BÖLÜM 97

SEREBELLUM VE BEYİN SAPININ HEREDODEJENERATİF HASTALIKLARI

Elif ACAR ARSLAN[1]

HEREDİTER ATAKSİLER

Giriş

Ataksi, serebellum ve yollarının bozukluğunun sonucu olarak motor inkoordinasyon sonucunda oluşur. [1] Ataksiler ya, doğuştan metabolik bozukluklardan veya doğuştan metabolik hastalık kaynaklı olmayan, ilerleyici dejeneratif ataksi nedeniyle oluşur. İlerleyici dejeneratif ataksiler, otozomal dominant, otozomal resesif, X'e bağlı ve mitokondrial hastalıklar sonucu olan ataksilerdir.

Otozomal Dominant Ataksiler: Bu grupta otozomal dominant ataksiler grubundan olan spinoserebellar ataksiler bulunmaktadır. Bugüne kadar 40'dan fazla tipi tanımlanmıştır. Bir kısmı tirnükleotid tekrar sayısından kaynaklanır. Bu tekrarlar gerek somatik gerek ise germline hücrelerde kararsızlığa yol açarak, hastalık oluştururlar. Bir sonraki jenerasyonlarda 'antisipasyon' özelliği nedeniyle, hastalığın daha erken yaşlarda olan, klinik yansımalarına neden olabilirler. Çocukluk yaş grubundan ziyade, daha çok erişkin yaş grubunda görülmektedir. Bu nedenle, bu yazı daha çok otozomal resesif ataksiler üzerine yoğunlaşmıştır.

Otozomal Resesif Ataksiler: Çocukluk çağı başlangıçlı olup, en sık bilinen alt grupları, Friedreich ataksisi, ataksi-telanjiektazi, ataksi okulomotor apraksi tip 1 ve tip 2'dir. Dört otozomal resesif ataksi, E vitamin eksikliği ile beraber olan ataksi, Refsum hastalığı, Co enzim Q10 eksikliğine bağlı ataksi ve serebrotendinömatoz ksantamatozis de otozomal resesif hastalıklar olup, tedavi şansları olan grupta oldukları için atlanılmaması gereken hastalıklardır.[2] Herediter atakilere genellikle serebellar atrofi eşlik eder. Bu grupta en sık olarak Friedreich ataksisi görülmektedir.

Friedreich Ataksisi

Herediter ataksiler, heterojen bir grup hastalık olup, en sık görüleni, Friedreich ataksisi olarak bilinmektedir. Frataxin geni 9. kromozomun uzun kolunda kodlanmaktadır. Hastaların çoğunda, frataxin geninin her iki alelinin intron 1'de GAA tekrar sayısının "ekspansiyonu" görülmektedir. GAA tekrarları, 66-100 arasındadır. [3,4] Normal alelde bu sayı genellikle 7-34 arasındadır.

Friedreich ataksisinin kliniğe yansıması da, GAA "ekspansiyonun" sayısına göre değişmektedir. Büyük GAA "ekspansiyonları",

[1] Doç. Dr., Karadeniz Teknik Üniversitesi Tıp Fakültesi, Çocuk Nörolojisi Kliniği, elifacararslan@gmail.com

Epizodik ataksi tip 6: SLC1A3 genindeki heterozigot mutasyondan kaynaklanır. Epizodik ataksi, migren, alternan hemipleji, nöbet gibi klinik olabilir. [49]

Epizodik ataksi tip 7 ise oldukça nadirdir.

TEDAVİ EDİLEBİLİR ATAKSİLER

Vitamin E eksikliği ile giden ataksi: Otozomal resesif olup, alfa tokoferol transfer protein genindeki patolojiden kaynaklanır. Yavaş ve ilerleyici ataksi, nöropati ile Friedreich ataksisine benzer. Bazı olgularda, retinitis pigmentoza da görülmektedir. [50,51] Malabsorbsiyona yol açan hastalıklarda da görülebilir. Yüksek doz E vitamini, nörolojik bulgularda düzelme sağlar.

Serebrotendinöz ksantamatozis: Otozomal resesif, ilerleyici nadir bir hastalıkdır. Mitokondrial sterol 27 hidroksilaz genindeki, safra asidi sentezindeki bloğa neden olan bir mutasyondan kaynaklanır. Ataksi, nöropati, katarakt, aşil tendondaki ksantomlar, ateroskleroz ile karekterizedir. Kolestanol, hastalıktaki, nörolojik toksisiteden sorumludur.

Refsum hastalığı: Refsum hastalığı, otozomal resesif ataksi grubunda olup, ihtiyozis, retinitis pigmentoza, nöropati ve ataksi ile karekterizedir. PHYH genindeki, mutasyondan kaynaklanır. Fitanik asidin yıkılmasındaki sorundan kaynaklanır. Diyette, fitanik asidin alımındaki kısıtlama, tedavide kullanılır.

Özet olarak, herediter ataksiler, otozomal dominant, otozomal resesif, X'e bağlı, mitokondrial ataksiler şeklinde sınıflandırılabilir. Otozomal dominant ataksiler, çocuklarda görece nadir olup, "antisipasyon" özelliği, dolayısı ile de, bir sonraki jenerasyonlarda, daha erken yaşlarda görülebilir. Otozomal resesif ataksilerinde, en sık görüleni, Friedreich ataksisi'dir. Derin tendon reflekslerinin alınmadığı olgularda, periferik nöropati, ekstremite ve yürüyüş ataksisi varlığında, kardiyolojik incelemede hipertrofik kardiyomiyopati saptanmasında, tanı, Friedreich ataksisi lehine değerlendirilmelidir. Frataxin geninde GAA üçlü tekrar "ekspansiyonu" ile olgunun genetik tanısı konulur. [52-53]

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olabilir. Saf ve komplike HSP olarak iki grupta olabilir. Pigmenter retinopati açısından, göz konsültasyonu önemlidir. Otozomal dominant HSP'lerin en sık bilinenleri HSP4 ve HSP3A'dır. Otozomal dominant HSP'ler, genellikle saf HSP'ye neden olurlar. Tedavide, fizik tedavi ve rehabilitasyon, iş-uğraşı terapisi önemlidir. Germe egzersizleri, spastisiteyi azaltmada ve denge ve güç kazanımı açısından önerilir. [13]

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hidrosefali, jeneralize beyaz cevher değişiklikleri ve diffüz kortikal anormallikler görülür. [41] Diğer nedenleri arasında ise, CASK ilişkili pontoserebellar hipoplazi, pontin tegmental 'cap' displazisi, serebellar agenezi ve prematüriteye sekonder hasar ile olan serebellar yıkım gelmektedir. [1]

Özet olarak; Serebellar hipoplazi, şekli normal olan serebellumdaki serebellar volümün azalmasına verilen isimdir [2,3] Serebellar hipoplazi, diğer beyin malformasyonları ile birlikte olabilir. Çocuklar, genellikle, global gelişim geriliği ve hipotoni ile kliniğe gelirler. [4] Serebellar bulgular, sonradan gelişir. Nörolojik bulgular arasında, trunkal ataksi, hipotoni, oküler hareketteki bozukluklar, disartri, intansiyonel tremor ve mikrosefali gelir. Genetik nedenler yanı sıra, konjenital enfeksiyonlar, metabolik bozukluklar, kromozomal anormallikler ile beraber görülebilir. Santral sinir sistemi gelişim malformasyonları, konjenital glikozilasyon defektleri, alfa distroglikanopatiler ile birlikte görülebilir. Diğer beyin sapı hipoplazileri ile beraber görülebilceği gibi, Dandy-Walker malformasyonları gibi sendromların komponentleri şeklinde de olabilir.

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PCH11: Yedi aile bildirilmiştir. [11,12] TBC1D23 geni sorumludur. PCH11 de, tıpkı PCH8 gibi, dejeneratif olmayan formudur. Ciddi gelişimsel gerilik, mikrosefali ve hipotonisite ile karekterizedir. Bazı olgular, bağımsız yürüme yetisini de kazanmışlardır. Olguların yarısında, ataksi gibi serebellar bulgular tanımlanmıştır. Beyin MRG'de, ponsda, ilerleyici olmayan hipoplazi ve korpus kallosum hipoplazisi ve serebellum hipoplazisi ile karekterizedir. [1,11,12]

Özet olarak, pontoserebellar hipoplaziler, serebellum ve ponsu ilgilendiren bir grup nörodejeneratif hastalıktır. [1,2] Kalıtımları, otozomal resesiftir. Pontoserebellar hipoplazi tip 1, bulbar ve spinal motor nöronlarda dejenerasyon ile karekterize olup, bu yönüyle spinal musküler atrofiye benzer. PCH2, ise jeneralize klonus, yutma bozuklukları, kore, distoni ve ilerleyici mikrosefali ile karekterizedir. PCH4, PCH2'nin daha ciddi olan klinik formu olup, uzamış neonatal klonus, hipertonisite, primer hipoventilasyon, polihidramnios ve konjenital kontraktürler gibi şiddetli klinik bulgular ile gider. PCH'ların günümüze kadar 11 alt tipi tanımlanmıştır.

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KIAA0226 İlişkili Salih Ataksisi/SCAR15

Erken başlangıçlı serebellar ataksi, motor gelişmede gecikme, dismetri, anormal göz hareketleri ve hiporefleksi ile karekterizedir. [30] Kraniyal MR görüntülemelerde hafif derecede serebellar atrofi ile karekterizedir.

İyonotrofik Glutamat Reseptör Delta-2 İlişkili Serebellar Ataksi/SCAR18

GRID2 geninin kodlamış olduğu glutamat reseptör kanal delta 2 subünitesi, özellikle serebellar purkinje hücrelerinde eksprese olur. [31] Nistagmus, hipotoni, psikomotor gelişmede gecikme, ataksi, disartri, okülomotor apraksi, dismetri ve disdiadokinezi, canlı derin tendon refleksleri, ektansör plantar yanıt ile karekterizedir. Kranial MR görüntülemelerinde serebral ve serebellar atrofi görülmektedir. [1,31]

ATG5 İlişkili İlerleyici Olmayan Serebellar Ataksi/SCAR25

Psikomotor gelişmede gecikme, trunkal ataksi, dismetri, nistagmus ve bilişsel gerilik ile karekterizedir. [32,33]

Bilişsel Gerilik, Optik Atrofi ve Deri Anormallikleri ile Beraber Görülen WDR73 İlişkili Serebellar Ataksi (CAMOS)

Ciddi gelişimsel gerilik, psikomotor gerilik, orantılı boy kısalığı, mikrosefali, optik atrofi, konuşma bozukluğu, serebellar atrofi ile karekterizedir. [1,28,34]

Mental Retardasyon ile Birlikte, İlerleyici Olmayan, CAMTA1 İlişkili Serebellar Ataksi (CANPMR)

CAMTA1, geninden kaynaklanan bu hastalıkta, hafif derecede bilişsel gerilik, erken başlangıçlı ataksi, konuşma gecikmesi görülür. [1,35,36] Şaşılık, infantil hipotoni, konuşma gecikmesi, miyoklonik nöbetler ve dismorfik bulgular bildirilmiştir.[1,36]

ATCAY İlişkili Serebellar Ataksi, CAYMAN Tipi.

İlk kez 1978'de Johnson ve ark. tarafından, Büyük Cayman Ada'larındaki izole bir popülasyonda tanımlanmıştır. Belirgin hipotoni, psikomotor gerilik, belirgin ve ilerleyici olmayan serebellar disfonksiyon, nistagmus, intansiyonel tremor, disartri ve geniş tabanlı yürüyüş ile karekterizedir.

KCNJ10-İlişkili Ataksi ve EAST/SESAME Sendromu

İnfant döneminde jeneralize nöbetler, psikomotor gelişmede gecikme, ataksi, mental retardasyon ve elektrolit bozukluğu ile karekterizedir. [37] Bilişsel gerilik bazen tabloya katılmayabilir. [38] Ataksi, sensoryal işitme kaybı, hipokalemik metabolik asidoz ve hipomahnezemi ile karekterize formları tanımlanmıştır. Kranial MR görüntülemede, kaudat nukleusda, T2'de hiperintensite görülebilir. [39]

Özetle, Birçok nadir görülen otozomal dominant veya resesif olarak kalıtılan, ilerleyici olmayan, konjenital ataksiler tanımlanmıştır. Özellikle, CACNA1A, GRID2, CAMTA1 mutasyonları erken başlangıçlı ataksi ile birlikte görülür. Bu gruptaki hastalıklarda, bilişsel gerilik, spastisite ve erken başlangıçlı nöbetler gibi eşlik eden bulgular görülebilir. [1]

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