BÖLÜM
11

PRİMER HİPERPARATİROİDİ: PATOGENEZ

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Giriş

Primer hiperparatiroidi (PHPT), hiperkalsemi ve artmış veya uygunsuz olarak normal parathormon (PTH) düzeyleri ile karakterize olan ve sık görülen bir endokrin bozukluktur. Bir veya birden çok paratiroid bezinde artmış PTH sekresyonu sonucu oluşur (1). Tanı biyokimyasal olarak konulur. Hiperkalsemili bir hastada uygun olmayan şekilde normal (>20 pg/ml) olan PTH seviyeleri PHPT tanısı ile uyumludur. Tekrarlanan laboratuvar testlerinde serum kalsiyum seviyeleri aralıklı olarak normal aralığa düşebilir; bu bulgu, hiperkalseminin 'tekrarlayan paterni' belirgin olduğu sürece PHPT tanısı ile uyumludur (1).

PHPT'li hastaların çoğunda tek adenomatöz (%80) veya çoklu hiperplastik (%15 ila %20) paratiroid dokusu vardır. Multiglandüler hastalık iki ve çok nadiren üç adenom olarak da kendini gösterebilir. Paratiroid karsinomu nadirdir ve tüm PHPT vakalarının <%1'ini oluşturur(2). Hiperkalseminin paratiroid dışı nedenleri (malignite veya granülomatöz hastalık gibi) baskılanmış PTH seviyeleri ile ilişkilidir. Paratiroid olmayan bir tümörden ektopik PTH salgılanması, nadiren geç evre malignitelerde belgelenmesine rağmen oldukça nadirdir (1). Tipik olarak yaklaşık on yıl daha genç olan hastalar, çok daha yüksek serum kalsiyum ve PTH seviyeleri ile başvurduğunda paratiroid kanseri şüphesi artmalıdır. Bu hastalarda, böbrek ve iskelet tutulumu sıklıkla bulunur(3).

Bu bölümde PHPT'nin gelişiminden sorumlu olan patogenetik mekanizmalar gözden geçirilecektir.

Primer Hiperparatiroidide Patogenez

Paratiroid adenomlarına paratiroid hücrelerinin DNA'sındaki mutasyonlar neden olur. Bu mutasyonlar, etkilenen hücrelere, normal hücrelere göre çoğalma veya hayatta kalma avantajı sağlar. Bu avantajın bir sonucu olarak, belirli bir paratiroid hücresinin soyundan gelenler, bir hücre klonu, bir

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Tablo 1: PHPT'nin kalıtımsal formları

Ailesel sendrom	Klinik manifestasyonlar	Gen (protein)	Kalıtım paterni
MEN 1	PHPT (%95), ön hipofiz adenomları (%30), pankreas nöroendokrin tümörleri (%40); diğer özellikler arasında adrenal adenomlar, karsinoid, lipomlar, anjiyofibromlar ve kollajenomlar yer alabilir	MEN1 (menin)	Otozomal dominant
MEN 2A	Medüller tiroid kanseri (%90), feokromositoma (%50), PHPT (%20)	RET (proto-oncogene c-Ret)	Otozomal dominant
MEN 4	PHPT (~80%), ön hipofiz tümörleri (~%40), pankreas nöroendokrin tümörleri; diğer özellikler karsinoid, adrenokortikoid tümörler, tiroid tümörleri, üreme organı tümörleri ve renal anjiyomiyolipomları içerebilir.	CDKN1B (p27)	Otozomal dominant
AIPHPT	İzole PHPT	MEN1 (menin) CASR (CASR) GCM2 (GCM motif protein 2, hGCMb olarak da)	Otozomal dominant
Hiperparatiroid-çene tümörü sendromu	PHPT (%80), sıklıkla paratiroid karsinomu (>%15), çene tümörleri (>%30); diğer özellikler arasında böbrek anormallikleri, rahim tümörleri, pankreas adenokarsinomu, testiküler mikst germ hücreleri ve Hürthle hücreli tiroid adenomları sayılabilir.	CDC73 (HRPT2 olarak da bilinir; parafibromin)	Otozomal dominant

AIPHPT, ailesel izole primer hiperparatiroidi; MEN, multipl endokrin neoplazi; PHPT, primer hiperparatiroidi.

etkiye sahiptir. MEN1 geni, sporadik vakalarda olduğu kadar AIPHPT'de önemli bir rol oynar ve bu genin protein ürününün işlevi ile ilgili çalışmalar devam etmektedir. CDKI genindeki mutasyonlar sporadik paratiroid adenomlarının gelişimine katılabilir. Tüm bu yeni keşifler, var oldukları neredeyse kesin olan paratiroid tümörünü tetikleyen diğer genlerin tanımlanmasını kolaylaştıracak gibi görünmektedir. Anormal paratiroid hücre proliferasyonu ile anormal hormonal düzenleyici fonksiyon arasındaki ilişkinin moleküler temelinin ve ayrıca paratiroid hastalığına özgü diğer problemlerin yakında açıklanabileceği ile ilgili umutlanmak için önemli göstergeler bulunmaktadır(8).

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