BÖLÜM 67

NÖROKÜTAN HASTALIKLARDA GENETİK VE GENETİK DANIŞMANLIK

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GİRİŞ

Fakomatozlar olarak da bilinen nörokütan hastalıklar cildi ve merkezi sinir sistemini belirgin olarak etkileyen heterojen bir grup hastalıktır. Bu hastalıkların çoğu ailesel geçiş gösterir ve ilkel ektodermin gelişimindeki genetik kusurlardan kaynaklanırlar.[1] Nörokütan hastalıklar genellikle otozomal dominant olarak kalıtılırlar ancak otozomal resesif veya X'e bağlı kalıtılan türleri de vardır. Diğer taraftan sporadik vakalar da görülebilmektedir.[2] Son yirmi yılda, İnsan Genom Projesi ve diğer araştırma konsorsiyumları aracılığıyla gen tanımlama çabalarında önemli bir artış olmuştur. Genetik teknolojilerin gelişimi ile birlikte birçok nörokütan hastalığın altında yatan moleküler mekanizmalar aydınlatılabilmiş böylece hastalara daha isabetli tanılar konulabilmiştir. Ayrıca ilişkili komplikasyonlara yönelik biyolojik tabanlı tedavi seçeneklerinin geliştirilmesine de katkıda bulunulmuştur.[2]

Bu hastalıkların önemli bir kısmı RAS/mitojen-aktive protein kinaz (MAPK) sinyal yolağını etkiler ve aynı zamanda RASopatiler olarak da adlandırılan grupta da yer alır. Bu yolak hücre çoğalması, farklılaşması ve hücrelerin hayatta kalmasında temel rol oynar. Nörofibromatozis tip 1, Legius sendromu ve çoklu lentigolar ile birlikte Noonan sendromu (eski adı LEOPARD sendromu) RAS/MAPK yolağının etkilendiği nörokütan hastalıklara örnektir.[3] Bir diğer sık gözlenen nörokütan hastalık tüberoskleroz kompleksi ise "rapamisinin memeli hedefi" (mTOR) sinyal yolağındaki aktivite artışı sonucu ortaya çıkar.[4]

Nörokütan hastalıklarda, hastalığın kalıtsal olup olmadığını belirlemek, kalıtım modelini netleştirmek, aile içindeki değişkenlikleri öğrenmek ve hastalığın doğal seyri hakkında bilgi sağlamak amacıyla alınan aile öyküsü tanı için kritik öneme sahiptir. Klinik bulguları iyi tanımlayarak ön tanılar oluşturmak ve bunlara özgü genetik testleri belirlemek daha verimli olmaktadır. Bir fenotipin kalıtsal olup olmadığının belirlenmesi, altta yatan genetik sebebin tespit edilmesi diğer aile üyeleri ve gelecek nesiller için risk tahmini yapmak ve genetik danışmanlık için elzemdir.

Bu bölümde başlıca, sık görülen nörokütan hastalıklar olan nörofibromatozis tip 1, nörofibromatozis tip 2, tüberoskleroz kompleksi ve Sturge-Weber sendromunun genetik sebepleri, moleküler test seçenekleri, genotip-fenotip korelasyonu ve bu hastalıklarda genetik danışmanlık anlatılacaktır.

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fertilizasyon sonrası oluştuğu için probandın kardeşlerinde GNAQ mutasyonu olma ihtimali genel popülasyonla aynıdır, risk artışı beklenmez.

SWS'de dikey bir ailesel geçişi gösteren güçlü kanıtlar bulunmamaktadır. Somatik mozaisizm nedeniyle teorik olarak probandın çocuklarına mutasyonu aktarma ihtimali %50'den azdır. SWS'li 52 erişkinin dahil olduğu bir araştırmadaki katılımcıların çocuklarının hiçbirinde (çocuğu olan 10 hastadan toplam 20 çocukta) SWS'ye rastlanmamıştır.[83] Burada da görüldüğü gibi pratikte SWS'li bireylerin hastalığı çocuklarına aktarma ihtimali çok düşüktür.

SWS'de aile üyelerinin artmış bir risk taşıdığı bilinmediğinden, aile üyeleri için genellikle prenatal tanı gerekli değildir.

SONUÇ

Nörokütan hastalıklar tek başlarına nadir olsalar da bir grup olarak pediatri, nöroloji, dermatoloji ve tıbbi genetik hekimleri tarafından sıklıkla karşılaşılan klinik ve genetik olarak heterojen geniş bir sendrom yelpazesini temsil eder. Bu hastalıklarda sorumlu genlerdeki mutasyonlar tek baz değişimleri ya da küçük insersiyonlar/delesyonlar şeklinde olabileceği gibi azımsanmayacak ölçüde ekzonları hatta tüm geni içine alan büyük delesyonlar şeklinde gerçekleşebilir. Bu nedenle sadece dizi analizi yapmak tanı için her zaman yeterli olmamaktadır. Delesyon/duplikasyon analizlerini de içeren basamaklı genetik test uygulaması daha uygun bir yaklaşım olarak kabul edilmektedir.

Genetik teknolojilerdeki ilerlemeler, klinik özelliklerin tanımlanmasına, tanı kriterlerinin belirlenmesine ve bu karmaşık hastalıklar için tedavi seçeneklerinin ortaya çıkmasına yardımcı olmuştur. Prenatal tanı ve PGT seçenekleri sayesinde patojenik varyantın tanımlandığı ailelerde sonraki kuşaklara bu hastalıkların aktarılması engellenebilmektedir. De novo mutasyon oranlarının yüksekliği, mozaisizm ihtimali ve bazı sendromların sadece somatik mutasyonlarla sporadik olarak ortaya çıkması ise genetik danışmanlığı karmaşık hale getirmektedir.

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