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Aile Hekimliği Alanında Akademik Araştırmalar

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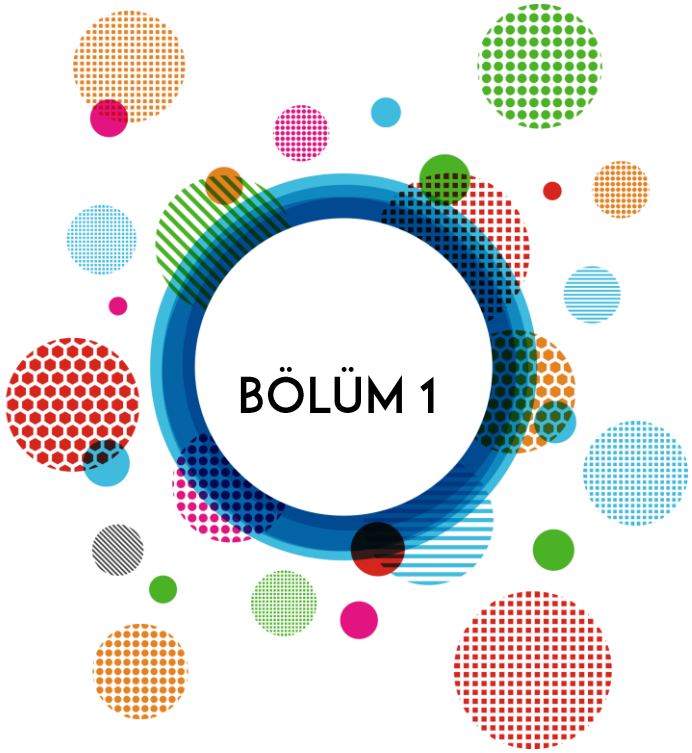

Aile Hekimliğinde Anemili Hastaya Yaklaşım

Harun Köseoğlu[1]

[1] Uzm. Dr., Kızılcahamam İlçe Sağlık Müdürlüğü ORCID: 0009-0002-8649-8008

1. Giriş

Anemi, vücuttaki oksijen taşıma kapasitesinin azalmasına neden olan, hemoglobin düzeylerinin yaş ve cinsiyete göre normalin altına düşmesiyle tanımlanan bir durumdur (WHO, 2011). Anemi tek başına bir hastalık olmayıp altta yatan bir nedenin sonucu olarak ortaya çıkan bir sendromdur. Etiyolojisi oldukça geniş olan anemi; yetersiz eritropoez, artmış eritrosit yıkımı (hemoliz) veya kan kaybına bağlı olarak gelişebilir (Camaschella, 2015). Bu sebep ile aneminin değerlendirilmesi her zaman sistematik ve çok boyutlu bir yaklaşım gerektirir.

Dünya genelinde özellikle kadınlar, çocuklar, adolesanlar, yaşlı bireyler ve gebeler arasında yüksek prevalansa sahip olan anemi, toplum sağlığı üzerinde ciddi etkiler yaratmaktadır. Dünya Sağlık Örgütü'ne göre dünya nüfusunun yaklaşık %25'inde anemi bulunmaktadır ve bu bireylerin çoğu düşük-orta gelirli ülkelerde yaşamaktadır (WHO, 2021). Türkiye gibi gelişmekte olan ülkelerde de anemi, özellikle demir eksikliği nedeniyle sık görülmekte; kadın sağlığı, çocuk gelişimi ve yaşlı sağlığı gibi temel halk sağlığı alanlarını doğrudan etkilemektedir (TNSA, 2018).

Anemi, yalnızca fizyolojik fonksiyonları değil; aynı zamanda bireyin yaşam kalitesini, iş gücünü ve bilişsel kapasitesini de olumsuz yönde etkileyebilir. Anemi özellikle ileri yaştaki bireylerde kardiyovasküler hastalık riskini artırarak ölüm oranlarını yükseltebilmektedir (Gaskell et al., 2008). Ayrıca, çocukluk çağındaki demir eksikliğine bağlı aneminin; öğrenme güçlükleri, gelişimsel gerilik ve davranış bozuklukları ile ilişkili olduğu gösterilmiştir (McLean et al., 2009).

Birinci basamak sağlık hizmetlerinde aneminin tanı, tedavi ve izleminde ilk temas noktasıdır. Aile hekimliği disiplini, bireyi yalnızca biyomedikal parametrelerle değil, aynı zamanda sosyal, çevresel ve psikolojik yönleriyle de değerlendirerek kapsamlı bir yaklaşım sunar. Bu bağlamda, anemiye yaklaşımda anamnez, fizik muayene, temel laboratuvar testleri ve uygun yönlendirme stratejileri aile hekiminin klinik pratiğinde önemli yer tutar (Clark, 2008).

Aile hekimleri, aneminin temel nedenlerini ve bu nedenlere bağlı gelişen patofizyolojik süreçleri anlamak ve uygun tanı basamaklarını uygulamakla sorumludur. Bu kapsamda etyopatogenez ve tanı süreci, etkili hasta yönetiminin temelini oluşturur (Camaschella, 2015).

2. Anemi Epidemiyolojisi

DSÖ'nün 2019 verilerine göre dünya genelinde yaklaşık 1.6 milyar kişi anemiktir. Bu durum, dünya nüfusunun yaklaşık %22'sine tekabül eder. En yüksek prevalans, 6–59 aylık çocuklar (%42,6), gebe kadınlar (%40,1) ve üreme çağındaki kadınlar (%29,9) arasında görülmektedir. Erkeklerde anemi prevalansı ise daha düşüktür (%12,7) (WHO, 2021).

Anemi, sıklıkla yetersiz beslenme, enfeksiyon hastalıkları, kronik hastalıklar ve genetik hemoglobinopatilerle ilişkilidir. Gelişmekte olan ülkelerde demir eksikliği en sık neden olurken, gelişmiş ülkelerde kronik hastalıklara bağlı anemi daha yaygındır (Kassebaum et al., 2014). Türkiye'de anemi sıklığı, yaş grubu ve cinsiyete göre değişkenlik göstermektedir. Türkiye Nüfus ve Sağlık Araştırması (TNSA) 2018 verilerine göre, 6–59 aylık çocuklarda anemi prevalansı %21,7, gebe kadınlarda ise %27,8 olarak saptanmıştır (TNSA, 2018). Ülkemizde özellikle düşük sosyoekonomik düzeye sahip bölgelerde demir eksikliği anemisi önemli bir halk sağlığı sorunu olmaya devam etmektedir. Ayrıca, ileri yaş grubunda da anemi yaygındır ve çoğunlukla kronik hastalıklar, malabsorpsiyon sendromları veya B12/folat eksiklikleri ile ilişkilidir. Türkiye'de yaşlı bireylerde anemi sıklığı %20–25 arasında değişmektedir (Öztürk & Turgay, 2019). Aneminin yüksek prevalansı ve çok çeşitli nedenleri, birinci basamak sağlık hizmetlerinde çalışan aile hekimlerinin bu durumu önleme, erken tanı koyma ve izleme yükümlülüklerini artırmaktadır. Özellikle risk gruplarının tanımlanması ve periyodik taramalar yoluyla aneminin erken dönemde saptanması, komplikasyonların önlenmesi açısından kritik önemdedir (Clark, 2008).

Aile hekimlerinin toplum tabanlı veri kaynaklarını kullanarak aneminin yerel düzeydeki yaygınlığını ve nedenlerini belirlemesi, koruyucu sağlık hizmetlerinin planlanmasında önemli bir adımdır. Ayrıca kadın ve çocuk sağlığı hizmetleri kapsamında verilen demir desteği programları da anemi yükünün azaltılmasında etkilidir.

3. Etyopatagonez ve Tanı

Dünya Sağlık Örgütünün anemi tanımına göre; hemoglobinin erkeklerde 13 g/dL‟nin, gebe olmayan kadınlarda 12 g/dL‟nin ve gebelerde 11 g/dL‟nin altında olmasıdır.

Anemi, genellikle üç ana mekanizmadan biri veya birkaçı sonucunda gelişirmektedir.

-Yetersiz Eritropoez: Kemik iliğinin yeterince eritrosit üretmemesi. En sık nedenleri arasında demir, B12 veya folat eksiklikleri; kemik iliği yetmezlikleri ve kronik hastalıklar yer alır (Means, 2016).

- Artmış Eritrosit Yıkımı (Hemoliz): Eritrositlerin yaşam süresi tamamlanmadan yıkılması. Otoimmün hemolitik anemi, kalıtsal hemoglobinopatiler gibi nedenlerle gelişebilir (Hoffbrand & Moss, 2016).

- Kan Kaybı: Akut veya kronik kan kaybı nedeniyle anemi gelişebilir. En yaygın nedenler arasında gastrointestinal sistem kaynaklı kanamalar yer alır (DeLoughery, 2017).

Tanı süreci, dikkatli bir öykü alma ve fizik muayene ile başlar. Ardından laboratuvar testleri ile desteklenir.Tam kan sayımında hemoglobin, hematokrit, MCV, RDW gibi temel parametreler değerlendirilmelidir. Periferik yayma hücre morfolojisinin değerlendirilmesini olanak sağlar. Kanda serum demiri, ferritin, TDBK ve transferrin satürasyonu ölçülerek demir eksikliği değerlendirilebilir (Cappellini et al., 2020). Vitamin B12 ve Folat Düzeyleri makrositik anemilerin tanısında önemlidir (O'Leary & Samman, 2010). Retikülosit sayısı kemik iliği yanıtını değerlendirmek için kritik öneme sahiptir. Gerekli durumlarda Coombs testi, hemoglobin elektroforezi, kemik iliği aspirasyonu gibi ileri testler yapılır (Clark, 2008).

4. Anemi Sınıflaması

Anemi, çeşitli nedenlere bağlı olarak ortaya çıkan, hemoglobin düzeyinde azalma ile karakterize bir durumdur. Aile hekimleri için doğru tanı ve uygun tedavi planlaması açısından aneminin sınıflandırılması büyük önem taşır. Bu sınıflandırmalar, hem laboratuvar parametrelerine hem de klinik özelliklere dayanarak yapılır (Camaschella, 2015).

1. Eritrosit MCV Değerine Göre Sınıflandırma

Anemi, eritrositlerin ortalama hacmi (MCV) esas alınarak üç ana gruba ayrılır:

- Mikrositik Anemi (MCV < 80 fL): Demir eksikliği, talasemi, kurşun zehirlenmesi (Cappellini et al., 2020).

- Normositik Anemi (MCV 80–100 fL): Kronik hastalık anemisi, akut kan kaybı, hemolitik anemiler (Means, 2016).

- Makrositik Anemi (MCV > 100 fL): Vitamin B12 veya folat eksikliği, alkolizm, hipotiroidizm (O'Leary & Samman, 2010).

2. Etiyolojik Nedenlere Göre Sınıflandırma

Anemiler etiyolojilerine göre aşağıdaki şekilde sınıflandırılır:

- Kan kaybına bağlı anemiler: Travma, gastrointestinal kanama gibi akut ya da kronik kan kayıpları (DeLoughery, 2017).

- Azalmış eritropoeze bağlı anemiler: Demir, B12, folat eksiklikleri; kemik iliği yetmezliği (Camaschella, 2015).

- Artmış eritrosit yıkımı (hemolitik anemiler): Kalıtsal sferositoz, orak hücre anemisi, otoimmün hemolitik anemi (Hoffbrand & Moss, 2016).

3. Klinik Seyrine Göre Sınıflandırma

Aneminin başlangıç süresi ve kliniği, sınıflamada önemli yer tutar:

- Akut Anemi: Ani kan kayıplarında ortaya çıkar; hipovolemi bulguları eşlik eder.

- Kronik Anemi: Yavaş gelişir; genellikle kompansatuar mekanizmalarla tolere edilir (WHO, 2011).

Aneminin doğru bir şekilde sınıflandırılması, altta yatan nedenin belirlenmesini ve uygun tedavi yaklaşımının seçilmesini sağlar. Aile hekimleri bu sınıflandırmaları kullanarak daha etkili bir hasta yönetimi sağlayabilir ve gerekli durumlarda ileri tetkik veya sevk kararlarını zamanında alabilir (Clark, 2008).

5. Demir Eksikliği Anemisi

Demir eksikliği anemisi (DEA), tüm dünyada en sık görülen anemi türüdür ve özellikle kadınlar, çocuklar ve yaşlılar arasında yaygındır (WHO, 2011). Birinci basamak sağlık hizmetlerinde sık karşılaşılan bu durum, çoğunlukla yetersiz beslenme, artmış gereksinim, emilim bozukluğu ya da kronik kan kaybı gibi nedenlere bağlı gelişir (Camaschella, 2015). Aile hekimleri, DEA'nın tanı, tedavi ve takibini üstlenerek hastalığın komplikasyonlarının önlenmesinde kritik bir rol oynar. En sık neden yetersiz demir alımı ya da kan kaybıdır (Cappellini et al., 2020). Risk grupları arasında regl gören kadınlar, gebeler, süt çocukları, ergenler, ve gastrointestinal sistem hastalığı olan bireyler yer alır.

1. Klinik Bulgular

DEA, başlangıçta asemptomatik olabilir. Klinik bulgular hemoglobin düşüklüğü düzeyiyle ilişkilidir ve şunları içerebilir:

- Halsizlik, yorgunluk, baş dönmesi

- Solukluk

- Çarpıntı

- Buz yeme (pagofaji), dilde yanma, saç dökülmesi gibi spesifik bulgular (Clark, 2008)

2. Tanı

Tanıda ilk adım hemogram incelemesidir. DEA tipik olarak mikrositik, hipokrom anemi şeklinde seyreder. Tanıyı destekleyen laboratuvar bulguları:

- Düşük hemoglobin ve hematokrit

- Düşük MCV ve MCH

- Düşük serum ferritin (en duyarlı parametre)

- Artmış TDBK, düşük serum demiri, düşük transferrin satürasyonu (DeLoughery, 2017)

3. Ayırıcı Tanı

DEA, özellikle talasemi taşıyıcılığı, kronik hastalık anemisi ve sideroblastik anemilerle karışabilir. Ayırıcı tanıda periferik yayma, demir paneli ve gerekirse hemoglobin elektroforezi yapılabilir (Means, 2016).

4. Tedavi

Tedavide temel hedef demir depolarının yeniden doldurulmasıdır:

- Oral demir preparatları (ferro sülfat, glukonat vs.) ilk basamak tedavidir.

- C vitamini emilimi artırır; süt ve kalsiyum içeren ürünlerle birlikte alınmamalıdır.

- Tedaviye yanıt 2-4 hafta içinde retikülosit artışıyla izlenir.

- Parenteral demir tedavisi; intolerans, malabsorpsiyon veya ciddi anemilerde düşünülmelidir (Camaschella, 2015).

6. Megaloblastik Anemi

Megaloblastik anemi, DNA sentezindeki bozukluk sonucu gelişen, eritropoezde olgunlaşma gecikmesiyle karakterize bir makrositik anemi türüdür (Hoffbrand & Moss, 2016). Genellikle vitamin B12 veya folat eksikliğine bağlı olarak gelişir. Aile hekimleri, bu anemi türünü tanımak, nedenlerini belirlemek ve uygun şekilde yönlendirmekle yükümlüdür (Akbulut, 2020).

Megaloblastik anemi, birinci basamakta dikkatle ele alınması gereken, tanısı ve tedavisi çoğu zaman mümkün olan bir durumdur. Aile hekimlerinin beslenme öyküsünü ayrıntılı alması, risk gruplarını tanıması ve zamanında yönlendirme yapması, komplikasyonların önlenmesinde kritik rol oynamaktadır.

Megaloblastik anemi genellikle aşağıdaki nedenlere bağlı gelişmektedir:

- Vitamin B12 eksikliği: Vegan beslenme, pernisiyöz anemi, gastrektomi, Crohn hastalığı

- Folat eksikliği: Gebelik, alkolizm, yetersiz alım, metotreksat gibi ilaç kullanımı

- Kombine eksiklikler: Özellikle yaşlılarda ve yetersiz beslenen bireylerde (Camaschella, 2015; Çelik et al., 2019)

1. Klinik Bulgular

Genel anemi semptomlarına ek olarak megaloblastik anemide:

- Glossit (dil iltihabı), ishal, iştahsızlık

- Nörolojik belirtiler (B12 eksikliğinde): parestezi, denge bozukluğu, hafıza sorunları

- Psikiyatrik belirtiler: depresyon, irritabilite (O'Leary & Samman, 2010; Taşkıran et al., 2022)

2. Tanı

Tanı aşağıdaki yöntemlerle konulur:

- Tam kan sayımı: Makrositik anemi (MCV > 100 fL), nötrofil hipersegmentasyonu

- Serum B12 ve folat düzeyleri

- Homosistein ve metilmalonik asit düzeyleri (özellikle subklinik B12 eksikliklerinde)

- Periferik yayma: Oval makrositler, hipersegmentasyon (Devalia et al., 2014)

3. Ayırıcı Tanı

Alkol kullanımı karaciğer hastalıkları, hipotiroidi ve ilaçlar (örn. hidroksiüre)gibi etkenler makrositik anemiye neden olabilecekleri için ayırıvı tanıya girmektedir (Means, 2016; Demirkan, 2018).

4. Tedavi

Tedavi eksik olan vitaminin yerine konmasına dayanır. Vitamin B12 eksikliği intramüsküler enjeksiyon veya yüksek doz oral B12 verilerek tedavi edilebilir. İntramüsküler yapılacaksa haftada bir olark 1000 mcg verilebilir. Oral tedavi önerilen hastalarda günlük 1000-2000 mcg kobalamin verilebilir. Folik asitte ise günlük oral olarak 1-5 mg verilmelidir (O'Leary & Samman, 2010; Akbulut, 2020).

6. Anemi Ne Zaman Sevk Edilmeli

Anemi, birinci basamakta sık karşılaşılan bir sağlık problemidir. Aile hekimi, anemiyi tanıma, değerlendirme, tedavi etme ve gerekirse ileri basamaklara yönlendirme sorumluluğunu taşır. Sevk kararı; hastanın kliniği, laboratuvar bulguları, tedaviye yanıtı ve aneminin etiyolojisine göre belirlenir (DeLoughery, 2017).

Tedaviye başlandıktan 2–4 hafta sonra hemoglobin düzeyinde beklenen artışın gözlenmemesi (≥1 g/dL), tedaviye yanıtsızlık olarak kabul edilir. Bu durumda malabsorpsiyon, tanı hatası veya altta yatan ciddi bir hastalık olasılığı açısından ileri değerlendirme önemlidir (Johnson-Wimbley & Graham, 2011).

Demir eksikliği, vitamin B12 ve folat eksiklikleri gibi sık nedenler dışlanmış ve halen aneminin nedeni belirlenememişse, daha ileri hematolojik, gastroenterolojik veya sistemik araştırmalar için hasta sevk edilmelidir (Camaschella, 2015). Hemoglobin düzeyinin kritik sınırların (<7–8 g/dL) altına düştüğü veya hastanın belirgin kardiyopulmoner semptomlarının olduğu durumlarda hastaneye yatırılarak tedavi ve izlem önemlidir (NICE, 2021). Tam kan sayımında lökoeritroblastik bulgular, anizositoz, trombositopeni ya da periferik yaymada blast görülmesi gibi bulgular hematolojik malignite şüphesi oluşturur. Bu tür durumlarda hastanın ivedilikle hematoloji uzmanına yönlendirilmesi gerekir (Cappellini, Musallam, & Taher, 2020).

Özel grup olan gebelerde hemoglobin düzeyinin 9 g/dL'nin altına düşmesi, fetal gelişim ve maternal sağlık açısından risklidir. Bu durumda anne adayı, obstetrik uzmanlığı olan merkezlere yönlendirilmelidir (WHO, 2011). Bir başka özel grup olan anemili çocuklarda ise özellikle büyüme geriliği, gelişimsel gecikme veya bilişsel bozulma gibi klinik belirtileri varlığı ileri tetkik gerektirebilir (McLean et al., 2009).

Aile hekimi, aneminin tanı ve tedavisinde olduğu kadar, uygun zamanda ve uygun gerekçeyle sevk yapılmasında da kritik rol üstlenir. Sevk, yalnızca bir yönlendirme değil, multidisipliner hasta yönetiminin önemli bir bileşenidir. Erken, doğru ve gerekçeli sevkler; tanının netleşmesini, tedavinin hızlanmasını ve komplikasyonların önlenmesini sağlar.

8. Sonuç

Aneminin etyopatogenezi ve tanı süreci, aile hekimliği pratiğinde etkili ve sistematik bir yaklaşım gerektirir. Anemiye neden olan mekanizmaların doğru anlaşılması ve uygun tanı testlerinin seçilmesi, tedavi başarısını doğrudan etkiler. Bu nedenle aile hekimlerinin anemiye yönelik klinik farkındalığı ve tanısal becerileri yüksek olmalıdır.

Anemi, birey sağlığı üzerinde kısa ve uzun vadeli etkileri olan, halk sağlığı açısından önemli bir klinik sendromdur. Gelişmekte olan ülkelerde hâlâ yüksek prevalansa sahip olan anemi hem morbidite hem de mortalite açısından dikkate alınması gereken bir durumdur (McLean et al., 2009). Birinci basamak sağlık hizmetlerinde çalışan aile hekimleri, anemiyi yalnızca bir laboratuvar bulgusu olarak değil; bireyin beslenme durumu, yaşam biçimi, kronik hastalıkları ve sosyoekonomik koşulları düşünerek birlikte değerlendirmelidir.

Aile hekimliği pratiğinde anemiye yaklaşımda en önemli unsurlardan biri erken tanıdır. Özellikle demir eksikliği, B12 veya folat eksikliği gibi kolay tedavi edilebilir nedenler, zamanında müdahale edilmediğinde geri dönüşsüz komplikasyonlara neden olabilir. Gebelerde düşük doğum ağırlığı ve prematürite için risk oluştururken, çocuklarda bilişsel ve fiziksel gelişim geriliği, yaşlılarda ise düşme, kırık ve bilişsel bozulma riskinde artış gibi sonuçlara yol açabilmektedir (Gaskell et al., 2008; WHO, 2011).

Tanı sürecinde sistematik yaklaşım, yani kapsamlı anamnez, fizik muayene ve hedefe yönelik laboratuvar testleri aile hekimi için yol göstericidir. Özellikle mikrositik, normositik ve makrositik anemilerin birbirinden ayrılması, uygun tedavi stratejisinin belirlenmesi açısından kritik öneme sahiptir (Means, 2016). Bu bağlamda, anemi sınıflamaları, aile hekimi tarafından hem klinik karar desteği hem de sağlık sistemindeki gereksiz tetkik ve sevklerin önlenmesi açısından aktif kullanılmalıdır.

Tedavi sürecinde, yalnızca farmakolojik ajanlar değil; hasta eğitimi, beslenme danışmanlığı, yaşam tarzı değişiklikleri ve riskli grupların izlenmesi de bütüncül bir yaklaşımın parçasıdır. Özellikle tekrarlayan anemi vakalarında altta yatan nedenlerin irdelenmesi ve gerekirse ikinci/üçüncü basamak sağlık hizmetlerine zamanında sevk edilmesi kritik öneme sahiptir (DeLoughery, 2017).

Sonuç olarak, aneminin tanı ve tedavisi birinci basamakta etkili şekilde yapılabilir. Ancak bu etkinlik, aile hekimlerinin güncel bilgiye erişimi, rehberlere hakimiyeti ve hastaya bütüncül yaklaşımı ile doğrudan ilişkilidir. Bu nedenle, birinci basamak düzeyinde çalışan sağlık profesyonellerinin anemi konusunda eğitimi hem bireysel hem toplumsal düzeyde sağlık çıktılarının iyileştirilmesine büyük katkı sağlar.

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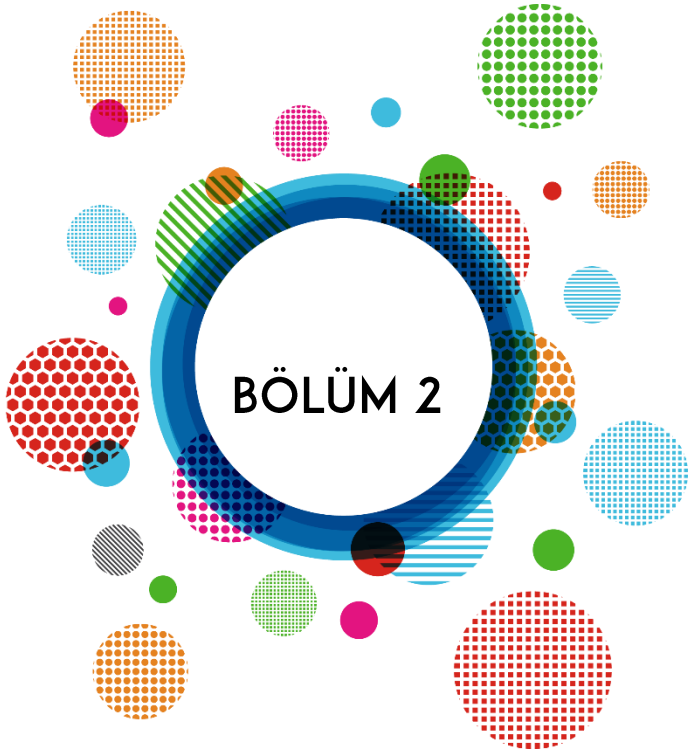

Mikrobiyotanın Hayatımızdaki Rolü ve Hastalıklarla İlişkisi

Aslı Türközen Erdoğan[1]

[1] Uzm. Dr., Isparta Gönen Toplum Sağlığı Merkezi, ORCID: 0000 0002 5516 7153

Giriş

Vücudumuzda yaşayan bakteriler, virüsler, mantarlar ve diğer mikroorganizmaların tümü insan mikrobiyotasını oluşturur. Bu mikroorganizmalardan insan vücuduna hem faydalı hem de zararlı diyebileceğimiz türler bulunmaktadır. Faydalı /zararlı oranının azalması ile fizyolojik durum bozulur ve sağlıklı olmayan flora anlamına gelen 'mikrobiyal disbiyozis' deyimi gelişir. Mikrobiyota, sindirim ve bağışıklık sisteminde, metabolizmada ve hatta beyin fonksiyonlarında rol alarak hastalıklardan korunma aşamasında önemli roller üstlenmektedir(Çakmak & İnkaya, 2021).

İnsan bedenindeki mikroorganizma sayısının, vücuttaki toplam hücre sayısının on katı olduğu bilinmektedir(Çelebi & Uygun, 2013). Bu mikroorganizmalar içerisinde en fazla bulunanı bakterilerdir. Bakteriler arasından da *Bacteroidetes* (*Bacteroides ve Prevotella* cinsleri) ve Firmicutes (*Clostridium, Ruminococcus, Enterococcus, Lactobacillus* cinsleri) anaerob bakterileri yoğun olarak tanımlanmıştır. Bunların dışında *Actinobacteria* (*Bifidobacterium, Proteobacteria* (*Helicobacter ve Escherichia*); *Fusobacteria, Spirochaetae ve Verrucomicrobia* türleri de yoğun miktarda bulunmaktadır(Yetkin, Yetiş, & Kayahan Satış, 2018).

İntestinal, oral, vajinal, deri ve akciğer mukozalarının kendine özgü mikrobiyal yapıları mevcuttur. Gastrointestinal sistem hem geniş yüzey alanına ve hem de besin öğeleri açısından zengin içeriğe sahip olması sebebiyle mikroorganizmalara kolonizasyon için uygun ortam yaratmaktadır. Bu yüzden intestinal sistem tek başına insan bedenindeki mikroorganizmaların %70' den fazlasını barındırmaktadır (Çelebi & Uygun, 2013; Yıldıran vd., 2019). Probiyotikler, mikrobiyotanın bir parçasıdır. Ancak tüm mikroorganizmalar probiyotik değildir. Probiyotik kullanımının bağırsak florasının dengelenmesinde olumlu etkileri olduğu bilinmektedir Kadakal & Unal, 2023;Taşdemir,2017). Probiyotikler, "yeterli miktarlarda alındığında konakçıya fayda sağlayan canlı mikroorganizmalar" olarak tanımlanır. Probiyotikler genellikle fermente gıdalarda (yoğurt, kefir, turşu gibi) bulunur veya takviye olarak alınabilir. Probiyotikler, sindirim sistemini düzenleyerek kabızlık, ishal, gaz ve şişkinlik gibi sorunları azaltır. Bağışıklık sistemini güçlendirir ve vitamin ve minerallerin emilimini arttırır. Ayrıca ruh sağlığı ve beyin fonksiyonları üzerinde olumlu etkiler gösterirler. Prebiyotikler ise probiyotiklerin beslenmesini ve çoğalmasını destekleyen bileşiklerdir(Yaşam, Yararlı, & Bakteriler, n.d.).

Mikrobiyotanın Oluşumu ve Gelişimi

Son yıllarda yapılan çalışmalar, büyük çoğunlukla doğumdan hemen sonra gelişmeye başlayan insan mikrobiyotasının, doğumdan önceki süreçte anne karnında da geliştiğini göstermiştir(D'Argenio, 2018). Maternal mikrobiyotanın bebeğe geçişi, gebelikte plasenta aracılığıyla, normal doğum esnasında vajinal kanaldan ve doğum sonrasında anne sütü beslenmesi ile olmaktadır. Annenin beslenme tarzı ve antibiyotik kullanımı, bebeğin gastrointestinal mikrobiyal çeşitliliğini etkilediği düşünülmektedir. Anne beslenmesinin hem gebelik döneminde hem de emzirme döneminde doymuş yağ asitleri gibi moleküllerden zengin olması mikrobiyal çeşitliliğin gelişmesine katkı sağladığı için bebek mikrobiyotasını pozitif yönde etkilemektedir. Gebelik döneminde kadınlar enfeksiyon hastalıklarına yakalanma konusunda daha duyarlı olabilmektedirler. Bu durum normal dönemlerine göre gebelikte artan antibiyotik kullanımı ile sonuçlanır. Gebelikte antibiyotik kullanımı yüksek olan annelerin çocuklarında alerjik hastalıkların ve obezite gelişiminin daha fazla görüldüğüne dair çalışmalar bulunmaktadır. Antibiyotik kullanımı hem intrauterin dönemde umblikal kord aracılığıyla fetüs kan dolaşımına geçerek, hem de annenin vajinal ve bağırsak mikrobiyota florası üzerinde değişiklik yaparak bebeğe aktarılmaktadır (Williams vd., 2017; Merter &Altay,2023; Zhong vd., 2021; Tapiainen vd., 2019).

Normal doğum ile dünyaya gelen bir bebek, annesinin vajinal florası ile doğum kanalından geçişi sırasında tanışmaktadır. Sağlıklı bir vajinal mikrobiyotaya sahip kadında yaklaşık 30 farklı tür mikroorganizma farklı oranlardan oluşan bir denge içerisinde bulunmaktadır. Vajinal floranın asidik pH yapısının devamlılığını sağlayan unsurlar arasında mikroorganizmaların ürettiği metabolitler, hormonlar ve vajinal sekresyonlar yer alır. Bu mikroorganizmalardan en baskın olanı *Lactobasiller'* dir. Laktobasiller östrojenin ürettiği glikojeni yıkarak laktik asit oluştururlar ve asidik pH' nın korunmasında en önemli katkıyı sunarlar. Doğarken doğum kanalı ile temasta olabilen yenidoğanın mikrobiyota zenginliğinin oluşmasını sağlayan bir durum olduğu kabul edilir. Sezaryen doğumda ise yenidoğanın ilk teması cilt florası ile olmaktadır (Williams vd., 2017; Dunn vd., 2017). Doğum şekline göre bebeklerin mikrobiyotaları kıyaslandığında sezaryen ile doğanlarda mikrobiyal çeşitliliğin daha az olduğu gösterilmiştir (Xu vd., 2018).

Doğum sonrası etkenlere baktığımızda bebeğin gestasyon yaşı mikrobiyota gelişimi için oldukça önemlidir. Preterm doğan bebeklerin mikrobiyotal çeşitliliği, zamanında doğan bebeklere göre farklılıklar gösterir. Pretermlerin bağırsak peristaltizminin tam olarak gelişmemiş olması ve yine preterm doğum sonrası bebeğin hastane yatışı, ilaç kullanımları, anne sütü veya mama kullanımı, hastane cihazlarına maruziyeti, bebeğin anne ile ten tene temastan uzak olması

da bebeğin mikrobiyal çeşitliliğini etkilediği bilinmektedir(Tauchi vd., 2019; Li vd., 2020). Anne sütü ile beslenmenin preterm bebeklerde de mikrobiyotanın gelişimine katkısının oldukça fazla olduğu bilinmektedir. Anne sütündeki moleküller, bebeğin intestinal sistemine patojen mikropların tutunmasını engelleyerek intestinal kolonizasyonu dengeler. Anne sütü probiyotiklerin çoğalmasını sağlamaktadır (Merter & Altay, 2023).

Mikrobiyotanın Hastalıklarla İlişkisi

Gastrointestinal sistem ve beyin arasında bağlantıyı sağlamakta görevli Nervus Vagus, Enterik Sinir Sistemi (ESS) ve Beyin- Bağırsak aksı dediğimiz kompleks yapılar mevcuttur. ESS, sindirim sisteminin kendi başına çalışan sinir sistemidir ve 'ikinci beyin' olarak da bilinir. Milyonlarca nöron içeren ESS, sindirim hareketlerini, salgılamayı ve kan akışını bağımsız olarak kontrol edebilir. ESS, sindirim sisteminin iç yüzeyinde bulunan sinir ağları aracılığıyla çalışır. Vagus siniri, ESS'den aldığı uyarıları beyine iletmekte görevli vücuttaki en uzun kraniyal sinirdir. Sindirim, kalp atış hızı, solunum ve bağışıklık sistemi gibi birçok önemli fizyolojik süreci düzenler. Beyin-bağırsak aksı; beyin, ESS ve bağırsak mikrobiyotası arasındaki kompleks iletişim ağıdır. Bu aks sinirsel, hormonal ve immünolojik yollarla çalışır. İntestinal kanaldaki mikroorganizmalar gerçekleştirdikleri biyokimyasal reaksiyonlar sonucunda bazı metabolitler oluştururlar. Bu metabolitlerden açığa çıkan moleküller bağırsak reseptörlerine bağlanıp Vagus siniri aracılığıyla beyine taşınırlar ve bazı fizyolojik değişikliklerin meydana gelmesini sağlarlar. Yine bağırsaktaki hücreler tarafından üretilen periferik serotonin ve bağırsak mikrobiyotasının tetiklemesiyle bağışıklık hücreleri tarafından salınan sitokinler de Vagus siniri aracılığıyla beyine ulaştırılır (Do vd., 2018; Sherman vd., 2015).

Mikrobiyota yapısının bozuk olmasının obezite, diyabet, aterosklerotik kardiyovasküler durumlar, inflamatuvar bağırsak hastalığı, irritabl bağırsak sendromu, kolelitiyazis, alkolik olmayan yağlı karaciğer hastalığı, bazı otoimmun hastalıklar, parkinson hastalığı, alzheimer hastalığı, multiple skleroz ve hatta otizm gibi birçok hastalıkla ilişkisinin bulunduğu tespit edilmiştir (Çakmak & İnkaya, 2021; Baydan T, 2021; Sugeçti vd., 2019; Salman vd., 2015). İnflamatuvar bağırsak hastalıklarından olan Crohn ve Ülseratif Kolit 'in remisyon ve atak dönemlerinde bağırsakta bakılan mikroorganizma oranların farklılık gösterdiğine yönelik çalışmalar mevcuttur (Salman vd., 2015). Sindirim sistemi ve karaciğer metabolizmada doğrudan birbiri ile ilişkilidir. Mikrobiyotanın devamlılığını sürdürmesindeki detoksifikasyon ve desensitizasyonunda karaciğer primer organdır. Son yıllardaki çalışmalar, genelde obezite ile birlikte görülen non alkolik karaciğer yağlanmasının patogenezinde sindirim kanalında aşırı artmış bakteriyel çoğalma ve bu bakterilerin ürettiği endotoksinlere intestinal geçirgenliğinde etkilenmesine bağlı olarak geliştiğini çalışmalar göstermiştir

(Seki & Schnabl, 2012). Gıda tüketimindeki düzensizlikler ve uygunsuz diyetler sonucunda meydana gelen bağırsak mikrobiyotasındaki değişimler ile intestinal lümende artan gram negatif bakterilerin ürettiği lipopolisakkaritlerin moleküler düzeyde yağlanma ve insülin direnci gelişmesinde etkili olduğu bilinmektedir (Blandino vd., 2016).

Nörodejeneratif hastalıklardan olan Alzheimer'ın etiyolojisinde ileri yaşlarda Beta-amiloid ve Tau proteinlerinin anormal şekilde birikmesi vardır. Bu proteinlerin fazlası santral sinir sisteminde nörodejenerasyon ve bilişsel sistemde bozulmayla sonuçlanır. İntestinal sistemde bazı bakteriler metabolit olarak amiloid ve lipopolisakkaritleri üretir. Bunların fazla üretimi sitokinler aracılığıyla beyine iletim yolaklarınıda etkileyerek beyinde beta-amiloid birikimini artırabildiği düşünülmektedir (Semercioğlu, 2022).

Bağırsak sağlığının bozulması ile ortaya çıkan hastalıklar son yıllarda önemli bir araştırma konusu olmuştur. Kanserler de dahil olmak üzere çok sayıda hastalığın intestinal flora ile ilişkisi olduğunun çalışmalarla saptanması, bağırsak mikrobiyotasını korumaya yönelik girişimlerin ne kadar önemli olduğunu bizlere kanıtlamıştır. Düzenli probiyotik alımı, vitamin ve mineraller açısından yeterli beslenme, glisemik indeksi düşük beslenme, mikrobiyota disbiyozisine engel olarak, intestinal sistemde patojen bakterilerin çoğalmasını engellemektedir.

Sonuç

Bu bölümde bağırsak mikrobiyotasının insan sağlığı üzerindeki derin ve çok yönlü etkilerine vurgu yapılmıştır. Mikrobiyota, sadece sindirim sistemimizin bir parçası olmanın ötesinde, bağışıklık sisteminden sinir sistemine, metabolizmadan ruh haline kadar geniş bir yelpazede fizyolojik süreçleri etkileyen karmaşık bir ekosistemdir. Probiyotikler, prebiyotikler, fekal mikrobiyota nakli ve diyet değişiklikleri gibi stratejiler, mikrobiyota dengesini iyileştirerek hastalık riskini azaltabilir ve mevcut hastalıkların seyrini iyileştirebilir. Ancak, mikrobiyota araştırmaları hala nispeten yeni bir alandır ve bu alanda daha fazla araştırmaya ihtiyaç vardır.

Sonuç olarak, bağırsak mikrobiyotasının korunması ve desteklenmesi, sağlıklı bir yaşam sürdürmek için vazgeçilmez bir unsurdur. Gelecekteki araştırmalar, mikrobiyota tabanlı yaklaşımların hastalıkların önlenmesi ve tedavisindeki potansiyelini daha da aydınlatacaktır.

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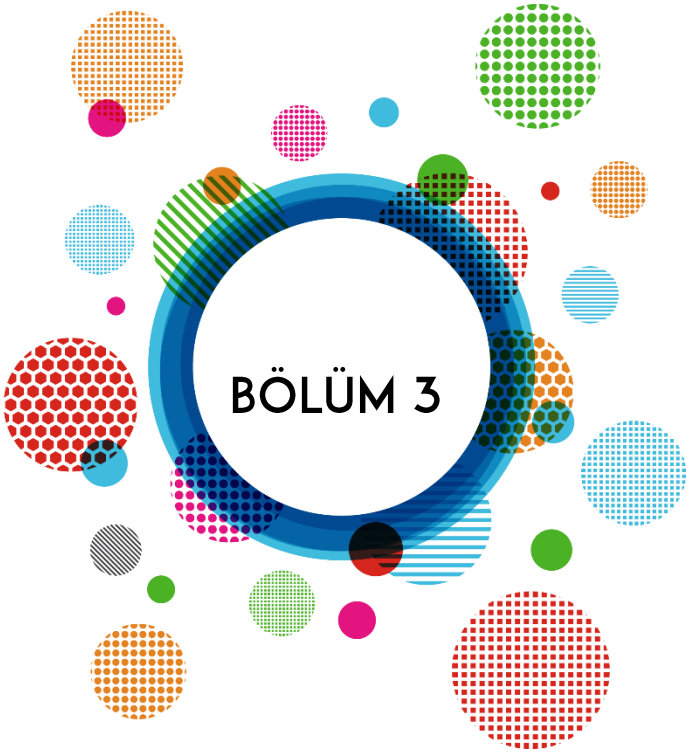

Approach to Adrenal Gland Diseases in Primary Care

***Recep Aktaş*[1]**

[1] Uzm.Dr. / Medical Doctor, Uşak Training and Research Hospital,
ORCID: 0000-0002-5576-6623

1. Introduction

The adrenal glands are bilateral endocrine structures located superior to each kidney and consist of two histological and functional regions: the cortex and the medulla. The adrenal cortex comprises three distinct zones: the zona glomerulosa, zona fasciculata, and zona reticularis, which are responsible for the synthesis of mineralocorticoids, glucocorticoids, and adrenal androgens, respectively (Xing et al., 2015). The adrenal medulla is composed of chromaffin cells and is responsible for catecholamine production (Tischler et al., 1989).

Adrenal hormones play a central role in the regulation of metabolic, hemodynamic, and immune responses. They are critically involved in stress response, fluid and electrolyte balance, blood pressure regulation, glucose homeostasis, sexual development, and overall physiological adaptation. Consequently, adrenal dysfunctions are often characterized by multisystemic manifestations and can present with life-threatening clinical conditions in certain cases (Pranckevicius et al., 2025).

Primary care services occupy a pivotal role in the recognition, differential diagnosis, and appropriate referral of patients with adrenal gland disorders. However, these pathologies frequently present with nonspecific symptoms such as fatigue, weight changes, hyperpigmentation, hypertension, electrolyte imbalances, and psychiatric manifestations, making the diagnostic process challenging and prone to delays. Such delays can negatively impact prognosis and may lead to unnecessary investigations and referrals.

This section will address the approach to adrenal gland disorders in primary care, including their pathophysiological basis, clinical diagnostic algorithms, fundamental laboratory assessments, and referral indications. The objective is to enhance clinical awareness among primary care physicians regarding adrenal pathologies, thereby promoting early diagnosis and appropriate management strategies.

2. Physiology of the Adrenal Gland

The adrenal glands are a vital component of the endocrine system and are responsible for the synthesis, storage, and secretion of numerous hormones that play central roles in maintaining homeostasis. Each adrenal gland is composed of two main regions of distinct embryological origin: the cortex, which is derived from the mesoderm, and the medulla, which originates from the neural crest. These two regions contain different cellular structures and produce functionally independent hormones.

2.1. Adrenal Cortex

The adrenal cortex consists of three functionally distinct zones arranged from outer to inner layers:

Zona Glomerulosa: This outermost layer primarily synthesizes aldosterone, the main mineralocorticoid. Aldosterone production is regulated by the renin-angiotensin-aldosterone system (RAAS), serum potassium levels, and adrenocorticotropic hormone (ACTH). It acts on the distal nephron to promote sodium reabsorption and potassium excretion, thereby maintaining fluid-electrolyte balance and regulating blood pressure (Tuffaha, 2021).

Zona Fasciculata: The middle layer is the primary site of glucocorticoid production. Cortisol secretion is regulated by the hypothalamic-pituitary-adrenal (HPA) axis: corticotropin-releasing hormone (CRH) from the hypothalamus stimulates the pituitary to release ACTH, which in turn triggers cortisol secretion from the adrenal cortex. Cortisol plays key roles in carbohydrate, protein, and fat metabolism, modulating immune responses, stress adaptation, and exerting anti-inflammatory effects (Angelousi et al., 2020).

Zona Reticularis: The innermost cortical layer is responsible for producing adrenal androgens, primarily dehydroepiandrosterone (DHEA) and androstenedione. These hormones are involved in the development of secondary sexual characteristics during puberty and influence libido, particularly in females (Nagliya et al., 2024).

2.2. Adrenal Medulla

The adrenal medulla is a neuroendocrine tissue located at the innermost part of the adrenal gland and functions as an extension of the sympathetic nervous system. It secretes the catecholamine hormones epinephrine (adrenaline) and norepinephrine (noradrenaline). Upon sympathetic stimulation, chromaffin cells release these hormones into the bloodstream in response to neural signals. Epinephrine increases heart rate, dilates bronchi, and enhances glucose mobilization, initiating the classic “fight or flight” response. Norepinephrine primarily acts by constricting blood vessels, thereby elevating blood pressure.

Hormones secreted by the adrenal medulla enable rapid and effective adaptation to acute stress conditions. These hormones also contribute to metabolic regulation by promoting glycogenolysis and lipolysis to meet increased energy demands. Unlike the adrenal cortex, which is regulated via the HPA axis, the adrenal medulla is directly controlled by the sympathetic nervous system, allowing for immediate physiological responses. Thus, the adrenal medulla is a

crucial component of homeostasis and the body's mechanisms for coping with stress (Dutt et al., 2023).

3. Adrenal Insufficiency

Adrenal insufficiency is a potentially life-threatening endocrine disorder characterized by inadequate synthesis of glucocorticoid and/or mineralocorticoid hormones by the adrenal cortex (Charmandari et al., 2014). Clinically, it presents with a broad range of often nonspecific symptoms, including hyponatremia, hyperkalemia, hypotension, fatigue, weight loss, and gastrointestinal complaints. Early recognition in primary care is crucial to reduce morbidity and mortality.

3.1. Classification

Adrenal insufficiency is classified into three main categories based on its etiopathogenesis:

Primary Adrenal Insufficiency (Addison's Disease): This form results from direct damage to the adrenal cortex, leading to decreased production of both cortisol and aldosterone. The most common cause is autoimmune adrenalitis. Other etiologies include tuberculosis, fungal infections, metastatic tumors, adrenalectomy, and genetic conditions such as congenital adrenal hyperplasia (Buonocore & Achermann, 2020).

Secondary Adrenal Insufficiency: This occurs due to insufficient secretion of ACTH from the pituitary gland, resulting in impaired cortisol production, while mineralocorticoid synthesis is usually preserved. The most frequent cause is suppression of the hypothalamic-pituitary-adrenal (HPA) axis following prolonged exogenous glucocorticoid therapy. Other causes include pituitary adenomas, surgical interventions, and radiotherapy (Hahner et al., 2021). Tertiary Adrenal Insufficiency: This form results from a deficiency of corticotropin-releasing hormone (CRH) at the hypothalamic level and often presents with clinical features similar to secondary adrenal insufficiency (Lewis et al., 2023).

3.2 Clinical Manifestations

Adrenal insufficiency typically has an insidious onset, and symptoms vary depending on the degree of glucocorticoid and mineralocorticoid deficiency. Multiple organ systems may be affected. General symptoms include weakness, persistent fatigue, unintentional weight loss, and anorexia. Gastrointestinal involvement commonly results in nausea, vomiting, abdominal pain, and diarrhea. Cardiovascular manifestations may include orthostatic hypotension and syncope. A hallmark of primary adrenal insufficiency is hyperpigmentation of the skin, especially in sun-protected areas. Electrolyte imbalances are also

notable, with hyponatremia, hyperkalemia, and hypoglycemia being the most frequent. Psychiatric symptoms such as depression, irritability, and difficulty concentrating may occur, reflecting the systemic impact of adrenal hormone deficiencies.

3.3 Diagnostic Approach

In primary care, adrenal insufficiency should be suspected when unexplained chronic fatigue, hyponatremia, hyperkalemia, and orthostatic hypotension are observed concurrently.

Laboratory Evaluation:

- Basal Serum Cortisol Level: Measured from a blood sample collected in the early morning (usually around 8:00 AM). A cortisol level <3 µg/dL (83 nmol/L) strongly suggests adrenal insufficiency, while a level >15 µg/dL (414 nmol/L) generally excludes it (Guia Lopes et al., 2025)

- ACTH Level: Helps distinguish between primary and secondary forms. ACTH is elevated in primary adrenal insufficiency and low in secondary forms.

- Synacthen (ACTH Stimulation) Test: Considered the gold standard for diagnosis. After administration of 250 µg synthetic ACTH (tetracosactide), cortisol levels are measured at 30 and 60 minutes. A suboptimal response supports the diagnosis (Shaikh et al., 2023; Okutan et al., 2024).

- Serum Electrolytes: May reveal hyponatremia, hyperkalemia, and hypoglycemia.

3.4 Emergency Management in Primary Care

An acute adrenal crisis is a life-threatening manifestation often triggered by stressors such as infection, trauma, or surgery. It presents with hypotension, dehydration, altered mental status, and shock. If suspected in primary care, immediate parenteral fluid resuscitation and glucocorticoid replacement should be initiated, and the patient should be urgently referred to a higher-level care center.

3.5 Referral Criteria

Certain clinical and laboratory findings in patients suspected of having adrenal insufficiency indicate the need for specialist evaluation. These include

unexplained electrolyte imbalances such as hyponatremia or hyperkalemia, low early morning cortisol levels, abnormal or elevated ACTH levels, or an insufficient response to ACTH stimulation testing. Patients with suspected adrenal crisis require emergency intervention. In such cases, referral to an endocrinologist is crucial for definitive diagnosis, advanced hormonal testing, and appropriate treatment planning.

4. Cushing's Syndrome

Cushing's syndrome is a clinical condition caused by chronic excess glucocorticoids and may result from either endogenous or exogenous sources. Endogenous Cushing's syndrome is associated with increased cortisol production due to adrenal or pituitary pathologies. Exogenous Cushing's syndrome is the most common form and develops following prolonged systemic glucocorticoid therapy (Reincke & Fleseriu, 2023)

4.1. Etiology and Classification

Cushing's syndrome is broadly classified into two categories: exogenous (iatrogenic) and endogenous. The exogenous form, which is most frequently encountered, results from the chronic administration of systemic glucocorticoids. In such cases, endogenous cortisol and ACTH production are suppressed via negative feedback mechanisms.

Endogenous Cushing's syndrome arises from increased endogenous cortisol production and is further subdivided into ACTH-dependent and ACTH-independent causes.

- ACTH-dependent Cushing's syndrome most commonly results from Cushing's disease, where a pituitary adenoma leads to excessive ACTH secretion. Another cause is ectopic ACTH syndrome, in which malignant tumors such as small-cell lung carcinoma or bronchial carcinoid tumors produce unregulated ACTH (Wagner-Bartak et al., 2017).
- ACTH-independent Cushing's syndrome is due to adrenal-origin hypercortisolism, commonly caused by adrenal adenomas, adrenal carcinomas, or bilateral adrenal hyperplasia. In these cases, ACTH levels are typically suppressed.

4.2 Clinical Manifestations

Cushing's syndrome usually has a subacute and progressive course, affecting multiple organ systems. Clinical features vary depending on the severity and duration of glucocorticoid excess.

Characteristic physical signs include central obesity, a dorsocervical fat pad ("buffalo hump"), and a rounded "moon face." Skin changes are typical and may include thinning of the skin, easy bruising, and wide, violaceous striae—especially in the abdominal area.

Musculoskeletal involvement often presents with prominent proximal muscle weakness, hypertension, and long-term osteoporosis. Metabolic disturbances such as glucose intolerance or diabetes mellitus are also common. Endocrine effects in women may include menstrual irregularities, hirsutism, and decreased libido. Psychiatric symptoms are prevalent and may include depression, irritability, and anxiety (Juszczak et al., 2024). The broad range of manifestations highlights the need for a multidisciplinary approach in diagnosis and management.

In primary care, the coexistence of central obesity, hypertension, glucose intolerance, and characteristic skin findings should prompt clinical suspicion of Cushing's syndrome.

4.3 Diagnostic Approach

In patients suspected of having endogenous Cushing's syndrome, diagnosis involves three main steps: confirming glucocorticoid excess, identifying the underlying etiology, and localizing the source. In primary care, initial screening tests should be used to identify potential cases and refer them to endocrinology for further evaluation.

Primary screening tests include:

- Late-night salivary cortisol: The circadian rhythm of cortisol secretion is disrupted in Cushing's syndrome, leading to elevated nighttime levels (Yaneva et al., 2004).
- Low-dose dexamethasone suppression test (DST): 1 mg of dexamethasone is administered at 11:00 PM, and serum cortisol is measured at 8:00 AM the following morning. A cortisol level >1.8 µg/dL (50 nmol/L) is considered abnormal (Rebelo et al., 2024).
- 24-hour urinary free cortisol (UFC): A value >50 µg/24 hours is considered pathological. Repetition of the test is recommended for confirmation (Ray et al., 2022).

If any of these screening tests yield abnormal results, the patient should be referred to endocrinology for advanced diagnostic testing and imaging.

4.4 Differential Diagnosis

Certain clinical conditions that mimic Cushing's syndrome without true cortisol excess are referred to as pseudo-Cushing's syndrome. These conditions may cause transient alterations in cortisol metabolism, leading to false-positive screening results. Common causes of pseudo-Cushing's include chronic alcohol use, obesity, psychiatric disorders such as depression and anxiety, polycystic ovary syndrome (PCOS), and use of medications like oral contraceptives and anticonvulsants.

In these cases, cortisol levels may temporarily resemble those of true Cushing's syndrome. However, hormone levels often return to normal once the underlying condition is resolved. Therefore, confirmatory testing such as the low-dose dexamethasone suppression test or late-night salivary cortisol should always be used to differentiate pseudo-Cushing's from true disease. This careful diagnostic approach is essential to avoid unnecessary treatments and misdiagnosis.

4.5 Referral Criteria

Timely referral of suspected Cushing's syndrome cases to a specialist is essential for effective diagnosis and management. Primary care providers should refer patients to an endocrinologist in the following situations:

- Abnormal results in one or more initial screening tests (low-dose DST, late-night salivary cortisol, or 24-hour UFC);
- Presence of the classic Cushing's phenotype (central obesity, buffalo hump, moon face) along with unexplained metabolic disturbances such as hypertension, diabetes, or osteoporosis;
- Clinical features suggesting a polyglandular endocrinopathy.

Early specialist evaluation and accurate diagnosis are crucial for preventing complications associated with hypercortisolism, including cardiovascular disease, metabolic syndrome, bone loss, and psychiatric disorders. Therefore, any case that raises suspicion in primary care warrants prompt referral for endocrinological assessment.

5. Primary Aldosteronism

Primary aldosteronism (PA) is a mineralocorticoid excess syndrome characterized by autonomous overproduction of aldosterone from the adrenal cortex. It may present with hypertension and hypokalemia, although many patients remain normokalemic. PA is one of the most common endocrine causes

of secondary hypertension. Recent data suggest that its prevalence may range from 5–20%, particularly among patients with resistant hypertension (Lenzini et al., 2023). Early diagnosis is essential for reducing cardiovascular morbidity and mortality.

5.1. Etiology and Pathophysiology

PA can arise from various adrenal pathologies that lead to excessive aldosterone secretion. The most common causes include aldosterone-producing adenoma (APA), also known as Conn's syndrome, and idiopathic bilateral adrenal hyperplasia (IHA). Less frequently, adrenal carcinoma, glucocorticoid-remediable aldosteronism (GRA, especially familial hyperaldosteronism type I), and ectopic aldosterone production may be involved. Excess aldosterone promotes sodium retention and potassium excretion, leading to volume expansion and hypertension, as well as hypokalemia and metabolic alkalosis. Additionally, aldosterone exerts direct fibrotic and hypertrophic effects on cardiovascular tissues, contributing to organ damage.

5.2. Clinical Manifestations

PA is often asymptomatic and is typically identified incidentally during evaluation for hypertension. It usually presents with early-onset or resistant hypertension that is difficult to control. Hypokalemia is a common finding and may occur spontaneously or be precipitated by diuretic use. Symptoms can include muscle weakness, paresthesias, palpitations, and constipation. Metabolic alkalosis, polyuria, and nocturia may also be present. Genetic forms should be considered in patients with a positive family history (Park et al., 2024).

5.3. Diagnostic Approach

In primary care, suspicion of PA should be raised by certain clinical clues, most notably resistant hypertension. Additional indicators include hypokalemia, especially if spontaneous or induced by diuretic therapy, early-onset hypertension, particularly with a family history, and the presence of an adrenal incidentaloma in hypertensive patients.

Screening Test:

- Aldosterone/Renin Ratio (ARR): Calculated from a morning serum sample taken while the patient is seated, by dividing plasma aldosterone concentration (PAC) by plasma renin activity (PRA).
- An ARR >20 (ng/dL:ng/mL/h) and PAC >15 ng/dL are highly suggestive of PA (Vorselaars et al., 2018).

Before testing, it is essential to consider that antihypertensive medications can influence ARR results. If feasible, beta blockers, ACE inhibitors, ARBs, and diuretics should be temporarily discontinued or substituted. Additionally, hypokalemia should be corrected prior to testing (Seiler et al., 2004).

Confirmatory Tests:

Patients with elevated ARR should undergo confirmatory testing to establish the diagnosis. These include oral or intravenous salt loading, the fludrocortisone suppression test, and the saline infusion test.

5.4. Differential Diagnosis

Differential diagnoses for PA include causes of secondary aldosteronism such as renovascular hypertension and renin-secreting tumors; pseudo-hyperaldosteronism such as Liddle syndrome; and conditions like Cushing's syndrome or chronic kidney disease-associated hyperaldosteronism.

5.5. Referral Criteria

Primary care providers should refer patients to endocrinology in the following scenarios:

- Elevated ARR accompanied by high PAC;
- Hypertension with unexplained hypokalemia;
- Early-onset hypertension with concurrent adrenal mass;
- Resistant hypertension.

Confirmation of diagnosis and determination of whether the condition is unilateral or bilateral must be conducted by an endocrinologist. Treatment varies accordingly—unilateral disease is typically managed surgically with adrenalectomy, whereas bilateral disease is treated medically with mineralocorticoid receptor antagonists.

6. Pheochromocytoma and Paraganglioma

Pheochromocytomas and paragangliomas are rare neuroendocrine tumors originating from chromaffin cells. Pheochromocytomas arise from the adrenal medulla and are characterized by catecholamine secretion. Paragangliomas, in contrast, develop from extra-adrenal sympathetic or parasympathetic paraganglionic tissues. They may be located along the sympathetic chain and typically secrete norepinephrine, whereas parasympathetic paragangliomas are mostly non-functional (Kumba, 2019).

These tumors commonly present with paroxysmal hypertension and symptoms due to catecholamine excess. Early diagnosis and treatment are essential to prevent serious cardiovascular complications and malignant transformation.

6.1. Etiology and Genetics

Approximately 30–40% of pheochromocytomas and paragangliomas are hereditary and associated with germline mutations. These tumors are often linked to genetic syndromes such as multiple endocrine neoplasia type 2 (MEN2A and MEN2B), Von Hippel–Lindau disease, and neurofibromatosis type 1. Mutations in the succinate dehydrogenase (SDH) genes, particularly SDHB and SDHD, also play a major role in tumor development. For this reason, genetic evaluation is a critical component of the diagnostic workup (Burnichon et al., 2011).

6.2. Clinical Manifestations

Pheochromocytomas and paragangliomas often present with the classic triad of sudden-onset headache, excessive sweating, and tachycardia. Other symptoms may include paroxysmal or sustained hypertension, anxiety or panic attack-like symptoms, tremor, pallor, nausea, glucose intolerance or hyperglycemia, and orthostatic hypotension. These symptoms usually occur episodically and can be triggered by stress, surgical procedures, trauma, childbirth, or medications such as beta-blockers and tricyclic antidepressants. In the presence of these symptoms, pheochromocytoma or paraganglioma should be suspected (Reus et al., 2021; Geroula et al., 2019).

6.3. Diagnostic Approach

Diagnosis relies on the biochemical measurement of catecholamine metabolites. In primary care, suspicion should be based on specific clinical signs and family history. Important indicators include young-onset, resistant, or paroxysmal hypertension, especially when accompanied by the classic triad (headache, sweating, tachycardia). A family history of related tumors or the presence of MEN2, Von Hippel–Lindau disease, or neurofibromatosis type 1 also warrant further evaluation.

The most sensitive and recommended initial test is the measurement of plasma free metanephrines. This test is highly reliable for ruling out the disease. If plasma results are borderline or unclear, 24-hour urinary fractionated metanephrines and catecholamines can be used for higher specificity. The accuracy of both tests depends on appropriate patient preparation, including stress reduction and avoidance of interfering medications (Lima & Kater, 2023).

If biochemical tests are positive, anatomical imaging is the next step. Computed tomography (CT) or magnetic resonance imaging (MRI) are used to localize adrenal or extra-adrenal tumors. These techniques provide detailed information on the tumor's size and location.

In cases of suspected metastatic disease, multifocal tumors, or biochemically confirmed tumors not visualized on standard imaging, functional imaging is indicated. Common modalities include ^{123}I-MIBG scintigraphy and PET-CT, which visualize the biological activity of tumor cells and are especially useful in complex or extensive cases (Ctvrtlik et al., 2018).

6.4. Differential Diagnosis

The differential diagnosis of pheochromocytoma and paraganglioma includes several clinical conditions that may present with similar symptoms, particularly due to paroxysmal manifestations and hypertension. These conditions include:

- Anxiety disorders and panic attacks: May mimic pheochromocytoma due to symptoms such as tachycardia, sweating, and palpitations.
- Hyperthyroidism: Symptoms like increased metabolism, tachycardia, weight loss, and nervousness can overlap with pheochromocytoma.
- Insulinoma: Causes hypoglycemia-induced symptoms such as sweating, palpitations, and anxiety that may resemble pheochromocytoma.
- Cushing’s syndrome: Shares features such as hypertension, glucose intolerance, and weight gain.
- Labile hypertension: Sudden surges in blood pressure can mimic pheochromocytoma episodes.

Given these similarities, biochemical testing and imaging are essential for accurate diagnosis and differentiation.

6.5. Referral Criteria

In primary care, timely referral to an endocrinologist is crucial when pheochromocytoma or paraganglioma is suspected. Referral is recommended in the following scenarios:

- Significant elevation of plasma or 24-hour urinary metanephrines
- Detection of an adrenal or extra-adrenal mass
- Presence of a genetic syndrome or relevant family history

- Classic symptom triad (headache, sweating, tachycardia) accompanying paroxysmal hypertension

Once the diagnosis is confirmed, patients must be prepared for surgery with preoperative alpha-adrenergic blockade (e.g., phenoxybenzamine or doxazosin), which is vital to prevent cardiovascular complications. Surgical excision (adrenalectomy or paraganglioma resection) follows. Postoperatively, patients should undergo regular monitoring due to the risks of recurrence and potential genetic inheritance.

7. Adrenal Incidentalomas

Adrenal incidentalomas are adrenal masses that are incidentally discovered during abdominal imaging, typically in the absence of clinical symptoms. Primary care physicians should refer patients for appropriate endocrinological evaluation upon identification of such masses in imaging reports.

7.1. Epidemiology

The prevalence of adrenal incidentalomas increases significantly with age. While their occurrence in the general population is approximately 1–4%, this rate rises to 7–10% in individuals over the age of 70. The widespread use of advanced imaging techniques, particularly computed tomography (CT) and magnetic resonance imaging (MRI), has led to an increase in the incidental detection of these lesions, resulting in a marked rise in diagnosis rates (Fassnacht et al., 2023; Suntornlohanakul et al., 2024).

7.2 Differential Diagnosis

The etiology of adrenal incidentalomas is diverse, and both their functional status and structural characteristics are critical for evaluation. Among benign lesions, the most commonly encountered are adrenal cortical adenomas. These may be either functional (hormone-producing) or non-functional (clinically silent). Cystic lesions are often incidental findings and are typically of no clinical significance. Myelolipomas, composed of adipose and hematopoietic tissue, are benign and generally asymptomatic (Collins et al., 2021).

Functioning lesions warrant closer clinical attention. Cortisol-producing adenomas may lead to subclinical Cushing's syndrome without overt symptoms, contributing to metabolic disturbances. Aldosterone-producing adenomas are a major cause of primary aldosteronism, presenting with hypertension and hypokalemia. Pheochromocytomas, which secrete catecholamines, manifest with symptoms related to sympathetic overactivity, such as paroxysmal hypertension, headache, sweating, and palpitations.

Although less common, malignant lesions are a critical aspect of the diagnostic process. Adrenocortical carcinoma is a rare but aggressive tumor that often produces hormones. Additionally, the adrenal glands are frequent sites of metastasis, particularly from malignancies such as lung, breast, and renal cell carcinoma. Therefore, incidental adrenal masses should be evaluated carefully for both hormonal activity and radiologic features to determine their clinical significance.

7.3. Evaluation and Diagnostic Approach

The evaluation of adrenal incidentalomas focuses on two primary clinical questions: whether the lesion is hormonally active and whether it has malignant potential. The answers to these questions guide both the diagnostic process and subsequent management strategies.

Assessment of hormonal activity is a fundamental initial step in the evaluation of any adrenal incidentaloma. A series of hormonal tests are employed for this purpose. To investigate subclinical Cushing's syndrome, a low-dose dexamethasone suppression test (1 mg DST) is conducted. In this test, 1 mg of dexamethasone is administered at night, and serum cortisol is measured at 8:00 AM the following morning. A cortisol level exceeding 1.8 μg/dL indicates insufficient suppression and suggests possible cortisol excess.

In addition, plasma fractionated metanephrines or 24-hour urinary metanephrines and catecholamines are measured to exclude pheochromocytoma. In patients with hypertension or hypokalemia, the plasma aldosterone-to-renin ratio (ARR) should be assessed, which is critical for the screening of primary aldosteronism. These hormonal evaluations form the cornerstone of determining the functional status of adrenal masses (Puglisi et al., 2024).

7.4. Radiological Evaluation

Characteristic features observed on computed tomography (CT) and magnetic resonance imaging (MRI) provide important clues regarding the benign or malignant nature of adrenal lesions. Lesions that are smaller than 4 cm in diameter, have a Hounsfield Unit (HU) value of less than 10, and appear well-defined and homogeneous are typically consistent with benign adenomas. In contrast, lesions larger than 4 cm, with heterogeneous structure, irregular borders, an HU value greater than 20, or those exhibiting delayed washout following contrast administration are considered more suspicious for malignancy (Bokhari et al., 2023). For incidentalomas with low probability of being functional or

malignant, follow-up imaging with CT or MRI at intervals of 6–12 months is generally recommended.

7.5. Approach in Primary Care

When an adrenal incidentaloma is identified in an imaging report, it is essential for primary care physicians to follow a structured evaluation pathway. Initially, a thorough clinical assessment should be conducted to identify symptoms such as hypertension, hypokalemia, weight changes, and dermatological findings. This should be followed by a comprehensive review of the patient's current medications and comorbidities. Initial laboratory investigations aimed at assessing hormonal activity of the lesion should be ordered. Additionally, the radiology report should be carefully reviewed for imaging characteristics suggestive of malignancy. Based on these findings, timely referral to an endocrinologist is recommended.

7.6. Referral Criteria

Referral to a specialized center for endocrinological and/or oncological evaluation is warranted under the following circumstances: presence of functional hormonal activity as indicated by biochemical tests, lesion size greater than 4 cm, imaging findings suggestive of malignancy, detection of rapid lesion growth (greater than 1 cm increase within 6–12 months), or bilateral adrenal lesions. In these cases, evaluation by an endocrinologist is strongly advised.

8. Laboratory and Imaging Approach in Adrenal Disorders

The evaluation of adrenal gland disorders relies heavily on both laboratory testing and imaging techniques, which play a pivotal role in confirming diagnoses and differentiating etiologies. Hormonal assays are essential for determining whether lesions are functionally active, while imaging studies provide guidance on anatomical localization, lesion characterization, and malignancy risk. For primary care physicians, appropriate selection and interpretation of these tests are critical for early diagnosis and accurate referral.

8.1. Laboratory Evaluation

Functional assessment of the adrenal glands is conducted through tests targeting the glucocorticoid, mineralocorticoid, androgen, and catecholamine axes. Laboratory samples should generally be obtained in the early morning and under optimal pre-analytical conditions (Birtolo et al., 2023).

8.1.1. Glucocorticoid Axis

- Morning Serum Cortisol
    - First-line test in suspected adrenal insufficiency.
    - <3 μg/dL: strongly suggestive of adrenal insufficiency
    - ≥15 μg/dL: effectively rules out adrenal insufficiency
- Adrenocorticotropic Hormone (ACTH)
    - Helps differentiate primary from secondary adrenal insufficiency.
    - Elevated in primary; decreased in secondary insufficiency
- Synacthen (Short ACTH Stimulation) Test
    - 250 μg of synthetic ACTH (tetracosactide) administered IM/IV; cortisol measured at 30 and 60 minutes.
    - A cortisol response <18–20 μg/dL suggests adrenal insufficiency.
- Low-Dose Dexamethasone Suppression Test (1 mg DST)
    - Used to screen for subclinical or overt Cushing's syndrome.
    - 1 mg dexamethasone given at 11:00 PM; serum cortisol measured at 8:00 AM.
    - <1.8 μg/dL: normal suppression; >5 μg/dL: abnormal (suggestive of Cushing's)

8.1.2. Mineralocorticoid Axis

- Plasma Aldosterone-to-Renin Ratio (ARR)
    - Screening test for primary aldosteronism.
    - ARR >20 with aldosterone >15 ng/dL indicates need for further evaluation.
    - Certain antihypertensives (e.g., spironolactone, ACE inhibitors, ARBs) should be discontinued prior to testing.
- Serum Electrolytes

- Hypokalemia and hyponatremia may indicate mineralocorticoid dysfunction (Hung et al., 2021).

8.1.3. Catecholamine Axis

- Plasma Free Metanephrines
  - Highly sensitive for diagnosing pheochromocytoma/paraganglioma.
  - Patient should be well-rested and in a supine position.
- 24-Hour Urinary Metanephrines / Catecholamines
  - An alternative diagnostic method, especially useful when plasma values are borderline.

8.1.4. Androgen Axis

- Dehydroepiandrosterone Sulfate (DHEA-S), Androstenedione
  - Used in the evaluation of adrenal-origin hirsutism, virilization, and congenital adrenal hyperplasia (CAH).

8.2. Imaging Modalities

8.2.1. Computed Tomography (CT)

CT is the first-line imaging modality for evaluating the adrenal glands. On non-contrast CT, lesions with Hounsfield Unit (HU) values below 10 are typically consistent with lipid-rich adenomas. In contrast, lesions that are larger than 4 cm, demonstrate delayed contrast washout, have heterogeneous structures, or irregular margins are considered suspicious for malignancy (Nagayama et al., 2025).

8.2.2. Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) is preferred in children, pregnant women, and individuals with contrast agent allergies due to its lack of ionizing radiation. Chemical shift sequences used in MRI play a crucial role in differentiating adenomas from other adrenal masses by demonstrating lipid content within the lesion.

8.2.3. Functional Imaging

Nuclear medicine imaging techniques significantly contribute to the assessment of adrenal lesions.[123] I-MIBG scintigraphy is especially useful for diagnosing pheochromocytomas and paragangliomas, as well as determining

disease extent. In addition, advanced modalities such as ^{18}F-FDG PET-CT or ^{68}Ga-DOTATATE PET-CT are preferred for identifying and evaluating metastatic or potentially malignant adrenal lesions.

8.3. Imaging and Test Selection in Primary Care

In primary care settings, the following diagnostic approach is recommended for suspected adrenal disorders:

- Suspected adrenal insufficiency → Morning serum cortisol and ACTH (Synacthen test if necessary)
- Hypertension with hypokalemia → Aldosterone-to-renin ratio (ARR)
- Typical features of Cushing's syndrome → 1 mg overnight dexamethasone suppression test (DST)
- Paroxysmal hypertension and symptom triad → Plasma free metanephrines
- Adrenal incidentaloma → Hormonal screening and CT/MRI

Accurate early diagnosis and referral are achievable through appropriate laboratory and imaging algorithms.

9. Differential Diagnosis of Adrenal Disorders

Adrenal gland disorders often present with hormonal hyperfunction or hypofunction syndromes and are frequently associated with systemic and nonspecific symptoms. As such, their clinical manifestations may overlap with those of other endocrinopathies, electrolyte imbalances, psychiatric disorders, and systemic inflammatory conditions. A systematic approach to differential diagnosis is essential to avoid misdiagnosis and to ensure appropriate referral and treatment.

9.1. Differential Diagnosis of Adrenal Insufficiency

In the evaluation of adrenal insufficiency, it is crucial to differentiate from various clinical conditions with overlapping symptoms. Chronic fatigue syndrome and fibromyalgia may mimic adrenal insufficiency due to shared symptoms such as fatigue, myalgia, and cognitive impairment. Psychiatric disorders, including depression and anxiety, can also present with appetite loss, weight loss, and concentration difficulties, resembling adrenal insufficiency.

Among endocrine disorders, hypothyroidism must be considered in the differential diagnosis due to common symptoms such as cold intolerance, constipation, and depressive mood. Electrolyte disturbances, particularly those leading to hyponatremia (e.g., syndrome of inappropriate antidiuretic hormone secretion [SIADH], diuretic use, or primary polydipsia), should be evaluated. However, adrenal insufficiency is often distinguished by the presence of both hyponatremia and hyperkalemia, along with hypotension—features that provide valuable diagnostic clues.

Additionally, gastrointestinal pathologies, especially malabsorption syndromes and inflammatory bowel diseases, may also mimic adrenal insufficiency due to associated weight loss and fatigue (Bhargav et al., 2008).

Nevertheless, the hallmark features that distinguish adrenal insufficiency include:

- Markedly low morning serum cortisol levels
- Elevated plasma ACTH concentrations
- Presence of hyperpigmentation
- Electrolyte abnormalities, particularly hyponatremia accompanied by hyperkalemia

These characteristic findings serve as clinically significant parameters in the differential diagnosis of adrenal insufficiency.

9.2. Differential Diagnosis of Cushing Syndrome

In the diagnosis of Cushing syndrome, it is necessary to evaluate several conditions that may present with similar clinical and biochemical findings. The most common scenario is central obesity, in which the hypothalamic-pituitary-adrenal (HPA) axis is usually intact, circadian rhythm is preserved, and cortisol levels are suppressed by the low-dose dexamethasone suppression test (DST), which helps differentiate it from true Cushing syndrome (van Rooijen et al., 2016).

Chronic alcohol use may lead to a pseudo-Cushing state, presenting with transient hypercortisolism-like features. In such cases, elevated liver enzymes and findings such as hepatic steatosis support the diagnosis of underlying liver pathology. Polycystic ovary syndrome (PCOS) is another endocrine disorder that can mimic Cushing syndrome. While PCOS often presents with hirsutism, menstrual irregularities, and insulin resistance, the HPA axis remains largely unaffected, and elevations in DHEA-S are generally mild. Major depression and

other severe psychiatric disorders may temporarily activate the HPA axis. However, cortisol suppression is usually achieved with DST, making it useful for differential diagnosis. Metabolic syndrome and insulin resistance may also share clinical features with Cushing syndrome, but the HPA axis typically functions normally in these patients (Keevil, 2021). Key diagnostic tests that confirm endogenous hypercortisolism include lack of suppression in the low-dose DST, elevated late-night salivary cortisol, and increased 24-hour urinary free cortisol levels. These tests, combined with clinical assessment, are critical in distinguishing Cushing syndrome from other mimicking conditions (Ceccato et al., 2022).

9.3. Differential Diagnosis of Primary Aldosteronism

Primary aldosteronism (PA) is a form of endocrine hypertension that should be evaluated particularly in patients with resistant hypertension and hypokalemia. However, during the diagnostic process, it is important to exclude other conditions that may present with similar clinical findings. The most commonly encountered condition is essential hypertension, which, like PA, may present with isolated hypertension. However, hypokalemia is rare, and the plasma aldosterone-to-renin ratio (ARR) is generally within normal limits.

Renovascular hypertension, or secondary aldosteronism, develops due to increased renin secretion caused by conditions such as renal artery stenosis. In these patients, plasma renin activity is markedly elevated, which helps distinguish it from PA (Nielsen & Jacobsen, 2009).

Cushing syndrome can also present with hypertension and hypokalemia; however, in these patients, the cortisol axis is disrupted, and cortisol levels fail to suppress during the low-dose dexamethasone suppression test, which helps in differentiation.

Liddle syndrome, a rare monogenic cause of hypertension, leads to elevated sodium channel activity, resulting in hypertension and hypokalemia. However, both plasma aldosterone and renin levels are suppressed in these patients, which differentiates them from PA.

Chronic kidney disease and nephrotic syndrome can also lead to a picture of secondary aldosteronism due to reduced renal perfusion, resulting in the activation of the renin-angiotensin-aldosterone system (RAAS). In such cases, renin levels are elevated, and aldosterone increase is secondary.

The most distinguishing laboratory findings for PA include high plasma aldosterone levels, low plasma renin activity, and a high aldosterone-to-renin

ratio (ARR). Interpreting these parameters together is critical to achieving an accurate diagnosis (Asbach & Reincke, 2022).

9.4. Differential Diagnosis of Pheochromocytoma and Paraganglioma

Pheochromocytoma and paraganglioma are rare but potentially life-threatening tumors characterized by paroxysmal hypertension, tachycardia, sweating, and headache. Several clinical conditions should be considered in the differential diagnosis. The most frequently mistaken conditions include panic disorder and anxiety attacks, which may also present with sudden palpitations, sweating, and dizziness. However, catecholamine levels are typically within normal limits, and the physical symptoms are of neurovegetative origin. Hyperthyroidism can mimic pheochromocytoma, especially with symptoms such as tachycardia and heat intolerance. Nevertheless, suppressed TSH levels and elevated free thyroid hormones aid in the differential diagnosis (Starkman et al., 1990).

Hypoglycemia, particularly when caused by insulinoma, can present with tremors, tachycardia, sweating, and neuroglycopenic symptoms. Simultaneous findings of hypoglycemia and elevated insulin levels help guide the diagnosis. Menopausal syndrome may present with hot flashes and palpitations that mimic pheochromocytoma. However, hormone evaluations are generally within normal limits, and there is no increase in catecholamine metabolites.

Additionally, the use of stimulant drugs such as amphetamines or cocaine can produce similar symptoms. In such cases, a detailed medication history and toxicology screening are important for differential diagnosis.

The most valuable biochemical indicators for diagnosing pheochromocytoma and paraganglioma are significantly elevated levels of plasma free metanephrines or 24-hour urinary metanephrines and normetanephrines. Due to their high sensitivity and specificity, these tests are recommended as first-line diagnostic tools. Reaching the correct diagnosis requires assessing both the paroxysmal nature of symptoms and biochemical evidence (Abdel-Aziz et al., 2015).

10. Primary Care Follow-Up and Referral Criteria

Primary healthcare services play a critical role in the early detection of adrenal gland disorders, conducting initial assessments, providing patient education, and ensuring timely referrals to higher levels of care when necessary. Since adrenal diseases often present with nonspecific symptoms, primary care physicians must maintain a low threshold for clinical suspicion and carefully plan their referral decisions.

10.1. General Follow-Up Principles

In the follow-up of adrenal gland disorders at the primary care level, attention must be paid to several fundamental principles. First, clinical symptoms and systemic signs such as hypertension, hypokalemia, weight changes, skin findings, and psychiatric symptoms should be monitored at regular intervals. Laboratory test results should be carefully evaluated; if borderline or suspicious values are found, repeat testing may be necessary. Additionally, in patients initiated on pharmacological treatment—particularly glucocorticoid replacement, mineralocorticoid antagonists, or antihypertensive therapy—adverse effects should be monitored, and patients should be thoroughly informed about the treatment process.

10.2. Referral Indications

Primary care physicians should refer patients to endocrinology, oncology, or surgical specialties under the following conditions:

10.2.1. Adrenal Insufficiency

- Morning cortisol level <3 µg/dL
- Elevated ACTH in combination with hyponatremia/hyperkalemia
- Inadequate response on the Synacthen test
- Clinical presentation of adrenal crisis: hypotension, altered mental status, vomiting, dehydration

10.2.2. Cushing Syndrome

- Post 1 mg DST cortisol >1.8 µg/dL
- Elevated late-night salivary cortisol or 24-hour urinary cortisol
- Cushingoid phenotype and metabolic disturbances (diabetes, osteoporosis, hypertension)

10.2.3. Primary Aldosteronism

- Elevated plasma aldosterone/renin ratio (ARR)
- Hypokalemia and resistant hypertension
- Presence of adrenal mass and evidence of hormonal activity

10.2.4. Pheochromocytoma / Paraganglioma

- Markedly elevated plasma metanephrines or urinary catecholamines
- Triad of paroxysmal hypertension, headache, tachycardia, and sweating
- Bilateral or extra-adrenal mass presence

10.2.5. Adrenal Incidentaloma

- Lesion diameter >4 cm
- Evidence of functional activity (elevated cortisol, aldosterone, or metanephrines)
- CT features such as >10 Hounsfield units, irregular borders, rapid growth, or heterogeneous structure
- Bilateral lesions

10.3. Conditions Requiring Follow-Up

Non-functional Adrenal Adenomas, <4 cm in Diameter

- Radiological follow-up (CT or MRI) every 6-12 months.
- Annual hormonal screening (cortisol, metanephrines, aldosterone/renin).

Subclinical Cushing's Syndrome

- Monitoring for clinical progression or development of metabolic complications.
- Further evaluation regarding surgical candidacy.

Medically Managed Primary Aldosteronism

- Monitoring of serum potassium levels and blood pressure.
- Adjustment of mineralocorticoid antagonist dosage.

10.4. Multidisciplinary Collaboration

Multidisciplinary collaboration plays a critical role in the effective and holistic management of adrenal diseases. This process necessitates close cooperation with various specialties, including endocrinology, nephrology, cardiology, psychiatry, and oncology. A multidisciplinary approach should be a fundamental principle, particularly in cases with suspected malignancy, instances of complex genetic

syndromes, and patients requiring surgical intervention. This ensures that the most appropriate decisions are made in the diagnostic, treatment, and follow-up processes, ultimately benefiting the patient."

11. Conclusion and Recommendations

Adrenal gland diseases represent rare yet potentially life-threatening disorders of the endocrine system. These conditions can manifest with hormonal hyperfunction or hypofunction. Given their often non-specific, insidious onset and multisystemic clinical presentations, the awareness of primary care physicians regarding these pathologies plays a crucial role in the diagnostic and referral processes.

Early diagnosis reduces disease-related morbidity and mortality; timely referral of appropriate patients to endocrinology or related specialties directly impacts treatment success. Therefore, at the primary care level, the following are important:

- Identification of at-risk patient groups (resistant hypertension, hypokalemia, unexplained weight changes, paroxysmal symptoms).
- Correct and timely utilization of simple and accessible screening tests.
- Appropriate interpretation of hormonal assessment results.
- Careful analysis of imaging findings for malignancy and functional activity.
- Recommendations;
- Education and Awareness Enhancement: Continuous medical education programs focusing on the recognition of adrenal pathologies in family medicine and internal medicine practice should be supported.
- Simplification and Implementation of Diagnostic Algorithms: Diagnostic steps, particularly for common conditions such as adrenal incidentaloma, Cushing's syndrome, and primary aldosteronism, should be integrated into primary care.
- Multidisciplinary Coordination: Strong communication networks should be established with endocrinology, radiology, nephrology, cardiology, and surgical branches, and diagnostic and treatment processes should be conducted through this collaboration.
- Patient Education and Follow-Up: Diagnosed patients or those under surveillance should be informed about medication adherence,

complication monitoring, and lifestyle modifications, and they should be followed up regularly.

- Supportive Role of Health Policies: The accessibility of hormone tests and imaging modalities used in the diagnosis and treatment of endocrine diseases should be increased."

In conclusion, the management of adrenal gland diseases can be effectively carried out at the primary care level through strong clinical suspicion, the selection of appropriate diagnostic tests, and timely referral. This approach will not only improve individual patient outcomes but also reduce the long-term burden on the healthcare system.

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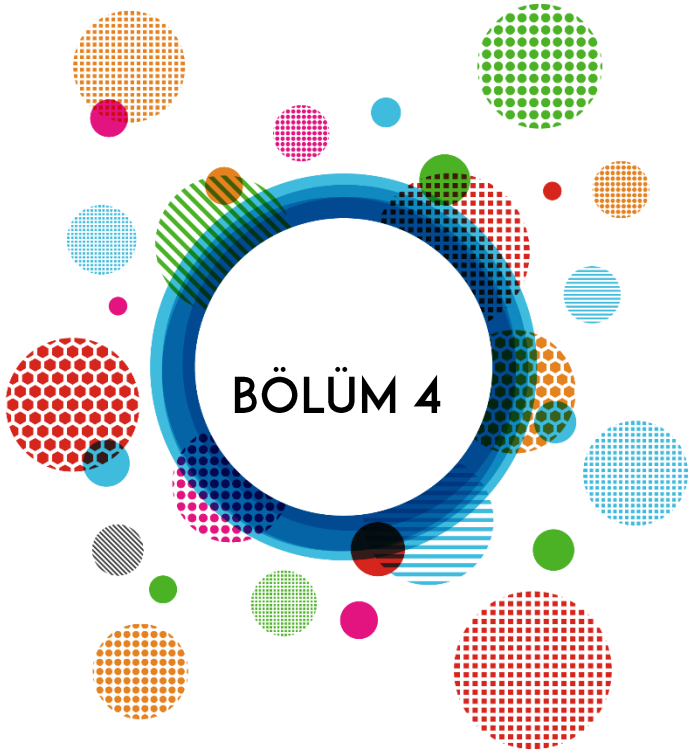

Approach to Pituitary Gland Disorders in Primary Care

***Recep Aktaş*[1]**

[1] Uzm.Dr. / Medical Doctor, Uşak Training and Research Hospital,
ORCID: 0000-0002-5576-6623

1. Introduction

As the master regulator of the endocrine system, the pituitary gland coordinates the functions of many peripheral endocrine organs through neuroendocrine connections with the hypothalamus. Adrenocorticotropic Hormone (ACTH), Thyroid Stimulating Hormone (TSH), Growth Hormone (GH), Prolactin (PRL), Follicle Stimulating Hormone (FSH) and Luteinising Hormone (LH) are released from the anterior pituitary. Together with Antidiuretic Hormone (ADH) and oxytocin released from the posterior pituitary gland, it plays a fundamental role in maintaining homeostasis (Gounden et al., 2023). Pathologies of the pituitary gland may be mostly asymptomatic or may first appear in primary care with nonspecific findings such as headache, visual disturbances, menstrual irregularities, loss of libido, infertility and fatigue (Jaursch-Hancke et al., 2021). The fact that these symptoms are common and related to different systems may make it difficult to recognise pituitary pathologies and cause delays in diagnosis. In this respect, it is of great importance for primary care physicians to comprehend the basic anatomical structure, physiopathological processes and clinical features of the pituitary gland and to use this knowledge effectively in clinical practice in terms of early diagnosis and referral.

Primary healthcare providers should be able to manage basic hormonal evaluations, appropriate laboratory analyses and clinical prioritisation processes before imaging by anticipating possible pituitary gland-derived endocrinopathies. Early diagnostic approach in individuals with suspected pituitary dysfunction can prevent secondary target organ damage and directly affect the patient's prognosis. In addition, lesions such as pituitary adenoma may require emergency intervention with mass effects in some cases, and in this context, primary care physicians should be competent in emergency referral decisions (Esquenazi et al., 2017). In this chapter, starting from the structural and functional characteristics of the pituitary gland, common pituitary diseases, clinical clues, diagnostic algorithms and management strategies in primary care will be discussed in detail. Thus, it is envisaged to increase the effectiveness of the primary care approach in the diagnosis and treatment of pituitary diseases.

2. Anatomy and Physiology of the Pituitary Gland

The pituitary gland is an endocrine organ weighing approximately 0.5 grams, located in the bony structure called sella turcica. Anatomically, it consists of two separate parts, the adenohypophysis (anterior lobe) and the neurohypophysis (posterior lobe); these two structures develop from embryologically different

origins. The adenohypophysis secretes six different trophic hormones by responding to hypothalamic secretory hormones through the portal vasculature: ACTH, TSH, GH, PRL, FSH and LH. The neurohypophysis stores ADH and oxytocin synthesised in the hypothalamus via axonal transport and releases them into the systemic circulation when needed (Ilahi & Ilahi, 2022; Dorton, 2000).

The physiology of the pituitary gland is based on a complex system of hormonal control regulated by negative feedback mechanisms. For example, corticotropin-releasing hormone (CRH) released from the hypothalamus stimulates ACTH production. In this process, cortisol released from the adrenal cortex suppresses the release of CRH and ACTH through a negative feedback mechanism on the hypothalamus and pituitary. Similarly, TRH released from the hypothalamus promotes TSH release in the adenohypophysis. Thyroid hormones (T3 and T4) released from the thyroid gland inhibit the release of TRH and TSH through negative feedback on the hypothalamus and pituitary. In addition, hypothalamic gonadotropin-releasing hormone (GnRH) stimulates the release of LH and FSH from the pituitary gland. Steroid hormones released from the gonads regulate the release of GnRH, LH and FSH through negative feedback mechanisms on the hypothalamus and pituitary (Nikrodhanond et al., 2006).

The physiology of the pituitary gland is based on a complex system of hormonal control regulated by negative feedback mechanisms. For example, corticotropin-releasing hormone (CRH) released from the hypothalamus stimulates ACTH production. In this process, the adrenal cortex These mechanisms help to precisely regulate hormone levels to ensure homeostasis of the endocrine system. Disturbances in the regulatory mechanisms of the pituitary gland can lead to the development of various clinical pictures characterised by hyperfunction, hypofunction or mass effects. Therefore, the anatomical location and physiological functioning of the pituitary gland is of critical importance both in diagnostic processes and in the evaluation of systemic symptoms (Hershman & Beck-Peccoz, 2023).

3. Clinical Findings and Classification of Pituitary Diseases

The pituitary gland is a central endocrine organ that maintains hormonal balance. Pituitary disorders can cause a wide range of clinical symptoms with disruption of this balance. Pituitary disorders are generally classified as hyperfunction, hypofunction and symptoms due to mass effect.

Clinical Presentations:

1. Hyperfunction: This condition is usually caused by pituitary adenomas.

- Prolactinoma: It manifests with symptoms such as amenorrhoea and galactorrhoea in women and loss of libido and infertility in men.
- Acromegaly: Growth of hands and feet, facial features, diabetes and cardiovascular complications occur in adults due to excess growth hormone.
- Cushing's disease: Weight gain, hypertension and glucose intolerance are observed due to excess ACTH.

2. Hypofunction: Pituitary insufficiency may be partial or complete. Symptoms vary depending on the missing hormone:

- TSH deficiency: Causes symptoms of hypothyroidism such as fatigue, cold intolerance and weight gain.
- ACTH deficiency: Symptoms of adrenal insufficiency such as fatigue, hypotension and hypoglycaemia may develop.
- Gonadotropin deficiency: Menstrual irregularities in women, erectile dysfunction and infertility in men may be observed.

3. Mass Effects: Macroadenomas or other pituitary masses may cause visual field loss (especially bitemporal hemianopsia), headache and symptoms of cranial nerve compression (Araujo-Castro et al., 2020; Samarasinghe et al., 2014; Hanberg, 2005).

Classification: Pituitary disorders are usually classified as follows:

- Functional adenomas: Hormone-producing tumours (prolactinoma, GH/ACTH-secreting adenomas).
- Non-functional adenomas: These are tumours that do not produce hormones and are usually symptomatic with mass effect.
- Idiopathic pituitary insufficiency: Hypofunction that develops without a known structural or tumoural cause.
- Pituitary apoplexy: It is an acute picture that develops due to sudden haemorrhage or infarction and requires urgent intervention.

Pituitary disorders can present with a wide variety of symptoms and an effective diagnostic process should include hormonal and structural assessment of the patient. The clinical approach is based on the identification of the hormone deficiency or excess and the assessment of the mass effect (Jho et al., 2014; Guijt et al., 2022; Garcia-Feijoo et al., 2024).

4. Adrenocorticotropic Hormone (ACTH) Disorders and Diagnosis

ACTH is a polypeptide hormone secreted from the adenohypophysis region of the pituitary gland and is the main regulator of glucocorticoid secretion from the zona fasciculata of the adrenal cortex. Disorders in ACTH levels have clinical reflections as hyposecretion and hypersecretion.

ACTH deficiency (hypo-ACTHaemia) develops as a result of disruption of the hypothalamo-pituitary-adrenal axis and is usually characterised by secondary adrenal insufficiency. This condition results in the inability of the adrenal cortex to synthesise adequate levels of cortisol due to inadequate ACTH production by the pituitary gland. Mineralocorticoid synthesis is usually preserved in secondary adrenal insufficiency because regulation of these hormones is mainly provided by the renin-angiotensin system (Bornstein et al., 2016).

Elevated ACTH is usually seen as part of endogenous hypercortisolism. One of the most common causes is pituitary-induced Cushing's disease, in which a pituitary adenoma secretes ACTH, driving the adrenal glands to overproduce cortisol. The other possibility is ectopic ACTH syndrome, in which non-pituitary tumours such as pancreas, thyroid or lung produce ACTH. These pictures are associated with systemic findings such as persistent hypertension, hyperglycaemia and muscle weakness. Diagnosis is based on high-sensitivity laboratory tests as well as dynamic tests and imaging modalities (Lacroix et al., 2015; Arlt & Allolio, 2003).

The diagnostic process usually starts with measurement of basal ACTH and cortisol levels. ACTH stimulation test is a reliable method used in the diagnosis of adrenal insufficiency. High dose dexamethasone suppression test helps to differentiate Cushing's disease from ectopic ACTH syndrome. In addition, invasive methods such as inferior petrosal sinus catheterisation are used to determine the source of ACTH. These tests are particularly important for treatment planning. (Dogra & Vijayashankar, 2024; Andrioli et al., 2006).

5. Hyperprolactinaemia: Causes and Evaluation Pathway

Hyperprolactinaemia is a condition in which the hormone prolactin in the blood exceeds normal reference ranges and may be due to various physiological, pharmacological or pathological causes. The most common physiological causes include pregnancy, breastfeeding and stress (Holt, 2008). Pathological causes include prolactin-producing pituitary adenomas, prolactinomas, hypothalamic lesions and hypothyroidism. In addition, some antipsychotic and antidepressant

drugs may increase prolactin levels with their dopamine antagonist effect (Malik et al., 2019)

The evaluation of hyperprolactinaemia requires a systematic approach and the patient's clinical history is critical in this process. Initially, medications should be questioned and a pregnancy test should be performed (Glezer et al., 2024). In addition, hypothyroidism should be excluded by measuring TSH level (Frieze et al., 2002).

Magnetic resonance imaging (MRI) is the main diagnostic method for the detection of pituitary adenomas in the evaluation of hyperprolactinaemia. Microadenomas (<10 mm) are frequently asymptomatic and are usually detected incidentally during routine evaluations, whereas macroadenomas (>10 mm) may compress the optic nerves and cause significant symptoms such as visual loss and headache. MRI findings play a critical role in treatment planning by providing detailed information about the size and extent of the tumour. In T2-weighted MRI examinations, the signal characteristics and homogeneity of prolactinomas may be helpful in predicting response to dopamine agonists; for example, tumours showing heterogeneous T2 signal have been reported to have a lower success rate in hormonal response (Burlacu et al., 2019)

Hyperprolactinaemia is an endocrine disorder that may develop due to many causes and systematic evaluation is essential for accurate diagnosis. Evaluation of clinical history, laboratory tests and imaging methods together is guiding in the diagnosis. Hormonal balance can be achieved and the quality of life of patients can be improved with agent-directed treatment. The approach to hyperprolactinaemia requires a multidisciplinary approach.

6. Diagnosis of Hypogonadism And Its Importance In Primary Health Care

Hypogonadism is an endocrine disorder characterised by inadequate production of sex hormones in men and women. This condition stands out as a common but frequently undiagnosed clinical problem in primary health care services. Inadequate production of sex hormones may lead to systemic effects such as infertility, osteoporosis, loss of libido and decreased muscle strength. In men, hypogonadism may be associated with testicular dysfunction (primary hypogonadism) or hypothalamo-pituitary axis disorders (secondary hypogonadism). Primary hypogonadism develops as a direct result of testicular dysfunction, whereas secondary hypogonadism results from dysfunction of the hypothalamus or pituitary gland (Darby & Anawalt, 2005). In women, hypogonadism is characterised by clinical symptoms such as amenorrhoea and

early menopause. It is vital for primary care physicians to be able to recognise the symptoms of hypogonadism and perform appropriate diagnostic tests for early diagnosis and treatment. Low serum testosterone levels measured in the morning and the presence of symptoms of hypogonadism are essential in the diagnostic process. In addition, assessment of serum LH and FSH levels is helpful in determining whether hypogonadism is primary or secondary. Early diagnosis and treatment play a critical role in preventing the long-term complications that hypogonadism can lead to (Ross & Bhasin, 2016).

7. Diagnostic Process in Patients with Suspected Hypogonadism

In case of suspicion of hypogonadism, the primary care physician should initiate the diagnostic process by first evaluating the patient's clinical symptoms. In symptomatic male patients, it is recommended to measure total testosterone levels twice in the morning. In female patients, it is important to evaluate estrogen levels, especially in the presence of amenorrhoea. In addition, LH and FSH measurements help to distinguish whether hypogonadism is of hypergonadotropic or hypogonadotropic origin. In the diagnostic process, it is also important to evaluate prolactin and TSH levels along with these hormone profiles, as hyperprolactinaemia and hypothyroidism are among the conditions that can lead to hypogonadism. Imaging modalities can be used especially to detect pituitary gland lesions. MRI is recommended to rule out pituitary adenomas, especially in the presence of hyperprolactinaemia (Ascoli & Cavagnini, 2006; Sibal et al., 2002). This holistic approach helps to identify the underlying causes of hypogonadism and plan appropriate treatment strategies.

8. Evaluation of Hormone Replacement in the Treatment of Hypogonadism

Testosterone replacement therapy (TRT) can be used to relieve the symptoms of hypogonadism and improve quality of life. Cardiovascular risks, prostate health and haematocrit levels should be carefully monitored before and during treatment. TRT does not increase the risk of cardiovascular events in the short and medium term, but there is insufficient data on its long-term safety. It has also been reported that TRT may increase the risk of benign prostatic hyperplasia and cause elevated haematocrit levels (Gagliano-Jucá & Basaria, 2019). Estrogen replacement therapy in women can be used to alleviate postmenopausal osteoporosis and vasomotor symptoms, but caution should be exercised because of the risk of endometrial hyperplasia. It is therefore important for primary care physicians to assess the risk-benefit balance of hormone replacement therapies on a patient-by-patient basis (Harper-Harrison, Carlson, & Shanahan, 2024).

The role of primary health care services in the diagnosis and management of hypogonadism is critical in both diagnosis and long-term follow-up. In this context, systematic questioning of symptoms, appropriate laboratory tests and referral of patients to specialist centres are essential. In addition, primary care physicians should follow current guidelines and be aware of new developments in hormone therapies. Effective and timely intervention can prevent the adverse consequences of hypogonadism and improve the quality of life of patients.

9. Approach to Pituitary Adenomas in Primary Care

Pituitary adenomas, although generally benign, can cause serious clinical conditions due to hormonal imbalances and mass effects. Therefore, it is crucial for primary care physicians to recognize pituitary adenomas early and refer patients appropriately. Prominent symptoms include headache, visual disturbances, menstrual irregularities, loss of libido, and galactorrhea. Family physicians who are aware of these symptoms can detect symptomatic forms of pituitary adenomas at an early stage.

When establishing referral criteria, particular attention should be paid to functioning adenomas with hormonal activity. For instance, symptoms related to hypercortisolism, acromegaly, and prolactinomas require further investigation and referral to endocrinology. In the presence of visual field loss or signs of optic nerve compression, urgent neurosurgical evaluation is indicated. Furthermore, even in asymptomatic cases, early referral is recommended for lesions that have reached macroadenoma size (Tritos et al., 2022).

In cases evaluated in primary care, initial screening should be performed using a basic hormonal profile, including prolactin, IGF-1, cortisol, TSH, FT4, LH, and FSH, and pituitary MRI imaging should be requested. In individuals with detected hyperprolactinemia, after excluding secondary causes, referral to endocrinology is recommended for the evaluation of a possible prolactinoma. Hormonal assessment is essential in patients presenting with nonspecific symptoms such as menstrual irregularities, infertility, and erectile dysfunction. Although these symptoms are often overlooked by patients, they can be identified through careful history-taking (Melgar et al., 2016).

Early recognition and referral of pituitary adenomas is critical for reducing complications and initiating treatment promptly. Increasing the awareness of primary care physicians on this subject will positively impact patient prognosis.

a. Imaging Requirements: When and Which Method?

Imaging techniques play a critical role in the diagnosis and follow-up of pituitary adenomas. MRI is the gold standard for detailed anatomical evaluation of the pituitary region, enabling precise determination of the size, location, and relationship of adenomas with surrounding structures. MRI has clear advantages over computed tomography (CT), particularly due to its superior soft tissue contrast and multiplanar imaging capabilities (Guy et al., 1991).

Imaging is indicated in patients with clinical or biochemical suspicion of a pituitary adenoma. MRI is especially recommended in cases of hormone excess syndromes such as hyperprolactinemia, acromegaly, and Cushing's disease, as well as in cases presenting with signs of hypopituitarism. Additionally, MRI should be used to evaluate the pituitary region in patients with unexplained headache, visual disturbances, or other neurological symptoms (Gruppetta, 2022).

Pituitary lesions incidentally discovered during imaging for unrelated reasons are referred to as pituitary incidentalomas. Initial MRI should assess the lesion's size and anatomical relationships. For macroincidentalomas (≥10 mm), follow-up MRI is recommended at 6 months and then annually. For microincidentalomas (<10 mm), a repeat MRI should be performed within the first year, followed by imaging every 1–2 years. If the lesion is in proximity to the optic nerve or chiasm, visual field testing should be conducted at baseline and at regular intervals thereafter. Hormonal evaluation, particularly for macroincidentalomas, should be performed initially and annually. Throughout follow-up, tumor growth, hormonal activity, and symptom development should be monitored to assess the need for surgical intervention (Freda et al., 2011; Paschou et al., 2016).

The frequency and modality of imaging should be individualized based on tumor size, growth rate, presence of symptoms, and hormonal activity. In particular, for lesions located near the visual pathways, urgent MRI evaluation is required if neurological symptoms develop.

b. Referral Criteria to Endocrinology and Follow-up Plan

Referral to an endocrinologist in the management of pituitary adenomas should be based on the patient's clinical status and tumor characteristics. Patients with hormone-secreting adenomas (prolactinomas, acromegaly, Cushing's disease) or signs of hypopituitarism should be promptly referred for endocrine evaluation and treatment. In addition, patients with tumor-related compression

symptoms due to mass effect also require referral due to the need for a multidisciplinary approach.

The follow-up plan should be tailored according to the tumor's functional status, size, and growth tendency. In non-functioning microadenomas, annual clinical and hormonal evaluations may be sufficient after the initial assessment. In macroadenomas, tumor growth should be monitored with MRI 6 months after diagnosis and then annually. In patients receiving radiotherapy, due to the risk of developing hypopituitarism, hormonal evaluation is recommended at 6 months post-treatment and annually thereafter. For tumors located near the visual pathways, regular ophthalmologic examinations should be conducted both at baseline and during follow-up (Pekic et al., 2024; Vie & Raverot, 2019).

c. Management of Pituitary Adenomas in Women Planning Pregnancy

The management of pituitary adenomas in women planning pregnancy requires special attention for the safety of both mother and fetus. These patients should be monitored by an endocrinologist before and during pregnancy, and evaluated by a multidisciplinary team when necessary. Close monitoring is important during pregnancy for potential tumor growth or hormonal changes. In women with functioning adenomas such as prolactinomas, pre-pregnancy treatment with dopamine agonists can reduce tumor size and lower the risk of growth during gestation (Taieb et al., 2024).

In women with microprolactinomas, dopamine agonists are usually discontinued once pregnancy is confirmed, and patients are monitored for symptoms. In cases of macroprolactinomas, if the tumor is close to the optic chiasm or has a high growth potential, continuation of dopamine agonists during pregnancy may be considered. In non-functioning macroadenomas, surgical treatment may be recommended before conception, depending on tumor size and location (Luger et al., 2021).

If symptoms such as headache, visual disturbances, or other neurological signs occur during pregnancy, urgent MRI evaluation is warranted. If serious symptoms such as visual field loss develop, transsphenoidal surgery may be required during pregnancy. Therefore, women with pituitary adenomas who are planning pregnancy must be managed with an individualized follow-up and treatment plan.

10. Diagnostic Strategies for Hypopituitarism in Pituitary Disorders

Hypopituitarism is a clinical syndrome characterized by insufficient production of one or more hormones of the pituitary gland. This condition may involve a deficiency of all pituitary hormones or present as an isolated hormone deficiency. The diagnostic process includes a detailed evaluation of clinical symptoms, laboratory tests, and imaging studies (Schneider et al., 2007).

Clinical signs and symptoms vary depending on the specific hormone deficiency. For example, corticotropin deficiency may manifest as fatigue and hypotension, while thyrotropin deficiency can present with weight gain and cold intolerance. Due to the typically slow progression of hypopituitarism, these symptoms are often subtle, which may lead to delayed diagnosis. Therefore, a high index of clinical suspicion is essential for diagnosis (Fleseriu et al., 2024).

Laboratory diagnosis involves measuring baseline pituitary hormone levels in morning fasting blood samples, assessed alongside target organ hormone levels. In some cases, dynamic tests such as the insulin tolerance test or ACTH stimulation test may be necessary. Additionally, pituitary MRI should be performed to investigate potential structural abnormalities (Toogood & Stewart, 2008).

Since delayed diagnosis increases the risk of morbidity and mortality, it is important to screen all individuals at risk for hypopituitarism in the context of pituitary disease. In particular, individuals with pituitary tumors, head trauma, or a history of cranial radiotherapy should undergo more aggressive diagnostic strategies (Prabhakar & Shalet, 2006). Early diagnosis allows for timely hormone replacement therapy, which can significantly improve quality of life and reduce complications.

11. Diagnosis and Referral Process of Pituitary Disorders in Primary Care

Primary care services play a critical role in the early diagnosis and appropriate referral of diseases. The recognition of rare but clinically significant conditions such as pituitary disorders depends on the careful evaluation by primary care physicians. Pituitary tumors often present with nonspecific symptoms; therefore, a systematic assessment of symptoms is essential for timely referral. In patients presenting with unexplained headache, menstrual irregularities, loss of libido, or visual disturbances, pituitary pathology should be considered. Additionally, slowly progressing symptoms due to hypopituitarism may be mistaken for general complaints such as depression or fatigue (Shukla et al., 2021).

An effective diagnostic process in primary care relies on a detailed medical history and thorough physical examination. During clinical evaluation, signs of hormonal imbalance should be considered, and appropriate laboratory tests should be planned. Assessment of hormone levels such as prolactin, ACTH, TSH, and insulin-like growth factor 1 (IGF-1) can aid in detecting pituitary dysfunction. Clues obtained from routine blood tests can be decisive in initiating further investigations. Furthermore, visual field assessment and evaluation of optic symptoms are critical when a mass lesion is suspected. In such cases, urgent referral to endocrinology or neurology specialists is required (Gendy & Rashid, 2017; Molitch, 2017).

The referral process is not limited to transferring suspected cases; it also enables the initiation of multidisciplinary follow-up. Pituitary disorders often require neuroendocrine monitoring and may involve various treatment modalities including surgery, medical therapy, or radiotherapy. Therefore, the primary care physician is expected to contribute not only to diagnosis but also to the follow-up process. Referring patients for scheduled follow-up visits, assessing treatment adherence, and early recognition of potential complications are essential aspects of comprehensive care.

12. Imaging and Laboratory Methods

a. Magnetic Resonance Imaging (MRI)

Contrast-enhanced MRI is the primary imaging modality for the evaluation of pituitary gland disorders. MRI is particularly sensitive for detecting microadenomas smaller than 1 cm. Sequential and dynamic contrast-enhanced images help distinguish adenomas from normal pituitary tissue. MRI also provides rapid diagnostic information in emergency situations such as pituitary apoplexy. Advanced imaging protocols help delineate tumor boundaries clearly, facilitating surgical planning. Multiparametric MRI techniques are valuable in differentiating adenomas from cysts, hypophysitis, and metastatic lesions (Davis et al., 1994).

b. Hormonal Profile Assessment

Since the pituitary gland is responsible for secreting multiple vital hormones, a detailed hormonal analysis is essential for functional evaluation. Hormone levels including prolactin, GH, IGF-1, ACTH, TSH, FSH, and LH are used to detect hypersecretion or hyposecretion syndromes. For example, elevated prolactin levels are diagnostic in suspected prolactinomas. Hormone samples should be collected in the morning, accounting for biological variation. Modern

immunoassay-based analytical systems provide rapid and reliable results. These biochemical evaluations also play a key role in treatment monitoring, not just in diagnosis (Schilbach & Bidlingmaier, 2019).

c. Endocrine Dynamic Testing (Stimulation/Suppression Tests)

In some pituitary hormone disorders, basal levels alone may be insufficient for diagnosis, and dynamic testing becomes necessary. Low- and high-dose dexamethasone suppression tests are used in ACTH excess, while arginine and insulin tolerance tests are applied in growth hormone deficiency. These tests assess the hormonal response to physiological stimulation or suppression. They play a crucial differential role, especially in diagnosing conditions such as Cushing's disease and acromegaly. When performed with appropriate timing and technique, these tests significantly enhance diagnostic accuracy (Caputo et al., 2022; Vilar et al., 2008).

d. Histopathological and Genetic Evaluation

Definitive diagnosis of pituitary masses is achieved through pathological examination following surgical excision. Immunohistochemical methods are used to identify which hormones are synthesized by tumor cells. Markers such as the Ki-67 proliferation index and p53 expression help assess tumor aggressiveness. Additionally, certain subtypes of adenomas have a genetic basis, with mutations in USP8 (ubiquitin-specific protease 8), GNAS (guanine nucleotide-binding protein alpha subunit), and AIP (aryl hydrocarbon receptor-interacting protein) shown to play a role. These molecular-level analyses may also guide therapeutic strategies (Guaraldi et al., 2024).

13. Treatment Methods

Treatment approaches for pituitary disorders vary depending on factors such as tumor presence, hormone excess, or deficiency. In one of the most common pituitary conditions, prolactinoma, medical therapy with dopamine agonists especially cabergoline and bromocriptine is effective in most patients. In disorders caused by growth hormone excess such as acromegaly, somatostatin analogs, GH receptor antagonists, and dopamine agonists are frequently used (Inder & Jang, 2022; Neggers et al., 2016; Ma et al., 2020).

Surgical treatment is often the first-line approach in cases of large pituitary tumors such as macroadenomas or in drug-resistant cases. Endoscopic transsphenoidal surgery is a widely used minimally invasive technique for removing pituitary adenomas, associated with relatively low complication rates. Postoperative normalization of hormone levels and improvement in visual

symptoms are commonly observed. However, in cases where surgery is inadequate or the tumor recurs, radiotherapy becomes necessary. Conformal radiotherapy and stereotactic radiosurgery can deliver high-dose targeted radiation, improving tumor control (Shaaban et al., 2024; Kowalchuk et al., 2023).

In ACTH deficiency, replacement therapy with hydrocortisone or equivalent glucocorticoids is vital to prevent adrenal crisis. In TSH deficiency, levothyroxine is used for thyroid hormone replacement; however, adrenal insufficiency should be ruled out before initiating levothyroxine, as thyroid hormones increase cortisol metabolism and may precipitate an adrenal crisis. In gonadotropin deficiencies, testosterone is replaced in men, while estrogen and progesterone are administered in women. It's important to note that oral estrogen can increase cortisol-binding globulin (CBG) levels, potentially raising total cortisol and complicating the diagnosis of ACTH deficiency (Donald et al., 2024). In growth hormone deficiency, GH replacement can improve quality of life and body composition; however, GH therapy can affect cortisol and thyroid hormone metabolism, requiring dose adjustments of hydrocortisone and levothyroxine (Fierro & Hoffman, 2020). Hormone replacement therapy is typically lifelong and requires regular clinical and laboratory monitoring (Alexandraki & Grossman, 2019; Smith, 2004).

In recent years, personalized medicine approaches have gained prominence in the treatment of pituitary diseases. Targeted treatment options based on the genetic and molecular profiles of tumors are being explored, with promising results especially in treatment-resistant adenomas. Moreover, lifestyle modifications and psychosocial support have become important components of care, particularly in patients with chronic hypopituitarism. Overall, a multidisciplinary approach is essential in the treatment of pituitary disorders, involving endocrinologists, neurosurgeons, radiation oncologists, and psychologists to create individualized and effective treatment plans.

14. Psychosocial Management of Pituitary Disorders: The Role of Primary Care Physicians

During follow-up, patients' symptom progression, hormonal levels, and imaging findings should be evaluated through a multidisciplinary approach. The response to medical treatment—particularly in endocrine disorders such as prolactinomas and Cushing's disease—must be closely monitored. Patient education, treatment adherence, and quality of life are essential components in the care of all pituitary disorders. Regular follow-up in primary care plays a

critical role in both preventing complications and identifying the need for early surgical intervention. This facilitates a patient-centered, holistic approach to the management of pituitary diseases.

Chronic pituitary disorders can significantly impact not only patients' physiological health but also their psychosocial functioning. Conditions such as hypopituitarism and acromegaly, due to long-standing hormonal deficiencies or excesses, may lead to neuropsychiatric symptoms including depression, anxiety, and social isolation. Therefore, a comprehensive approach addressing both medical treatment and patients' psychological and social needs is required (Biermasz, 2019).

Psychosocial support plays a vital role in improving quality of life and enhancing treatment adherence in these patients. Studies have shown that psychological counseling, group therapies, and social support programs can lead to a reduction in depressive symptoms, an increase in self-efficacy, and higher treatment compliance. Especially in conditions like acromegaly and Cushing's disease, psychosocial interventions can help mitigate self-esteem issues arising from changes in physical appearance (Santos et al., 2021).

In the treatment process of chronic pituitary disorders, achieving hormonal balance alone is not sufficient; psychosocial needs must also be addressed comprehensively. Psychosocial support interventions improve patients' psychological adaptation, enhance their motivation for treatment, and significantly improve their overall quality of life. Structured psychosocial support models integrated into clinical practice should be an indispensable component of the multidisciplinary approach in managing pituitary disorders (Siegel et al., 2021).

15. Conclusion and Recommendations

Recognizing pituitary disorders in primary healthcare is a critical step that directly affects disease prognosis and patient quality of life. Due to their non-specific symptoms, pituitary diseases are often overlooked by primary care physicians. Early detection of conditions such as hypopituitarism and pituitary adenomas is essential to prevent neurological and endocrine complications. Physicians need to be made aware of key clinical signs, such as headaches, visual disturbances, loss of libido, and fatigue, to ensure early suspicion and investigation. Additionally, the early initiation of advanced diagnostic tools such as hormonal assessment and brain imaging can accelerate the diagnostic process.

Training programs targeting primary healthcare workers can greatly enhance the recognition of pituitary disorders. Given the rarity of these conditions, simplified summaries of clinical guidelines can support physicians in daily practice. Establishing a rapid referral system to endocrinology for diagnosed cases enables earlier initiation of treatment.

In conclusion, effective management of pituitary disorders in primary care requires raising awareness, improving healthcare staff education, optimizing referral pathways, and adopting a multidisciplinary approach to strengthen the delivery of integrated healthcare services.

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