. (29)

**5. Classification Criteria**

The Assessment of SpondyloArthritis International Society (ASAS) developed the ASAS classification criteria in 2009 due to the low performance

of the 1984 Modified New York classification criteria in identifying early-stage patients (Table 1 and Table 2). (19, 30)

Modified New York Criteria (1984) (31): A definitive diagnosis of AS requires meeting the radiological criterion and at least one clinical criterion.

Clinical Criteria:

1. Chronic low back pain and stiffness for more than 3 months that improves with exercise and is not relieved by rest.
2. Limitation of motion in the sagittal and frontal planes of the lumbar spine.
3. Reduced chest expansion compared to age- and gender-matched normal values.

Radiological Criteria: Bilateral grade 2 or unilateral grade 3-4 sacroiliitis.

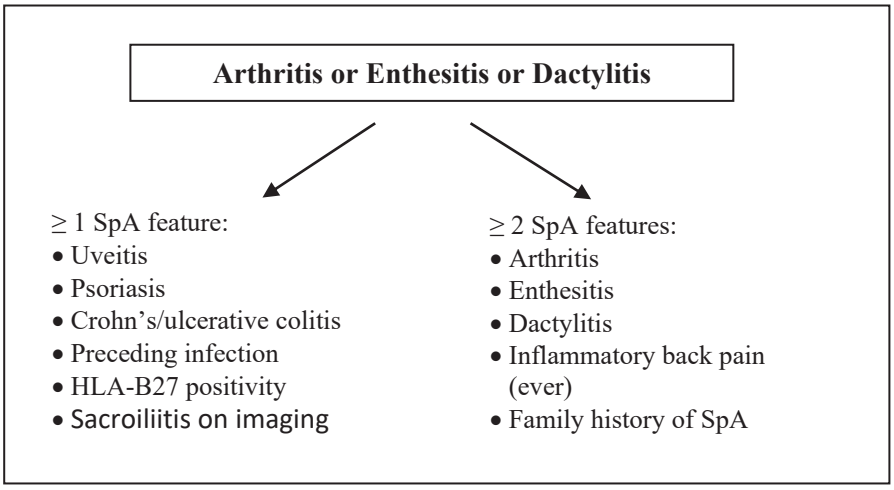
**Table 1:** ASAS Classification Criteria for Axial SpA: (30)

| | | |
|---|---|---|
| Sacroiliitis on imaging*<br>Plus<br>≥1 SpA Features | OR | HLA-B27<br>Plus<br>≥2 SpA Features** |
| *Sacroiliitis on imaging:<br><br>-Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA<br>Or<br>-Definite radiographic sacroiliitis according to Modified New York criteria | | **Spa Features:<br><br>-Inflammatory back pain<br>-Arthritis<br>-Enthesitis (heel)<br>-Uveitis<br>-Dactylitis<br>-Psoriasis<br>-Crohn/ulcerative colitis<br>-Good response to NSAIDs<br>-Family history for SpA<br>-HLA-B27<br>-Elevated CRP |
| Sensitivity: 82.9%, Specificity: 84.4%. For the imaging arm alone: Sensitivity: 66.2% vs. Specificity: 97.3%. | | |

SpA: Spondylarthritis; HLA: Human leucocyte antigen; MRI: Magnetic resonance imaging; NSAID: non-steroidal anti-inflammatory drug; CRP: C-reactive protein

In 2009, the ASAS group divided Spondyloarthritis (SpA) into "axial SpA," where axial involvement predominates, and "peripheral SpA," where peripheral involvement predominates. Axial SpA is further classified into AS (radiographic SpA), where radiographic sacroiliitis is evident, and non-radiographic axial SpA, where significant radiographic changes are not present, based on the Modified New York criteria. (30)

**Table 2**-ASAS Criteria for peripheral spondyloarthritis: (19)




### 6. Differential Diagnosis

Other seronegative spondyloarthritis, diffuse idiopathic skeletal hyperostosis, osteitis condensans ilii, and infectious sacroiliitis should be considered in the differential diagnosis. (32)

### 7. Laboratory

In AS patients, only 40-50% may have elevated C-reactive protein (CRP) and sedimentation rates. Normal values do not rule out the diagnosis or the presence of active disease. Elevated CRP levels are associated with radiographic structural damage. HLA-B27 can be positive in up to 90% of cases. (1)

### 8. Imaging

Several imaging modalities can be used for the imaging of AS, such as conventional radiography, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound.

***8.1. Radiography:*** Erosion and ankylosis of the sacroiliac joint are distinctive features of AS. Sacroiliitis is often the initial sign of the disease and is typically bilateral and symmetric. Radiographic staging of sacroiliitis; Stage 0: Normal appearance, Stage 1: Suspicious appearance (blurring at the joint margins), Stage 2: Minimal abnormality (erosions and sclerosis areas with preserved joint space, partial ankylosis), Stage 3: Definite abnormality (sclerosis on both joint surfaces, erosions causing widening or narrowing of the joint space), Stage 4: Complete ankylosis. (33)

Sclerosis, also known as a shining corner or Romanus lesion, manifests in the initial stages of spinal imaging, particularly at the points where the annulus fibrosus connects to the anterior corners of the vertebral endplates. The presence of erosions and squaring of the vertebral bodies is also evident. Syndesmophytes may become prominent in later stages. The progressive growth of syndesmophytes results in the characteristic appearance of the bamboo spine. (34)

***8.2. Magnetic Resonance***: Active inflammatory lesions in the sacroiliac joint include subchondral or periarticular bone marrow edema (BME) /osteitis, synovitis, enthesitis, or capsulitis of the sacroiliac joint. BME is an indicator of active sacroiliitis but can also be seen due to different causes. Structural lesions of the sacroiliac joint include subchondral sclerosis, erosions, fat deposition, and bone bridges/ankylosis. In MRI, for sacroiliitis to be diagnosed, BME (hyperintense on STIR-short-tau inversion recovery images) or osteitis (hypointense on T1 post-Gadolinium sequences) should be clearly present in a typical anatomical localization (subchondral or periarticular bone marrow). The presence of other active inflammatory lesions like synovitis, enthesitis, or capsulitis without concomitant BME/osteitis is not sufficient for the diagnosis of sacroiliitis on MRI. Structural lesions such as fat deposition, sclerosis, or bone ankylosis often reflect prior inflammation but are not considered sufficient for a positive MRI diagnosis on their own. BME indicative of active inflammation must be present in at least two consecutive segments, or multiple BME lesions must be present in a single slice for each MRI slice. (35)

Spondylitis, spondylodiscitis, arthritis of the facet joints, and arthritis of the costo-vertebral and costo-transverse joints are typical spinal lesions indicative of an active disease. Bone erosions, focal fat infiltration, and bony spurs (syndesmophytes, ankylosis) are commonly observed. Enthesitis is also widespread and can affect interspinal and supraspinal ligaments. (35)

***8.3. Computed Tomography:*** CT can show structural damage such as erosions, sclerosis, new bone formation, and ankylosis. However, it does not provide information about active inflammatory lesions.

***8.4. Ultrasonography:*** Enthesitis and peripheral arthritis can be evaluated by ultrasonography.

***8.5. Scintigraphy:*** Scintigraphy's diagnostic use for sacroiliac joint imaging is limited. In established AS and pre-radiographic AS, it has a sensitivity of around 51.8% and 53.2%, respectively. (36)

## 9. Treatment

AS is a potentially severe condition requiring a multidisciplinary treatment approach. The optimal treatment strategy combines pharmacological and non-pharmacological approaches. The primary objective of treating AS patients is to enhance their long-term health-related quality of life through the management of symptoms and inflammation, the prevention of progressive structural damage, the maintenance and normalization of functions, and the encouragement of social participation. The treatment of AS should be individualized according to the patient's current symptoms and problems (such as pain and morning stiffness), disease activity, the presence of extra-spinal and extra-articular involvement, comorbid conditions, and psychosocial factors. (37)

### *9.1. Non-Pharmacological Treatments*

***9.1.1. Patient Education:*** It is essential to educate patients on the significance of lifelong exercise, maintaining correct posture, and managing comorbidities.

***9.1.2. Cessation of Smoking:*** Cigarette smoking is linked to more active and severe disease and increases cardiovascular risk. Smoking can also impede the therapeutic response to TNF antagonists. (38, 39)

***1.1.3. Physical Therapy:*** Physical therapy interventions are an important non-pharmaceutical component of AS treatment. Regular exercise has been shown to decrease disease activity, pain, and stiffness, enhance thoracic expansion and spinal mobility, and improve cardiorespiratory capacity and depressive symptoms. (40)

### *9.2. Pharmacological Treatments*

***9.2.1. Non-Steroidal Anti-Inflammatory Drugs:*** For active AS patients with pain and morning stiffness, NSAIDs are the first-line therapy. NSAIDs are

suggested for regular use in order to reduce disease activity despite uncertainty about their disease-modifying effects, taking into consideration gastrointestinal, renal, and cardiovascular comorbidities. Before switching to a second NSAID, each NSAID should be examined for its effectiveness in reducing pain and stiffness symptoms during at least 2-4 weeks of regular treatment at the maximum anti-inflammatory dose. There is conflicting information on whether continuous NSAID treatment reduces spine radiographic progression as compared to on-demand use. Continuous NSAID therapy was found to be more effective in individuals with baseline syndesmophytes and increased CRP levels in one study. (41)

***9.2.2. Tumour Necrosis Factor Inhibitors:*** Despite the use of NSAIDs, TNF inhibitors are advised for patients with active axial AS and non-radiographic axial SpA.

Although treatment guidelines do not specify a preferable TNF inhibitor, monoclonal antibodies such as etanercept are favored in the presence of AS-related comorbidities such as uveitis and inflammatory bowel disease. (42) A decrease in radiographic progression has been shown in patients treated with TNF inhibitors, but this effect has only been observed with long-term use, typically 8-10 years. (43, 44) This effect is amplified in patients who initiate treatment early (57). A shorter duration of disease, younger age, elevated CRP levels, and high disease activity have been associated with a better response to TNF inhibitors. (45)

***9.2.3. Interleukin-17 Inhibitors:*** It is recommended to consider switching to IL-17 inhibitors in patients with active AS who have not responded to Anti-TNF therapy or when Anti-TNF therapy is contraindicated, particularly in those who are primarily non-responders (rather than switching to a second TNF inhibitor). This recommendation is also relevant in cases where TNF inhibitors are contraindicated due to congestive heart failure and demyelinating diseases. (42) However, it is not advised for patients with concurrent inflammatory bowel disease because it is ineffective and may even exacerbate colitis. (46) Its effectiveness in uveitis has also not been demonstrated. (47)

***9.2.4. Janus Kinase Inhibitors:*** Tofacitinib, a Janus kinase inhibitor, has shown beneficial results in both clinical and imaging outcomes in axial disease in a Phase II study. (48)

***9.2.5. Conventional Synthetic Disease-Modifying Antirheumatic Drugs:*** Sulfasalazine and methotrexate have not shown an effect on axial disease and are primarily recommended for use in patients with peripheral arthritis. (42)

Methotrexate may be preferred in the presence of concomitant psoriasis, while sulfasalazine may be chosen for inflammatory bowel disease. (49)

***9.2.6. Corticosteroids:*** There is insufficient evidence to demonstrate the effectiveness of systemic corticosteroids in pure axial disease. In patients with peripheral arthritis, corticosteroids can be used in both systemic and intra-articular injection forms. Patients with enthesitis may benefit from local injections. (42)

***9.2.7. Analgesics:*** Analgesics such as acetaminophen and opioids can be used in patients where other treatments have failed, are contraindicated, not tolerated, or in those with residual pain. (37)

***9.3. Surgical Treatment:*** Total hip arthroplasty is recommended for patients with advanced hip arthritis. However, elective spinal osteotomy is not recommended for patients with severe kyphosis except in selected cases. (42)

## 10. Conclusion

AS is predominantly a chronic inflammatory rheumatic disease that affects the sacroiliac joints, spine, and entheses. It is strongly associated with genetic susceptibility, specifically the HLA-B27 gene. To prevent permanent deformities and maintain spinal mobility, early diagnosis and treatment are essential. Physical therapy, nonsteroidal anti-inflammatory medications (NSAIDs), local corticosteroids, and sulfasalazine are the mainstays of treatment. In cases where no response has been achieved, treatment with anti-TNF agents and non-TNF biologics may be necessary.

**Keywords:** Ankylosing spondylitis, Arthritis, Sacroiliitis, Spondyloarthritis

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# CHAPTER IV

# UREMIC AND HEPATIC ENCEPHALOPATHY

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## 1. Uremic Encephalopathy

Uremic Encephalopathy (UE) is a cerebral dysfunction caused by accumulation of uremic toxins in acute or chronic kidney failure (CKD). (1-3) Cognitive functions generally start to deteriorate when the glomerular filtration rate (GFR) falls within the range of 40-60 mL/min, but evident UE develops when GFR drops below 15 mL/min, and unless kidney failure is treated, UE progresses. (1, 3-5)

Cognitive dysfunction is common in patients with CKD, and its pathogenesis may include vascular injury, endothelial inflammation/dysfunction, an inbalance between inhibitory and excitatory neurotransmitters, neuronal degeneration, or the direct effects of neurotoxins. (3, 4, 6, 7) The common mechanism underlying these processes is the accumulation of neurotoxins, which disrupt mitochondrial function, increase the production of free oxygen radicals, and consequently lead to endothelial dysfunction, myelin and neuronal damage. (8, 9)

The presentation of UE varies among patients depending on the rate of progression of renal failure. In the early stages of CKD, patients commonly experience weakness, cachexia, myalgia, and nausea, with a gradual and progressive decline in cognitive functions. (10) In late-stage kidney failure patients, more severe symptoms such as confusion, delirium, seizures, and coma may occur. (7, 11) In early-stage CKD patients, precipitating factors like infection, sepsis, hypotension, hypo-hyperglycemia, and electrolyte disturbances can lead to uremic encephalopathy. In hemodialysis patients, UE can develop

due to arteriovenous fistula dysfunction, dialysis non-compliance, or inadequate dialysis. (12)

UE is a clinical diagnosis, and there is no specific test for its diagnosis. In the differential diagnosis, other causes of encephalopathy, metabolic factors (sepsis, hyperosmolar coma, hypo-hyperglycemia, etc.), and toxic exposures should be considered.

In uremic patients, MRI findings can seen in three different ways:

1) Cortical involvement, which is the most common type and is part of posterior reversible encephalopathy syndrome (PRES), characterized by vasogenic edema.

2) Basal ganglion involvement, typically describing vasogenic and cytotoxic edema that develops in diabetic uremic patients (Figure 1).

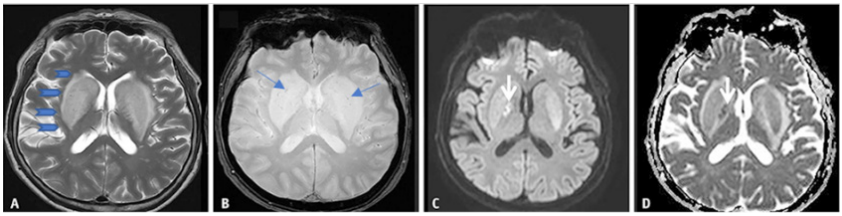


**Figure 1.** In the context of uremic encephalopathy in diabetic patients, T2-weighted images in A and B show bilateral hyperintense vasogenic edema (arrowheads) in the basal ganglia and areas of focal hemorrhage (thin arrows). In C and D, diffusion and apparent diffusion coefficient (ADC) images demonstrate areas of cytotoxic edema (arrows) in the basal ganglia associated with vasogenic edema. (13)

3) White matter involvement is the occurrence of cytotoxic edema in the white matter in non-diabetic uremic patients (Figure 2).

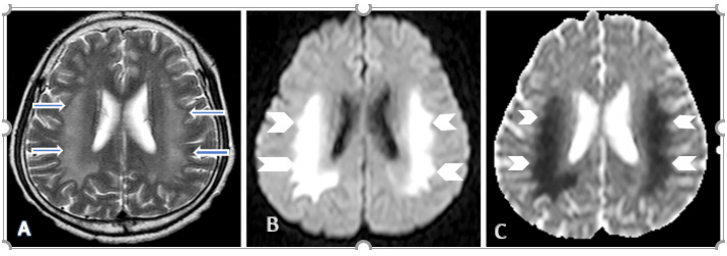


**Figure 2.** In a non-diabetic uremic patient, A) T2-weighted images demonstrate bilateral periventricular hyperintense involvement (arrows), and B) and C) show widespread diffusion restriction (arrowheads) in these areas due to cytotoxic edema. (13)

## 2. Hepatic Encephalopathy

Hepatic Encephalopathy (HE) is a neuropsychiatric syndrome characterized by cognitive and motor impairments that can occur in the course of acute or chronic liver failure (30-45% of patients with cirrhosis, 24 to 53% of patients with TIPS). (1) Early symptoms may include disturbances in sleep patterns, apathy, irritability, restlessness, and neglect of personal care. In more severe cases, symptoms such as hyperreflexia, rigidity, myoclonus, asterixis, delirium, and coma can occur. HE is considered a poor prognostic factor, with a one-year survival rate of 42% and a three-year survival rate of 23%. (15)

The pathogenesis of HE has not been fully elucidated in the research conducted so far, and it is believed to result from a combination of various factors, including disorders in ammonia metabolism. Ammonia is separated from protein by the action of the urease enzyme produced by intestinal flora, absorbed from the villi into the bloodstream. In patients with portosystemic shunting, some of the ammonia bypasses hepatocytes and goes directly into the systemic circulation, while the ammonia that reaches hepatocytes cannot be properly metabolized, resulting in elevated blood ammonia levels in these patients. The presence of high blood ammonia levels and HE in non-cirrhotic patients with spontaneously or surgically created portosystemic shunts can be explained by this mechanism.

Hyperammonemia can accumulate in the central nervous system; it accumulates in the basal ganglia and cerebellum of cirrhotic patients, which can be observed on MRI scans. It is believed that this condition contributes to motor dysfunction and an increase in extrapyramidal symptoms in these patients.

Other factors likely to play a role in the pathogenesis of HE include decreased branched-chain amino acids, reduced serotonergic neurotransmitters, and increased aromatic amino acids, gamma-aminobutyric acid (GABA), nitric oxide, and inflammatory cytokines. Thus, the pathophysiology of HE is the result of multiple factors rather than a single mechanism. (16-18)

Hepatic Encephalopathy can be classified according to the West Haven Criteria or the World Gastroenterology Organization Criteria. (19)

The diagnosis of Minimal Hepatic Encephalopathy (HE) can be confirmed through psychometric tests, while the diagnosis of severe HE is made by excluding conditions such as sepsis, stroke, hypoglycemia, which can present with similar symptoms. Typical clinical presentation and medical history are often sufficient for diagnosis. Blood ammonia levels can support the diagnosis and may correlate with the severity of the disease. In MRI scans, T1-weighted images may show hyperintensity in the bilateral globus pallidus, putamen, and

substantia nigra due to manganese accumulation. T2 and diffusion-weighted images may reveal increased intensity around the corticospinal tract (thalamus, posterior horns of the internal capsule, and periventricular white matter) along with cytotoxic edema, often involving the hemispheric white matter (Figure 3).

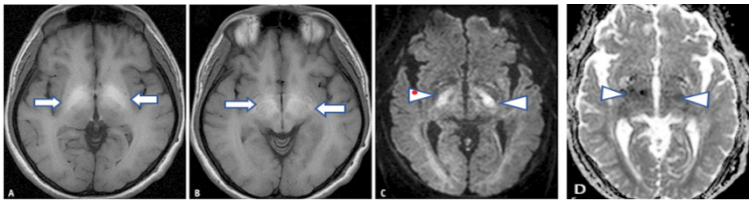


**Figure 3.** In a 44-year-old patient with hepatic encephalopathy, A) and B) show hyperintensities in the globus pallidus and cerebral peduncles on T1-weighted images due to manganese accumulation (arrowheads), while C) and D) demonstrate diffusion restriction in the thalamus (arrowheads). (13)

In treatment:

a) Correction of precipitating factors (Infection, hypovolemia, hypoglycemia)

b) Increasing intestinal acidity by administering lactulose/lactitol (This promotes the conversion of ammonia to non-absorbable ammonium)

c) Reduction of urease-producing bacteria with antibiotics (Rifaximin, neomycin, vancomycin)

d) Providing oral protein intake with high-fiber plant-based proteins (1-1.5 g/kg)

e) L-Ornithine L-Aspartate and L-ornithine phenylacetate, sodium benzoate, L-Carnitine (increasing urea and glutamine synthesis to reduce blood ammonia levels)

f) Surgical treatments: Closure of TIPS (Transjugular intrahepatic portosystemic shunt) in severe cases and liver transplantation. (20-23)

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# CHAPTER V

# SUICIDAL BEHAVIOR IN THE GERIATRIC AGE

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## 1. Introduction

Suicide is an important public health problem. Every year, just about one million people throughout the world die by suicide. (1) Despite its prevalence, suicide in the elderly receives little attention from healthcare providers. (2) The tendency to view depression and thoughts of death as an usual characteristic of the aging process may be one of the important causes of this condition. The backlog of physical diseases, disabilities, life occurrences, and losses can be recognized as a supposedly rational description for giving up on this last stage of life. (3) Health professionals working with older adults are increasingly encountering older adults who express a willingness to confront suicide in the absence of a significant mental disorders. (4) In this text; The aim of this study was to evaluate suicidal behavior in geriatric age.

## 2. Geriatric Age and Suicidal Behavior

A study investigating the prevalence of suicide among adults aged 65 and over found a 60% increase from 10.4 per 100,000 to 16.67 per 100,000 from 2009 to 2019 (5). The use of firearms is more common in suicide attempts in the elderly, and suicide tries in this age group can often be lethal in the first try because methods are fatal and there is no opportunity to save. (6) In the review of 40 studies by Conejero et al., it was determined that 45% of suicide victims visited a primary health care institution in the month before the suicide, and only 20% of them consulted a psychiatrist in the same time. (7) We can

say that training of health professionals other than mental health professionals about "suicidal behavior in the geriatric age" may contribute to reducing the prevalence of suicide.

### *2.1. Comorbid Physical Diseases*

Systemic studies show that older adults who die by suicide differ from younger suicide victims. Older suicide victims have less proof of maladaptive temperament and character traits and the main part do not fulfill the diagnostic entrance for psychiatric disorders. (8)

In a systematic review by Fassberg et al., it was shown that suicidal behavior in the geriatric age group may be associated with physical diseases such as malignant diseases, neurological disorders, pain, cancer, chronic obstructive pulmonary disease, liver disease, male genital disorders, and arthritis/arthrosis. (9) Table 1 shows the physical diseases associated with suicidal behavior in the geriatric age.

**Table 1.** The Physical Diseases Associated with Suicidal Behavior in the Geriatric Age

| |
|---|
| Malignant diseases |
| Neurological disorders |
| Pain |
| Cancer |
| Chronic obstructive pulmonary disease |
| Liver diseases |
| Male genital disorders |
| Chronic cardiac diseases |
| Chronic endocrine diseases |
| Arthritis/arthrosis |

Studies have reported that pain, cancer, and chronic diseases cause an increase in the risk of suicide in the geriatric age group, and the risk of suicide increases significantly as the number of diseases increases. (10) In the study of Choi et al., it was reported that physical health problems play a catalyst role in geriatric suicides. (10) In the study of Günak et al., it was shown that a recently diagnosed mild cognitive impairment may also be associated with the threat of progression to dementia and suicide attempt. (11)

### *2.2. Increasing Social Connectivity*

Given the large number of physical, psychological, and sociodemographic components that contribute to suicidal ideation, one component may perhaps have small worth. But, in the study of Beautrais and Fergusson, it was shown that reducing social isolation reduces the risk of suicide by 27%. (12) This study shows how important it is to provide socialization in the geriatric age group. Studies show that loneliness and social isolation increase the risk of suicide, and the quality of perceived social support is associated with health situation. (7)

In addition to poor social integration and sense of belonging, the death of close relatives is an important risk factor for suicide. Mogensen et al. reported that the highest risk of suicide occurs within 6 months after the loss of a close relative. (13) It has been reported that the highest suicide probability rates are seen in people aged 45 and over who lost their partner in the last month. (13)

### *2.3. Moving from the extended family model to the nuclear family model*

Considering our country, the sociocultural transition from extended family to nuclear family may also play a role in the increasing suicide rates in the geriatric age group in recent years. It can be said that the extended family model, which provides the elderly with the opportunity to establish more social relations, also indirectly contributes to the reduction of the risk of suicide.

### *2.4. Comorbid psychiatric diseases*

In the studies carried out, depression, anxiety disorder, bipolar disorder, alcohol and substance use disorders, schizophrenia and post-traumatic stress disorder were determined as suicide-related psychiatric diseases in the geriatric age group. (19) Table 2 shows the psychiatric diseases associated with suicidal behavior in the geriatric age.

Table 2. The Psychiatric Diseases Associated with Suicidal Behavior in the Geriatric Age

| |
|---|
| Depression |
| Anxiety disorder |
| Bipolar disorders |
| Alcohol and substance use disorders |
| Schizophrenia |
| Post-traumatic stress disorder |

In studies conducted, it was determined that there is a high prevalence of depression ranging from 10% to 46% among the geriatric population. (15) In older adults with mild to severe depressive symptoms, the diagnosis of depression may be overlooked in care settings or in the presence of comorbid medical diseases, especially cancer. (16) The impact of depressive symptoms on survival should not be underestimated. Major depressive disorder, which is a common disease in older adults with a serious relationship with suicide, can be effectively treated with antidepressants and electro-convulsive therapy. (17) It has been shown that non-drug treatments, especially psychotherapy and exercise, are effective in mild to moderate depression and in patients who cannot tolerate drug treatments. (17)

In the presence of comorbid anxiety disorder and depressive disorder, the risk of suicide also increases. (18,19) In the study of Zeppegno et al., it was reported that anxiety disorders associated with depression are associated with one out of every six elderly adult suicides. (14) Clinicians should also pay attention to the fact that depression and anxiety symptoms can manifest themselves as "somatic" complaints in the geriatric age group, and that in most patients, symptoms of neurological, cardiovascular, respiratory system, endocrinological diseases and symptoms of anxiety and depression can be found together. (18,19)

### 3. Recommendations to reduce the risk of suicide

The average human lifespan is getting longer and the number of the geriatric age group is increasing. The geriatric age group, which is currently around 9 percent in our country, is expected to be around 25 percent in 2050. (18,19) These numerical data point out how important it will be to prevent suicide in the geriatric age group. Table 3 shows the recommendations that can be applied to reduce the risk of suicide in the geriatric age.

**Table 3.** Recommendations for Reducing the Risk of Suicide in the Geriatric Age

| |
|---|
| Preventing the possession of firearms at home, restricting access to firearms |
| Effective treatment of major and minor mood disorders, especially depression |
| Treatment of specific physical diseases |
| Ensuring continuity in medications, nutrition programs, physical therapy and exercise programs |
| Providing emotional support for social disconnection and isolation |
| Strengthening social support |
| Provide internet-based services for healthcare providers when needed |

## 4. Conclusion

It is known that most of the people who died by suicide in the geriatric age group applied to primary care or emergency health services rather than a mental health specialist in the last year. It seems very important for elderly individuals that primary care and emergency service personnel receive training on "suicidal behavior in the geriatric age". Recognition and appropriate treatment of depression, especially in elderly patients, will also contribute significantly to reducing the prevalence of suicide in the geriatric age group.

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CHAPTER VI

# ATOPIC DERMATITIS IN CHILDHOOD

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## 1. Introduction:

Atopic dermatitis (AD) is a chronic, recurrent inflammatory and pruritic disease characterized by the disruption of skin barrier integrity.(1) In the 1800s, clinical descriptions of atopy encompassed symptoms like skin rash, hay fever, asthma, and gastrointestinal sensitivity. However, in 1914, Hebra emphasized that the involvement of skin folds was more frequent, with pruritus being the predominant symptom. In 1980, Hanifin and Rajka published the diagnostic criteria for AD, and in 1994, Williams et al. revised and updated these criteria.(2)

## 2. Epidemiology:

Atopic dermatitis is a common health problem. The increase in the incidence of atopic diseases cannot be explained only by genetic factors and advances in disease diagnosis. Studies examining the relationship between environmental factors and atopy have brought up the 'hygiene hypothesis'. With improving conditions, reduced exposure to microorganisms necessary for the maturation of the immune system, increased bathing frequency, and more exposure to allergens have led to an increase in atopy.(3) In industrialized countries, the changing environment and lifestyle have also contributed to a higher incidence compared to rural areas.(3) The prevalence of AD varies between 0.5% and 39%.(4) It is known to affect approximately 5–10% of children worldwide.(5) In our country, various prevalence rates have been reported in studies conducted to demonstrate the frequency of AD. In Turkey, the ISAAC study group reported a lifetime prevalence of AD in children as 17.1% and a prevalence in the last

year as 8.1%.(6) Similarly, a large-sample study conducted among children in 27 different cities using the ISAAC protocol reported the presence of AD as 20.6%.(7) Atopic dermatitis can occur in children of all age groups, but it is especially prevalent in the group under the age of 5, with an occurrence rate of 85%.(8) Approximately 25% of pediatric AD patients are thought to continue to be affected by the disease in adulthood.(9)

### 3. Factors Affecting the Development of Atopic Dermatitis:

Atopic dermatitis has a complex etiology involving genetic and environmental factors, particularly causing disruption in the skin's protective barrier and immune system dysregulation.(10) Atopic dermatitis is part of the atopic triad, known as the 'atopic march,' which can start simultaneously or sequentially and includes AD, allergic rhinoconjunctivitis, and asthma.(8) These patients have a defective barrier in the skin and mucosa of the respiratory and gastrointestinal tract, leading to symptoms.(8)

#### *3.1. Genetic Factors:*

The genetic load is important in AD development. If one of the parents is atopic, the likelihood of developing atopic symptoms in the child is greater than 50%. In cases where both parents exhibit atopic symptoms, there is an approximate 80% probability that their children will also exhibit atopic symptoms.(11) The presence of AD in multiple individuals within families has brought attention to the relationship between AD and genetic predisposition, leading to the identification of certain genes associated with the condition. These genes are involved in two mechanisms, namely structural and functional abnormalities of the skin and skin inflammation.(11) It is well known that natural moisturizing factors derived from filaggrin are crucial for maintaining epidermal hydration and low acidity, thus preserving the barrier function of the outermost stratum corneum.(12) Filaggrin plays a role in the development and differentiation of keratinocytes to maintain epidermal integrity. Recently, it has been reported that variations in an filaggrin gene contribute to the risk of AD, depending on the affected locus.(13) In individuals with these mutations, the risk of developing AD is known to increase by 3.1 to 4.7 times. It is also observed that in these patients, the clinical presentation of AD begins earlier, is more severe and persistent, and carries a higher risk of developing asthma and complications such as eczema herpeticum compared to others.(13) A decrease in skin hydration leads to an increase in skin pH, a decrease in β-glucocerebrosidase activity, and delayed

epidermal barrier recovery.(14) High pH, on the other hand, leads to a decrease in the catalytic activity of acidic sphingomyelinase.(14) The significance of these enzymes lies in their role in the synthesis of essential lipids, namely ceramides, which are effective in maintaining the epidermal barrier's integrity.(15) This, in turn, leads to itching, which exacerbates the penetration of allergens in flaking, rough, and dry skin, thus giving rise to the characteristic clinical feature of AD. While the trigger for skin inflammation remains unknown, the mechanism blamed for it is the infiltration of CD4+ cells. The immune system, both the innate and adaptive components, plays a role in the development of AD. Cellular immune dysfunction has been demonstrated in 80% of patients, with a detected maturation defect in T lymphocytes.(16,17) Antigens taken up by cells from the skin, namely Langerhans cells and dendritic cells, travel to regional lymph nodes after capture, promoting Th2 differentiation via IL-4. Keratinocytes release chemokines, complicated by potential bacterial infections. As a result, staphylococcal exotoxins stimulate Langerhans and dendritic cells to produce IL-1β and Tumor necrosis factor -α.(17,18) With the help of mediators, the expression of chemokines increases. In AD, the majority of skin-resident cells are CLA+ (cutaneous lymphocyte-associated antigen) T cells, which secrete more IL-5 and IL-13 but less IL-4.(19) IL-4 triggers IgE production. An increase in eosinophil granule proteins such as eosinophilic cationic protein, eosinophil-derived neurotoxin, and major basic protein is a common finding in AD patients and is associated with disease activity.(17,20)

### *3.2. Environmental Factors:*

A history of food allergy also plays a significant role in the development of AD.(8) Food hypersensitivity can either cause AD or exacerbate symptoms in approximately 10% to 30% of patients.(21) The majority of food-induced AD symptoms or exacerbations are associated with eggs, milk, peanuts, soy, and wheat.(22) Increased exposure to cigarette smoke and heightened environmental pollution has also been observed to elevate the prevalence of AD.(10) The factors triggering lesions are listed in Table 1.(23)

| Table 1. Triggers of Lesions in Atopic Dermatitis | |
|---|---|
| **Aeroallergens** | Mites, pollens, danders, cockroaches and molds |
| **Food allergies** | Cow's milk, egg, wheat, peanut, fish, soy |
| **Microorganisms** | Bacteria (S. aureus, Streptococcus)<br>Fungi (Malassezia furfur, Trichophyton, Candida albicans)<br>Viruses (Herpes simplex virus, Molluscum, Varicella) |
| **İrritants** | Hot water, soap, cigarette smoke, detergent, alcohol, wool, disinfectant, synthetic clothing, wool |
| **Climatic conditions** | Hot dry climate |
| **Emotional stress** | Anxiety, sorrow |

**4. Clinical Findings:**

Atopic dermatitis typically begins to manifest its symptoms in infancy. Clinical findings often include recurrent, severe itching, dryness, and eczematous plaques on the body. Lesions seen in AD can be categorized as acute (swollen, reddened wheals and plaques and/or vesicles), subacute (redness, crusting) or chronic (thick plaques with lichenification and scales). Different stages of lesions may coexist in the same patient.(1,20) The distribution of eczematous lesions in AD varies according to age group and is divided into three categories based on the age group in which they are observed: the infantile period for those under 2 years of age, childhood period for those aged 2-12 years, and adolescence for those 13 years and older. The areas affected by the disease differ depending on the age group. In infants, edematous papules and plaques with vesicles or crusts, which can involve the scalp, face, and extensor extremities, develop. AD lesions affecting the diaper area of infants are rarely observed. In children with AD, rashes are typically found on the head, neck, and flexor areas of the extremities. Adults withAD commonly exhibit chronic lichenified lesions on the hands.(20) Severe itching, which significantly affects the quality of life of children at every stage of the disease, disrupts their sleep at night, school performance, and social activities. Skin dryness is always present and becomes more pronounced during the chronic course of the disease.(24)

**5. Diagnostic Evaluation:**

AD is diagnosed based on history, specific regional distribution of skin lesions and associated symptoms. There are no specific diagnostic laboratory

findings or histopathological features specific to AD.(24) In recent times, some validated diagnostic criteria have been defined for the diagnosis of AD. Among these, the most commonly used ones is the Hanifin-Rajka criteria.(25) The Hanifin-Rajka Criteria consist of four major and twenty-three minor criteria. To diagnose AD, there should be at least three major and three minor criteria present (Table-2)(25,26).

**Table 2. Hanifin-Rajka Diagnostic Criteria**

| **Major criteria** | |
|---|---|
| **1.** Itching<br>**2.** Typical appearance and distribution of skin lesions (flexural in adolescents and adults, extensor areas and face in infants and young children)<br>**3**. Chronic, recurrent dermatitis<br>**4.** Personal or familial history of atopy | |
| **Minor criteria** | |
| 1. Ichthyosis/palmar hyperlinearity/ keratosis pilaris<br>2. Reactivity on type-1 skin tests<br>3. Increased serum IgE<br>4. Early onset<br>5. Proneness to skin infections<br>6. Tendency towards nonspecific hand and foot dermatitis<br>7. Nipple eczema<br>8. Cheilitis<br>9. Recurrent conjunctivitis<br>10. “Dennie-Morgan” infraorbital folds<br>11. Keratoconus<br>12. Xerosis | 13. Anterior subcapsular cataract<br>14. Orbital darkening<br>15. Pallor or erythema on the face<br>16. Pityriasis alba<br>17. Front folds of neck<br>18. Itching due to perspiration<br>19. Disturbance to wool and lipid solvents<br>20. Perifollicular accentuation<br>21. Food intolerance<br>22. Susceptibility to environmental and emotional factors<br>23. White dermographism |

Another commonly known diagnostic criterion is the United Kingdom Working Party Diagnostic Criteria (UK Diagnostic Criteria), which consists of one mandatory criterion and five major criteria. For a diagnosis, the mandatory criterion must be present along with three major criteria.(Table-3) (26,27)

| Table-3: The United Kingdom Working Party Criteria |
|---|
| **Must have criteria**<br>• The presence of dermatitis accompanied by itching (or in young children, such a condition reported by the parents) is required for diagnosis. |
| **Other criteria**<br>1. Involvement of the flexor faces (popliteal and antecubital region, neck, anterior part of the ankles; also cheeks in children under 10 years of age).<br>2. History of asthma or allergic rhinitis (family history of atopy in children under four years of age).<br>3. Symptoms of dry skin observed over a wide area (within the last year).<br>4. Lesions in flexural areas (extensor areas of the face and extremities in children under four years of age).<br>5. The onset of lesions before the age of two years (this criterion is ignored in children under four years of age). |

In the patient's history, the presence of dry skin, the recurrent nature of lesions, and the presence of itching must be inquired about. Dry skin and itching are the most common accompanying findings in the clinical presentation of AD. If itching is not present, the diagnosis of AD should be reconsidered. It should be noted that the clinical presentation can spontaneously go into remission or with applied treatments. Investigating triggering factors such as irritants, allergens, infections, and stress that can lead to acute exacerbations and the recurrence of clinical signs is crucial. The presence of other concurrent atopic diseases in the family and/or the patient (allergic rhinitis, asthma, food allergies) should also be determined.(24,26)

In children with early-onset, moderate to severe AD, especially when there is insufficient clinical response to appropriate treatment or when the condition frequently recurs, approximately half of them may have a concurrent food allergy. In such cases, it's important to inquire with the family if there is any suspected food trigger. The relationship between food intake and the onset of clinical symptoms in AD can vary due to the involvement of both IgE (type I - immediate) and non-IgE mediated (cellular - delayed) mechanisms in the immunopathogenesis of AD.(20,24) In cases where both immune mechanisms are involved, clinical symptoms can develop both in the early and late stages. Therefore, identifying the suspected food trigger by the family may not always be straightforward.(24) In cases of gastrointestinal system involvement such as proctocolitis, inquiries and investigations associated with food allergy

symptoms are of utmost importance in order to identify potential food allergy associations.

The extent of skin lesions is the most important parameter indicating the severity of AD clinical presentation.(24) Various scoring systems are used to assess clinical severity. Among these, the most commonly used is the "Scoring Atopic Dermatitis" (SCORAD). In this scale, the extent of skin involvement, characteristics of the lesions (erythema, edema/papulation, oozing/crusting, excoriation, lichenification, dryness), and their adverse effects on the patient (itching and sleep disturbance) are calculated within an algorithm. According to this scale, below 25 is considered mild, 25-50 is moderate, and above 50 is severe AD.(28)

Currently, there is no in-vivo or in-vitro test in use that possesses diagnostic capabilities for AD. Skin prick tests and/or serum allergen-specific IgE measurements can be conducted to investigate aeroallergen and/or food sensitivities as potential triggering factors for the disease.(22) A negative result in these tests does not rule out the diagnosis of AD and does not imply insensitivity. Additionally, the presence of atopy does not always demonstrate a clinical relationship with AD symptoms and these allergens. (24) A short-term diagnostic diet elimination can be performed to determine the relationship between the identified food sensitivity and AD. In cases where a response is observed during the diagnostic diet elimination, a food challenge test with the same food should be conducted for an adequate duration (at least 2 weeks), and the recurrence of AD symptoms should be monitored closely.(24) Due to the risk of developing acute systemic hypersensitivity reactions during food challenge testing, it is crucial that this procedure be conducted in experienced allergy clinics where all necessary interventions can be provided.(29)

**6. Differential Diagnosis:**

AD can exhibit clinical symptoms similar to many other diseases; therefore, the following conditions should be considered in the differential diagnosis. (Table-4) (26,30)

| Table-4: Differential Diagnosis of Atopic Dermatitis | |
|---|---|
| • Scabies (scabies) | • Dermatomyositis |
| • Seborrheic dermatitis | • Dermatophytosis |
| • Infections | • Hartnup syndrome |
| • Allergic-irritant contact dermatitis | • Hurler syndrome |
| • Psoriasis | • Hyperimmunoglobulin E syndrome |
| • Numular dermatitis | • Ichthyosis |
| • Keratosis pilaris | • Letterer-Siwe disease |
| • Acrodermatitis enteropathica | • Netherton syndrome |
| • Agamaglobulinemia | • Phenylketonuria |
| • Ataxia telangiectasia | • Severe combined immunodeficiency |
| • Carboxylase deficiency | • Wiskott-Aldrich syndrome |
| • Dermatitis herpetiformis | • HIV associated dermatoses |

**7. Atopic Dermatitis Treatment:**

Atopic dermatitis is a clinical condition characterized by periods of exacerbation and remission, necessitating long-term and continuous treatment with multiple components. It demands a comprehensive approach to therapy. The proper implementation of this multifaceted treatment and treatment success are highly contingent on patient and family education. Treatment should be tailored to the financial situation and educational level of the patient and family.(26)

***7.1. General Precautions:***

In AD, irritants, allergens, microbes, and stress are triggering factors for acute exacerbations (Table 1) (23) It is essential to avoid agents that irritate and dry the skin. Wool and synthetic fabrics that cling to the body and irritate the skin should be avoided. Newly purchased clothing should be washed before wearing. Perfumed fabric softeners should not be used when washing clothes, and laundry should be rinsed thoroughly with plenty of water to ensure that detergent residues do not remain on the garments. Maintaining the room temperature between 18-22°C is ideal. Exposure to allergens such as food allergens, house dust mites, pet dander, and pollen, to which the patient is sensitized, can trigger exacerbations of AD. Therefore, environmental measures should be taken to avoid exposure to the allergen in children diagnosed with AD. Maintaining room humidity at 40-50%, using non-permeable pillow, duvet, and mattress covers and vacuum cleaners for dust mites, and minimizing the presence of items in the

child's bedroom are some of the environmental measures that can be applied to combat dust mites.(23,26,31)

### *7.2. Topical Treatments:*

Can be grouped around three purposes.

#### *7.2.1. Strengthening the Barrier Function:*

In individuals with AD, the protective function of the epidermis is impaired, leading to dryness as a fundamental symptom. Regular, daily use of moisturizers helps maintain and repair the stratum corneum. Moisturizers have a place in the treatment of every patient with AD.(32) In mild forms, they can be used as a standalone treatment option. Moisturizers increase skin hydration while reducing symptoms. Ideally, they should be applied to the entire body 1-3 times a day, depending on the dryness of the skin, preferably within the first 5 minutes after a bath, after excess water has been removed with a towel. They should not be used concurrently with other topical agents and should be applied at least 1 hour apart from other treatments.(26) Consistent and appropriate treatment is crucial for individuals with atopic dermatitis to enhance disease control and manage skin symptoms.(33)

#### *7.2.2. Controlling Inflammation:*

Corticosteroids, calcinorin inhibitors and wet dressing application are effective.

Topical corticosteroids (TCS) are the first-choice option in anti-inflammatory treatment.(24) Short-term, high-potency products should be applied to areas where eczema is primarily present, with caution to avoid regions with high absorption rates, such as the eyelids, scrotum, and the hairy scalp, especially after moisturizing.(26) The strength and formulation of TCS should be selected based on the patient's age, the location of affected body areas, the characteristics of the lesions, and the site of application. According to the Niedler classification, TCS are categorized from mild (group I) to potent (group IV).(24) The use of very potent TCS (group IV) is generally not recommended in children. Mild TCS (group I) should be used, particularly for lesions on the face and eyelids.(26) In cases where symptoms persist despite regular moisturizing and protection from triggering factors, TCS can be added to the treatment plan, especially during acute exacerbations. Side effects such as skin thinning, telangiectasia, stretch marks, pigment disorders, acne-like lesions,

hypertrichosis and local infections may be observed and their frequency varies depending on the patient's age, duration of use and application site. Prolonged use of potent TCS, especially in young children, can lead to systemic side effects like suppression of the hypothalamic-pituitary axis, Cushing's syndrome, or growth retardation.(29) The treatment duration should not exceed 2-4 weeks, and daily use should not exceed twice.

Topical calcineurin inhibitors (TCIs) are another anti-inflammatory treatment option used in AD.(34) They exert their effects by inhibiting calcineurin phosphatase, thereby suppressing the synthesis of inflammatory cytokines in T cells and keratinocytes.(34) The primary purpose of these drugs in treatment is to reduce the need for corticosteroid use.(24) They are preferred in areas where the use of topical corticosteroids is avoided due to concerns about side effects. Pimecrolimus (%1) and tacrolimus (%0.03) are used in individuals aged two and above, while the %0.1 tacrolimus formulation is used in those aged 15 and above.(35) TCIs should be the preferred choice, especially in cases requiring prolonged use of topical corticosteroids, cases developing resistance to corticosteroids, or cases experiencing side effects due to corticosteroid use.(35) The most common local side effects of topical calcineurin inhibitors are usually a burning sensation, stinging, and itching of the skin, which typically occur in the early days of treatment.(36) These symptoms begin within five minutes after application, may last for about an hour, and usually subside within a few days. (36) Informing patients about these side effects is necessary to prevent them from discontinuing treatment prematurely.

Wet wrap therapy is beneficial in enhancing the effectiveness of topically applied agents in moderate to severe AD.(37) Wet wrap therapy facilitates the absorption of topical treatments through the skin, prevents water loss from the skin, and creates a physical barrier against itching. During wet wrap treatment, caution should be exercised regarding potential skin damage and secondary infections that may arise from the use of topical corticosteroids.(37) When secondary S. aureus infection is detected during exacerbations of AD or in the case of viral infections, short-term systemic antibiotics or antiviral medications should be used.(24)

### *7.3. Systemic Treatments:*

In systemic treatment, immunosuppressive or immunomodulatory (biological agents) drugs are used. Corticosteroids, cyclosporine, azathioprine, mycophenolate mofetil, methotrexate, alitretinoin, apremilast, intravenous

immunoglobulin, and interferon-γ are systemic treatment options that can be used in AD.(38) Systemic corticosteroids and cyclosporine A are the most commonly used immunosuppressive drugs in AD treatment.(24) Azathioprine, mycophenolate mofetil, methotrexate, and interferon-γ therapies are less frequently used immunosuppressive drugs.(38) Prolonged use of these drugs is limited due to variations in treatment effectiveness among patients and potential serious side effects.(26) Recently, immunomodulatory treatments under research have offered hope in the treatment of these challenging patients. Dupilumab, which received FDA approval in 2017 for the treatment of moderate to severe AD in patients aged twelve and above who are uncontrolled with topical treatments, has also been available in our country since last year.(26) Additionally, biological agents such as omalizumab, an IgE monoclonal antibody, can be used in the treatment of AD, but the study results regarding their superiority in treatment are conflicting. Evaluating study results, it has been shown that better clinical responses are achieved, especially in patients with serum total IgE levels above 700 kU/L.(39)

### *7.4. Allergen Immunotherapy:*

Allergen immunotherapy is an immunological desensitization treatment to the allergen to which the patient is clinically sensitive. In allergen immunotherapy, patients are gradually exposed to specific allergens, starting with increasing doses, and then maintenance doses are administered.(40) There are studies indicating the benefits of allergen immunotherapy, especially in AD patients who are sensitive to aeroallergens like dust mites.(41)

### *7.5. Phototherapy:*

Phototherapy can be used in children (>8 years old) and adults who are capable of standing alone in the cabin and following treatment instructions.(26) Elementary school children, adolescents, and adults with chronic AD resistant to first-line topical treatments can benefit from phototherapy.(42) Phototherapy can be used as a second-line treatment option when trigger factors are avoided, effective skin moisturization is ensured, and clinical control cannot be achieved despite topical anti-inflammatory treatments (TCS, TCI). (24)

### *7.6. Vitamin D:*

The results of clinical studies evaluating the relationship between Vitamin D and AD are conflicting. However, there are many studies that report a negative

correlation between disease severity and serum vitamin D levels.(43,44) Especially in AD patients who have a resistant course despite general preventive measures and medical treatments, there is evidence that vitamin D therapy can reduce disease severity.(44)

**8. Prognosis and Comorbidities:**

Atopic dermatitis represents the initial step in the natural progression of atopic diseases.(8) Children with AD have a three-fold higher risk of developing asthma by the age of six compared to those without AD.(45) The risk of developing allergic rhinitis also increases two to threefold, with approximately half of the cases developing AD.(46) Food sensitivity is also more common in patients with AD. The course of AD is highly variable in terms of severity, exacerbations, and persistence. Some earlier studies have shown that the clinical symptoms of AD improve with age in most patients.(26) However, recent research results indicate that in many cases that begin in childhood, symptoms persist for years.(47)

Atopic dermatitis encompasses complications both within and outside the skin, including comorbidities. Skin-related complications are the most commonly observed. Bacterial and viral skin infections are the most frequent complications in children with AD. Extra-cutaneous complications encompass not only classical atopic comorbidities such as asthma and allergic rhinitis but also non-atopic complications like ocular problems, sleep disturbances, and mental health conditions.(48) In this patient group, a decrease in quality of life, social isolation, nutritional imbalances, and a sedentary lifestyle are frequently observed. Individuals with AD may avoid daily activities and social interactions due to discomfort arising from the appearance of their skin.(49) Factors such as itching due to AD, disrupted sleep, time spent on skin care, and stress caused by skin care in pediatric patients can also contribute to a reduced quality of life. Recent studies have revealed that AD increases the risk of cardiovascular disease, obesity, and diabetes and predisposes individuals to neuropsychiatric and musculoskeletal disorders.(50)

**9. Conclusion:**

Atopic dermatitis is a common childhood condition whose prevalence has been steadily increasing in recent years. It can co-occur with other allergic diseases such as asthma and allergic rhinitis and can lead to significant comorbidities in children. Clinicians being knowledgeable about the clinical symptoms of AD, its differential diagnosis, and their ability to identify and prevent other comorbid

conditions that may accompany the disease at an early stage will have a positive impact on the treatment and management of AD.

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CHAPTER VII

# A VİEW OF DEPRESSİON FROM THE PERSPECTİVE OF THE ENTERİC PEPTİDES

**Çiğdem SEVİM**

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## 1. Introduction

Depression, a persistent and recurring mood disorder, ranks among the significant concerns for contemporary society's well-being. (1) The World Health Organization (WHO) reports that it impacts over 264 million individuals globally. Remarkably, an estimated 76–85% of those afflicted in low- to middle-income nations do not receive adequate treatment for this mental ailment. (2) Presently, the clinical efficacy of widely utilized antidepressant medications, designed to modulate brain monoaminergic systems by enhancing serotoninergic and noradrenergic neurotransmission, often falls short, with just about one-third of patients experiencing full relief from depressive symptoms post-therapy. (3) As a result, there is an ongoing quest for therapeutic alternatives that operate differently from traditional antidepressants to enhance the overall effectiveness of depression treatment. (1) Current biomedical theories regarding depression depict it as a disorder affecting neural networks, leading to alterations in extensively distributed brain regions. (4) Effective antidepressants are seen as enhancers of synaptic plasticity and regulators of monoamines like serotonin, noradrenaline, and dopamine. (5) While guidelines endorse a holistic biopsychosocial approach for depression treatment, evidence suggests that psychological interventions, social support, and physical activity play crucial roles. (6) Nevertheless, in cases of moderate or severe depression, medication

often remains a necessary component. Despite the efficacy of antidepressants, a significant portion of individuals with Major Depressive Disorder (MDD) fails to respond to multiple antidepressant trials, and many may only experience partial relief. (7) Those who do not respond to two trials of antidepressants are often classified as having treatment-resistant depression (TRD). Typically, individuals must endure at least a four-week waiting period before potential responses to current antidepressants materialize, and common side effects like sexual dysfunction, decreased libido, headaches, gastrointestinal symptoms, anxiety, and agitation frequently occur. (4)

The enteric nervous system (ENS) emerged in the course of evolution prior to and independently of the central nervous system (CNS). (8) With a neuron count ranging from 200 to 600 million in humans, the ENS boasts a neuron population equal to that of the neural tube, making it the largest component within the peripheral nervous system (PNS). (9) Functioning as a sophisticated and self-governing nervous system, the ENS orchestrates all digestive activities. It establishes links with the CNS through the sympathetic, parasympathetic, and sensory systems. Particularly noteworthy is its connection to the brain via the vagus nerve, which facilitates the transmission of information about food content and hunger. (10,11) Lately, there has been growing recognition of a two-way interaction between the gut and the brain. This intricate communication system not only plays a crucial role in maintaining gut stability but also appears to have numerous impacts on mood, drive, and higher mental functions. (12) People often become conscious of this communication when changes in gut functioning affect their perception of bodily sensations like queasiness, fullness, or discomfort. Conversely, stressful encounters can result in modifications in intestinal activities and secretions (13) These interrelations are commonly referred to as the “gut-brain axis” or the “brain-gut axis”. (14)

Although the relationship between the gut and the brain axis has gained popularity in recent years, the effects of locally produced metabolites and hormones have not been fully clarified. However, it is predicted that these factors may be effective in neurodevelopmental disorders such as depression and schizophrenia. The fact that receptors specific to peptides produced by enteroendocrine cells in the intestine are also found in different parts of the brain strengthens the connection between them. The enteroendocrine system is responsible for generating peptide hormones that play a crucial role in regulating metabolism by coordinating various aspects such as digestion, absorption, nutrient utilization, and appetite control. These gut hormones possess a diverse

array of targets, not only within the gastrointestinal tract but also beyond it. It is noteworthy that most of these hormones serve multiple physiological functions, and likewise, several hormones perform similar physiological roles. Given the considerable diversity in the types and quantities of foods we consume and the various tissues that utilize absorbed nutrients, it is understandable that the gastrointestinal system releases approximately 20 active hormones with overlapping functions and shared targets. In this section, the relationship between prominent peptide hormones produced by the enteroendocrine system and depression is examined.

## 2. Enteric peptides

### *2.1 Ghrelin*

Nutritional changes activate chemical pathways in the brain that activate many mechanisms that affect mood. Ghrelin is a peptide hormone produced primarily in the stomach. It is known for its role in stimulating the release of growth hormone (GH) and for its appetite-stimulating effects. Ghrelin levels typically increase before meals, signaling hunger and promoting food intake. Researchs have focused on understanding the neural circuits in the brain that regulate the actions of ghrelin. (15) Ghrelin plays a significant role in the hypothalamus by controlling the synthesis and secretion of various neuropeptides that influence nutrition and energy balance. (16) The effects of ghrelin generally oppose those of leptin, another hormone involved in appetite regulation, which is produced by adipose tissue and plays a role in suppressing appetite and increasing energy expenditure. The interaction between ghrelin and leptin is very important for maintaining energy balance. (17)

Ghrelin is produced both peripherally (after crossing the blood-brain barrier) and centrally (in the hypothalamus). Its role in regulating various functions of the central nervous system is pivotal. Exposure to stress can induce fluctuations in ghrelin levels, leading to substantial effects on neuro-endocrinological parameters, with potential consequences for metabolism, behavior, and mood. Ghrelin exhibits dual roles, acting as both anxiolytic (anxiety-reducing) and anxiogenic (anxiety-inducing) agent, indicating its involvement in modulating anxiety-related behaviors. The increase in ghrelin levels during stressful situations is proposed to serve as an intrinsic mechanism for coping with stress, potentially preventing excessive anxiety. Studies have associated elevated ghrelin levels during depression with antidepressant effects, suggesting its role

in mood regulation. Ghrelin's influence on stress and associated conditions is connected to changes in the hypothalamic-pituitary-adrenal (HPA) axis, which plays a vital role in the body's response to stress. Additionally, ghrelin influences the autonomic nervous system, particularly the sympathetic nervous system, and serotonergic neurotransmission. A reciprocal relationship exists between ghrelin and corticotropin-releasing hormone (CRH), which controls the release of stress-related hormones. Ghrelin facilitates the conversion of serotonin, a neurotransmitter tied to mood regulation. In turn, serotonin regulates ghrelin signaling, which can influence anxiety-related behaviors. This information underscores the intricate connection between ghrelin and the central nervous system, especially within the context of stress, anxiety, and mood regulation and it emphasizes the significance of ghrelin in comprehending physiological and behavioral reactions to stress and mood disorders. (18)

The discoveries indicate that ghrelin's involvement in controlling human dietary habits is more intricate than previously believed. Beyond merely sparking hunger, it seems that cognitive functions also come into play. Administering ghrelin intravenously from external sources is proposed to have the potential to boost appetite, independently of its immediate impact on leptin. The fatigue and bad mood observed in certain individuals following ghrelin administration highlight the broad behavioral impacts of this hormone. (19,20) The potential involvement of the ghrelin receptor as a candidate gene linked to depressive and panic disorders has come to light. Additionaly, Nakashima and colleagues delved into the relationship between the Leu72Met gene polymorphism in human ghrelin and the incidence of major depressive disorder and panic disorder. Their research suggested that while the Leu72Met polymorphism may play a role in depressive disorder, it might not have a significant impact on the development of panic disorder. (21)

Ghrelin, which is a hormone, appears to have potential effects on mood improvement, acting similarly to antidepressants and anxiety-reducing medications. These effects may be linked to the way neurons in specific brain areas, such as the ventral tegmental area and hippocampus, interact. These brain regions express a receptor known as the growth hormone secretagogue receptor (Ghsr), and they undergo changes in synapse formation when exposed to ghrelin. These alterations in synaptic connections are crucial for regulating mood. (22-24) Researchers conducted a study to explore the antidepressant properties of ghrelin. Interestingly, they discovered that the antidepressant-like impact of calorie restriction depended on the presence of orexin neurons.

Furthermore, it is believed that ghrelin's influence on mood may result from its direct or indirect activation of orexin-containing neurons situated in the lateral hypothalamic region. Supporting this notion, ghrelin has been observed to trigger c-Fos expression in orexin neurons and boost the activity of isolated orexin neurons. (25,26) A study by Lutter and colleagues revealed that when mice lacked orexin, the antidepressant-like effects of ghrelin in the forced swim test (FST) were not observed. (27)

Moreover, the recurrent yet inconsistent discovery that ghrelin enhances noradrenergic transmission within the hypothalamus serves not only as a bridge between the nervous and endocrine systems but also as a component within a circuit implicated in depression, exerting a pivotal role in regulating sleep. (28-30) This lends support to its potential as an antidepressant agent. The theory of decreased central monoaminergic function stands as a well-established hypothesis in the genesis of depression. In contrast, the inhibitory impact of ghrelin on the central release of another monoamine, specifically serotonin, may imply a potential for inducing depressive effects, akin to its stimulatory influence on the HPA axis which serves as an alternate model for the onset of depression. (29,31,32) Furthermore, the antidepressant-like outcome observed with antisense DNA targeting ghrelin in rats may suggest a somewhat depressogenic effect. This perspective gains additional support from research indicating that psychopathological improvements following electroconvulsive therapy and psychopharmacological treatment in depressed patients are correlated with reductions in ghrelin plasma levels. Reports on ghrelin plasma levels in untreated depressed individuals compared to healthy controls have yielded conflicting results, showing similarities, increases, or decreases. (33-35) Thus, despite reasons to believe that ghrelin plays a role in mood regulation, the current body of evidence does not permit us to anticipate how ghrelin might impact the overall symptomatology of depression in affected patients.

### *2.2. Vasoactive intestinal polypeptide (VIP)*

Vasoactive intestinal polypeptide (VIP) was first identified in pig intestines and is a neuropeptide hormone present in both the peripheral and central nervous systems. It serves various functions, one of which is protecting nervous tissue by inhibiting inflammatory agents. Initial research on VIP revealed its significant presence in regions associated with emotions, such as the amygdala, hippocampus, and prefrontal areas. These regions are renowned for their involvement in emotional learning processes, including anxiety, depression.

(36,37) Vasoactive intestinal peptide (VIP), a significant regulator of synaptic transmission in the hippocampus, plays a role in exploration and hippocampal-dependent learning in rodents. Two forms of synaptic plasticity known as homosynaptic long-term depression (LTD) and depotentiation are associated with the acquisition of behavioral adaptability and the detection of spatial novelty. VIP, via the activation of the VPAC1 receptor, naturally inhibits the CA1 hippocampal LTD/depotentiation process. This inhibition relies on GABAergic transmission and may also include a specific adjustment of the stratum radiatum interneurons that connect to pyramidal cell dendrites. This function plays a role in limiting hippocampal-dependent memory processes associated with behavioral adaptability and detecting discrepancies, thus promoting memory stability rather than its constant reconstruction. Therefore, targeting VPAC1 receptors could be a promising approach in treating conditions characterized by abnormal saturation of LTD. (38)

In a conducted research using fluoxetine, chronic fluoxetine treatment was found to reverse the behavioral changes observed in depressed rats. Moreover, the use of fluoxetine significantly mitigated the extent and severity of histological indications. Administering fluoxetine at a therapeutic dosage of 10 mg/kg effectively enhanced VIP expression in the duodenum of depressed rats. Some findings suggest that antidepressants could potentially modulate other brain-gut peptides or unidentified factors, thereby mitigating the harm caused by chronic stress-related gastrointestinal disorders. (39)

Several magnetic resonance imaging (MRI) investigations conducted on human subjects have established a connection between anxiety and depression and irregularities in the structure and operation of areas rich in VIP (vasoactive intestinal peptide), which are associated with the processing and regulation of emotions. (40) However, there hasn't been a direct link established between VIP itself and these conditions. To illustrate, research has shown that the volume of the amygdala is inversely related to trait anxiety in individuals without anxiety disorders. (41,42) Additionally, decreased structural integrity in the white matter pathways connecting the amygdala to prefrontal regions has been identified as a predictor of trait anxiety. Furthermore, disruptions in the resting-state functional connectivity between the amygdala and the orbitofrontal cortex (OFC) have been observed in individuals with anxiety disorders. In a therapeutic study, patients with chronic inflammatory response syndrome were administered intranasal VIP treatment, which was subsequently associated with an increase in grey matter volume within the amygdala. (43) However, there remains limited knowledge

regarding the relationship between VIP and brain volume in healthy individuals. While these findings in humans suggest a potential connection between mood disorders and VIP neuropeptides, the specific role of VIP in the central processing of emotional regions, such as the amygdala, in healthy individuals remains poorly understood. Additionally,while research on VIP has extensively explored its connections to anxiety, depression, fear conditioning, and memory in animal models, there is a scarcity of human studies on this topic. Among the limited human research available, one study stands out, which investigated the relationship between VIP and psychological aspects. A study endeavor delving into the VIP levels within the cerebrospinal fluid among individuals with non-endogenous depression revealed that the CSF-VIP levels (with an average of 16 pmol/1) were notably lower when compared to those of the control group (averaging at 32 pmol/1) and individuals suffering from endogenous depression (measuring at 36 pmol/1). (44)

### *2.3. Glucagon-like peptide (GLP-1)*

Numerous research investigations have indicated that individuals suffering from depression exhibit compromised metabolism in the gut-brain axis, disruptions in appetite regulation, and abnormalities in gut hormone levels. (45,46) Consequently, the prevailing perspective on depression, once regarded solely as a neurological condition, has evolved to encompass its characterization as a systemic ailment. This broader viewpoint recognizes that depression encompasses the dysfunction of not only the HPA axis but also immune system dysregulation and disturbances within the gut-brain axis. (47) Multiple factors and signaling pathways are interconnected with the malfunction of the gut-brain axis, theoretically contributing to the development of depression. (45) Glucagon-like peptide-1 (GLP-1) stands as a peptide hormone predominantly produced within the gastrointestinal tract. It travels through the bloodstream and holds a vital function in controlling glucose metabolism within the gut-brain connection. (45) Additionally, a select group of neurons in the hindbrain also releases GLP-1. GLP-1 receptors (GLP-1Rs) can be found in numerous body parts, such as the pancreas, lungs, stomach, intestines, kidneys, heart, as well as various regions of the brain. (45) The frequent association of depression and diabetes, along with the parallel brain alterations noted in animal models of these conditions, suggests that both diseases may involve metabolic disruptions within the central nervous system. (48,49) Several hormones that play a role in regulating glucose levels, including insulin and glucagon-like peptide-1 (GLP-

1), are recognized for their ability to promote neurotrophic processes and exhibit neurotrophic effects. Besides the neuroprotective qualities of GLP-1, ongoing research is delving into its role in stimulating the HPA axis. According to our present comprehension, it seems that this effect may stem from the stimulation of catecholamine neurons located in hindbrain areas that extend toward the hypothalamic paraventricular nucleus (PVN). It also results from the direct influence of GLP-1 on the corticotropin-releasing hormone (CRH) gene. (50) Contemporary scientific findings also suggest the potential involvement of insulin in adjusting HPA axis function. (51) Nevertheless, it remains uncertain whether this impact is achieved through insulin's direct interaction with CRH-expressing neurons. (48)

GLP-1 has been found to stimulate the production of anti-inflammatory cytokines in various bodily organs, including the adipose tissue, pancreas, and even the brain. Furthermore, under conditions of inflammation, GLP-1 has the capacity to enhance the infiltration of immune cells and the generation of pro-inflammatory cytokines. An investigation conducted showed that when human pancreatic islet cells were treated with Exendin-4, a peptide agonist of GLP-1, at a concentration of 50 nM, it resulted in a reduction in the expression of pro-inflammatory genes like NF-κB p65 and TNF receptor superfamily member 1A. (52) Additionally, administering a DPP-4 inhibitor to diabetic mice led to an increase in the levels of anti-inflammatory cytokines and heightened activation of regulatory T cells, which implies a role in the progression of diabetes. Another study demonstrated that treating STZ-induced diabetic rats with the DPP-4 inhibitor vildagliptin at a dose of 10 mg/kg effectively lowered plasma TNF-α concentrations and inhibited serum nitric oxide concentrations. (53) In the context of the brain, the application of GLP-1 exhibits a proactive impact in hindering the advancement of Alzheimer's disease-related pathology in rats. Specifically, administering Exenatide-4 at a dosage of 20 μg/kg/day as a form of GLP-1 treatment effectively reduced the TNF-α levels in a rat model of Alzheimer's disease induced through the injection of STZ. (54) Furthermore, GLP-1, when applied at a concentration of 50 nM, played a protective role in mitigating synaptic dysfunction in the rat hippocampus, which had been provoked by the injection of lipopolysaccharide (LPS). (55) GLP-1 seems to mitigate the progression of neuroinflammation while protecting both neurons and glia when faced with oxidative stress in the depressive brain. (45)

Unlike the stable neurotransmitter secretion seen in a healthy brain, the depressive brain experiences fluctuations. This fluctuation suggests that

GLP-1 could serve as a valuable therapeutic tool in managing depression. It implies that the irregular shifts in neurotransmitter levels within a depressed brain contribute to mood disturbances and cognitive deterioration. (45) The brainstem raphe nuclei receive signals from the endogenous ligands of GLP-1-producing neurons, as revealed by recent research. (56) Additionally, a separate investigation demonstrated that administering the GLP-1 agonist exendin-4 had an impact on the dopamine system, resulting in a decrease in food-related reward behavior in rats. (57) Moreover, GLP-1 has the ability to enhance dopamine turnover in the brain's amygdala through the activation of dopamine receptor 2. Furthermore, GLP-1 receptors (GLP-1Rs) have been shown to effectively promote the release of various neurotransmitters, including GABA, glutamate, serotonin, and dopamine, in the cortex and hippocampus when depolarization occurs. (58) Furthermore, GLP-1 presents itself as a promising candidate for depression treatment since impaired neurogenesis and reduced neuronal differentiation are associated with several depressive symptoms. (45) GLP-1, by addressing synaptic dysfunction in the depressive brain, subsequently fosters an improvement in cognitive function. Consequently, GLP-1 may play a pivotal role in ameliorating cognitive decline in individuals suffering from depression. (45)

### *2.4. Neuropeptide Y, peptide YY and pancreatic polypeptide*

The neuropeptide Y (NPY) family comprises biologically active peptides, namely NPY, peptide YY (PYY), and pancreatic polypeptide (PP). (59) These peptides are produced by various cell systems along the gut-brain axis, each exhibiting differential expression levels. PYY and PP are primarily confined to the digestive system, whereas NPY is distributed throughout the gut-brain and brain-gut axis. PP, as its name suggests, is secreted postprandially from the pancreas, where it originates from endocrine F cells within the pancreatic islets. (59) Furthermore, PP is detected in a limited number of endocrine cells within the small and large intestines, distinct from PYY-positive cells. Both the release of PP and its effects on digestion and appetite, primarily mediated by Y4 receptors, depend on signaling through the parasympathetic vagus nerve. (60) Although Y4 receptors are also present in the brain, the absence of Y4 receptors is associated with decreased anxiety- and depression-related behaviors. (59,61)

The primary supplier of PYY within the gastrointestinal system is the endocrine L cell, which is most abundant in the lower part of the digestive tract. (62) Additionally, these PYY-positive L cells also contain glicentin, a peptide

derived from proglucagon, as well as glucagon-like peptide-1 and glucagon-like peptide-2. (62,63) These L cells, which also express gustducin, a G protein related to taste, along with bitter and sweet taste receptors, are considered essential chemosensors in the intestine. There are also smaller contributors of PYY in the digestive system, including the enteric neurons found in the stomach and the pancreatic endocrine cells.

In contrast to PP and PYY, NPY is found throughout the gut-brain and brain-gut communication pathways, with enteric neurons, primary afferent neurons, various neural circuits in the brain, and sympathetic neurons being the major systems expressing this peptide. In the gastrointestinal tract, enteric neurons serve as the primary source of NPY. NPY is present in the two main enteric nerve plexuses and has been identified in specific interneurons, as well as descending inhibitory motoneurons within the myenteric plexus, and noncholinergic secretomotor neurons within the submucosal plexus. It's worth noting that in inhibitory motor neurons, NPY is often found together with vasoactive intestinal polypeptide and nitric oxide synthase. (63)

There is a growing body of evidence indicating that NPY, by acting through Y1 and Y2 receptors, plays a significant role in the regulation of anxiety and depression-like behaviors in rodents. Nevertheless, the involvement of other Y-receptors, such as Y4 receptors, in this process remains poorly comprehended. Tasan and colleagues conducted experiments with male mice that were either single knockout for Y2 or Y4 receptors, or double knockout for both Y2 and Y4 receptors, within behavioral paradigms aimed at assessing changes in motor activity as well as anxiety and depression-related behaviors. (61) Their findings revealed an increase in locomotion induced by novelty and a decrease in depressive behaviors specifically in male mice lacking Y4 receptors. (61) The combined impact of deleting both Y4 and Y2 receptors on emotional behaviors appears to be cumulative, in line with the observed phenotype in Y2/Y4 double knockout mice. (61) Notably, the abundance of Y4 receptors in certain brain regions of mice, such as the nucleus of solitary tract or the area postrema, suggests that Y4 receptors may be implicated in the regulation of emotionally driven autonomic responses, which are likely to influence the ultimate expression of emotional responses. (61)

Inflammatory processes within the gastrointestinal tract have been identified as a factor that can heighten feelings of anxiety. In a study conducted by Painsipp and colleagues, they set out to investigate whether inducing experimental colitis, in combination with the genetic removal (knockout) of

PYY and NPY, could lead to modifications in emotional and affective behavior. (64) Their findings revealed that, much like the absence of the neuropeptide NPY, the absence of the gut hormone PYY amplifies behaviors associated with depression. (64) Conversely, anxiety-related behaviors are intensified with the deletion of NPY but not PYY. It was emphasized in their study that NPY and PYY seem to function as opposing forces, with their effects being mediated by distinct receptors situated at different cellular locations. (64) Additionally, the researchers noted that within the brain, postsynaptic Y1 and presynaptic Y2 receptors play crucial roles in mediating the contrasting outcomes brought about by Y1 and Y2 receptor agonists. For example, they influence anxiolytic and antidepressant responses resulting from Y1 receptor stimulation, while producing opposite effects when presynaptic autoinhibitory Y2 receptors are stimulated. (64)

## 3. Conclusion

Intestinal enteroendocrine cells (EECs) are specialized sensory cells found within the lining of the digestive tract. Their primary role is to act as vital detectors, monitoring changes within the gastrointestinal (GI) tract. EECs are responsible for not only facilitating communication with microorganisms in the GI tract through microbial byproducts but also playing a role in connecting with various systems within the human body through neuroendocrine hormones.

A growing body of research suggests a unique involvement or potential pathogenic influence of the gut-brain axis and gut microbiota in neurological and psychiatric conditions, in which EECs may play a role. Current treatment approaches largely revolve around administering external substances that either mimic (e.g., using GLP1 for conditions like schizophrenia, visceral pain hypersensitivity, and depression) or block (e.g., serotonin for visceral pain) the effects of these molecules. Alternatively, exploring methods to enhance the natural production of these neuroendocrine substances could be considered as a novel therapeutic strategy.

There is a mounting body of evidence linking the brain-gut-microbiota axis to the development and regulation of neurological and psychiatric disorders. Future research efforts should prioritize understanding the characteristics of healthy EECs and how to restore EECs' equilibrium in disease states. The quantity and composition of EECs are influenced by both internal factors like intestinal epithelial stem cells and external factors such as the microbial environment in the gut.

Hence, a promising approach may involve focusing on differentiating and maintaining EECs' balance within the intestinal lining. Additionally, optimizing EECs' functionality could be achieved by regulating the gut microbiota and dietary intake, particularly through the use of probiotics and prebiotics. However, it is important to acknowledge that the precise mechanisms underlying these processes remain unclear due to current limitations in available techniques and evidence.

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