BÖLÜM 24

HEREDİTER NÖROPATİLERDE KÖK HÜCRE TEDAVİSİ

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HEREDİTER NÖROPATİLER

Herediter nöropatiler periferik sinirleri etkileyen en yaygın kalıtsal nöromusküler hastalıklardır.[1] Enfeksiyöz, immün aracılı, metabolik, toksik, vasküler ve idiopatik formların hepsinde klinik benzerdir. En yaygın tiplerini; Charcot-Marie-Tooth (CMT) hastalığı (Herediter Motor Sensoriyal Nöropati-HMSN), herediter sensoriyal ve otonomik nöropati (HSAN veya herediter sensoriyal nöropati-HSN), herediter motor nöropatiler (HMN) ve küçük lif nöropatileri (SFN-Small Fiber Neuropathies) oluşturmaktadır.[2]

Etiyolojiye sebep olan 30'dan fazla gen tanımlanmıştır ve genetik hastalığın tutulumuna göre de 2 ayrı sınıflamaya ayrılmıştır (Tablo 1).[3] Hastalık; otozomal dominat, otozomal resesif veya X'e bağlı olarak kalıtılır ve de novo mutasyonlu vakalar da tanımlanmıştır.[3]

Herediter nöropatilerin kliniğinde; CMT'de ilerleyici kas güçsüzlüğü, kas atrofisi, duysal semptomlar, pes kavus, peroneal sinir felci, proprioseptif reflekslerin kaybı, baş parmakta çekiç deformitesi sıklıkla görülürken, edinsel nöropatilerde daha çok duysal semptomlar hakimdir.[3] Nöropatik ağrı, iskelet deformiteleri, bilişsel bozukluklar, sağırlık, yutma ve solunum güçlüğü CMT'ye eşlik edebilen diğer bozukluklardır.[4] CMT'nin birkaç ana tipi ve her ana tipin de alt tipleri mevcuttur. CMT'nin sık görülen ana formları: CMT 1, CMT 2 ve CMT-X'den oluşmaktadır (Tablo 2).[5] CMT 1 myelin oluşumundaki anormallikler ile ilişkilidir ve tüm CMT vakalarının %60-80'ini oluşturur. Aksonal hücre ölümü nedeniyle oluşan CMT 2'de myelin anormallikleri yoktur ve vakaların %20 -40'ını oluşturur. CMT X ise, hem aksonal hücre ölümü hem de myelin anormalliklerden oluşur ve yaklaşık %10 sıklıktadır.[6]

Tablo 1. Genetik hastalığın tutulumuna göre nöropati sınıflandırması.[3]

Nöropatinin hastalığın ilk veya birincil nedeni olduğu durumlar
Charcot-Marie-Tooth Hastalığı (CMT)
Herediter Basınca Duyarlı Nöropati (HNPP)
Herediter Sensöriyal ve Otonomik Nöropatiler/ Herediter Sensöriyal Nöropati (HSAN/HSN)
Distal Herediter Motor Nöropati (dHMP)
Herediter Nöraljik Amyotrofi (HNA)
Nöropatinin yaygın bir nöromusküler hastalığın parçası olduğu durumlar
Familyal Amiloid Polinöropati
Lipid Metabolizma Bozuklukları
Porfiriler
DNA Tamir Bozuklukları
Mitokondriyal Hastalıklar
Herediter Ataksiler

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tedir.[60, 61] Spesifik olarak, CMT1B gibi periferik nöropati durumlarında, hücreleri her sinire doğrudan enjekte etmek çok zordur.[6] MKH'lerin avantajı, diğer remiyelinizan hücre tiplerinin aksine, bu hücrelerin sistemik olarak uygulandıklarında hasarlı dokuya doğrudan göç aktivitesine sahip olmalarıdır. Bu durum beyin hasarı, kalp ve böbrek yetmezliği durumlarında gösterilmiştir.[62-64]

CMT1B İÇİN MEZENKİMAL KÖK HÜCRE ÇALIŞMALARI

Mezenkimal kök hücreler, çeşitli enflamatuar ve dejeneratif hastalıkların tedavisi için hem hayvan modellerinde hem de klinik deneylerde sistemik olarak uygulanmıştır. Ayrıca diyabetik nöropati ve kemoterapi ilişkili nöropati ile ilgili MKH tedavi çalışmalarında oldukça güzel sonuçlar alınmıştır.[65, 66]

Mezenkimal kök hücrelerin oldukça büyük hücreler olduğu bilinmesine rağmen (polimorfonükleer lökositlere kıyasla 2-3 kat daha büyük), klinik deneylerde mikrokapillerlere yapışıklık gibi herhangi bir yan etki bildirilmemiştir.[67, 68]

Etkinlik için optimum hücre sayılarını belirlemek amacıyla CMT1B'li hastalarda allojenik mezenkimal kök hücrelerin doz artırıcı bir denemesi önerilmektedir. Kemik iliği kaynaklı allojenik MKH'nin in vivo proliferasyonu nispeten düşük olması nedeniyle diğer MKH kaynakları düşünülebilir.[69] Örneğin, yaklaşık 19.6 saatlik bir ikiye katlanma oranına sahip olan ve "Endometrial Rejeneratif Hücreler" olarak adlandırılan adet kanından türetilen bir MKH popülasyonu rapor edilmiştir.[26] Bu çalışmada endometrial rejeneratif hücrelerin 9 farklı hücreye farklılaşma yeteneğinden bahsedilmiştir; osteojenik, kardiyomyositik, solunum epiteli, endotel, miyosit, pankreatik, hepatik, adipositik ve nörositik. Ayrıca bu hücre popülasyonunun ekstraksiyon kolaylığı ve pluripotensi göz önüne alındığında gelecekte, mevcut kök hücre kaynaklarına iyi bir alternatif olacağı düşünülmektedir.

Diğer tüm çalışmalarda olduğu gibi, tedavide başarı kritik olarak hastaların seçimi ile ilişkilidir. Ayırıcı tanılar iyi yapılmalıdır. Fizik muayene ve elektrofizyolojik testler CMT1B klinik belirtilerini göstermeli ve diğer nöropati nedenleri dışlanmalıdır. CMT'ye neden olan mutasyonun tanımlanması da CMT alt tiplendirmesi için faydalı olacaktır. Maalesef henüz CMT1B hastalığına neden olan patofizyolojiye müdahale mevcut değildir.

Sonuç olarak; MKH tedavileri; remiyelinizasyona olanak sağlaması, nöroprotektif/antiapoptotik ve antienflamatuar etkileri nedeniyle herediter nöropatiler için iyi bir seçenek olabilir. Bu konuda yapılacak tedavi ve çalışmalar diğer nörodejeneratif hastalıklara da ışık tutacaktır.

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