BÖLÜM 96

NÖRONAL SEROİD LİPOFUSİNOZİS (NCL, CLN)

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GİRİŞ

Nöronal seroid lipofusinozis (NCL, CLN) çocukluk çağında demans kliniğine neden olan, en yaygın kalıtsal nörodejeneratif hastalık olarak bilinmektedir. Lizozomal depo hastalığı olarak sınıflandırılan CLN, görme kusuru, epilepsi, demans ve motor beceri kaybına yol açmaktadır, çoğunun kesin tedavisi olmayan heterojen bir depo hastalığı olarak tanımlanmaktadır.[1]

Etiyolojide yer alan temel patolojik değişiklik, santral sinir sisteminde (SSS), spesifik olarak lizozomlarda biriken ve lipopigment (lipofuscin) kümeleri olarak adlandırılan protein kümelerinin toksik seviyeleridir.[2] Bu agregatlar histopatolojik olarak sarı-kahverengi bir pigment içeren ince otofloresan granüller olarak görünmektedir. Granüllerin içinde mitokondriyal ATP sentazın (SCMAS) protein C alt birimi ile sfingolipid aktivatör proteinler (SAP) A ve D gibi lipid ve protein karışımı bulunmaktadır.[3] Biriken lizozomal lipofuskin, nöronal hücre iskeletini ve hücresel trafiği etkileyerek, nöronal kayıp ve patolojik glial proliferasyon ve aktivasyona sebep olmaktadır.[4]

CLN insidansı 1:12.500 ila 1:100.000 arasında değişmektedir.[3] CLN önceden başlangıç yaşına göre, yani infantil, geç infantil, juvenil ve erişkin form olarak sınıflandırılmakta, yaygın şekilde Batten hastalığı olarak adlandırılmaktaydı.[5] Ancak, "Batten hastalığı" terimi sadece jüvenil başlangıçlı formu temsil etmektedir. Son 20 yılda, moleküler genetik alanındaki gelişmeler ışığında en az 14 farklı CLN formu tanımlanmaktadır.[1] Aynı gen üzerindeki mutasyonlar farklı hastalık seyrine yol açabilse de genetik olarak 13'ü otozomal resesif ve biri de otozomal dominant şekilde aktarılmaktadır ve bunların her biri lizozomal proteinde fonksiyonel kusurlar içermektedir.[6] Daha spesifik olarak, kusurlu proteinler, salgılanan lizozomal proteinleri (CLN1, CLN2, CLN5, CLN10 ve CLN13) ve lizozomal transmembran proteinlerini (CLN3, CLN4, CLN6, CLN7, CLN8, CLN12 ve CLN14) içermektedir.[7]

Hastalığın en yaygın 4 tipi CLN1 hastalığı ("İnfantil NCL" olarak da bilinmektedir), CLN2 hastalığı ("Geç İnfantil"), CLN3 hastalığı ("Juvenil NCL") ve CLN6 hastalığıdır.[8] Her bir NCL alt tipindeki ana klinik bulguların bir

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Tablo 3: ***Devamı***

Farmakolojik tedavisi	**CLN1**	-Sisteamin bitartarat ve N-asetil sistein (klinik deneme) -Fosfosisteamin, fingolimod ve teriflunomid (fare) -Flupirtin, retiagabine ve anti-caspase-4 (insan kültüre lenfoblast)
	CLN2	-Flupirtin ve retiagabin (insan kültüre lenfoblast) -Gemfibrozil (fare ve çocuklar
	CLN3	-Rolipram, roflumilast, PF-06266047 ve AMPA res. antagonisti (fare) -Flupirtine ve retiagabin (insan kültüre lenfoblast) - Trehaloz, MK2206 ve mikofenolat (fare, insan kültüre fibroblast ve klinik deneme) -Fingolimod ve teriflunomid (fare) -prednisolon göz damlası ve intra-vitreal triamsinalone (izole vaka)
	CLN6	-Flupirtin ve retiagabin (insan kültüre lenfoblast) -Curcumin, minosiklin ve DHA (fare)

Şu anda, olası herhangi bir terapötik yaklaşımla ilgili herhangi bir çalışma mevcut değildir.

CLN14

CLN14 hastalığı, progresif miyoklonik epilepsi (EPM3) olarak da bilinmektedir. Meksikalı bir ailede, görme kaybı, bilişsel ve motor gerileme, erken ölüm ve belirgin NCL tipi depolama materyali olan bir hastalığa neden olan mutasyon bildirilmiştir.[109]

Potasyum kanalı tetramerizasyon alanının protein 7'sini kodlayan KCTD7 genindeki mutasyonlar hastalığa neden olmaktadır.[110] Hastalık genellikle 8-24 aylık bebeklerde miyoklonik nöbetlerle (infantil PME) kendini göstermekte, bunu gelişimsel gerileme ve görme bozukluğu izlemektedir. Bu proteindeki diğer mutasyonlar opsoclonus-miyoklonius ataksi benzeri sendromlara neden olmaktadır. Otofüloresan lipopigment depolama materyalinin hücre içi birikimi, cilt biyopsisi yoluyla elde edilen fbroblastlar, nöronlar ve ekrin salgı epitel hücrelerinde belirgindir.[111]

CLN14 hastalığı için şu anda, olası terapötik yaklaşımla ilgili herhangi bir çalışma mevcut değildir. Tün NCL tipleri için araştırılan tedavi seçenekleri Tablo 3'de sunulmuştur.

SONUÇ

Sonuç olarak CLN'nin erken teşhisi kritik öneme sahip görünmektedir. Özellikle yenidoğan tarama programları içerisinde lizozomal hastalıkların da bulunması, doğumdan sonraki kısa sürede tanıyı sağlayacaktır. Bu şekilde bebekler asemptomatik evrede olsalar bile erken tedavi olanağına kavuşacak ve hastalığın seyri tamamen olmasa da kısmen hafifletilebilecektir. CLN'lerin tedavisi konusunda gün ışığına çıkmayı bekleyen pek çok tedavi seçeneği araştırılmaktadır. Bu tedaviler sayesinde hastalığın ilerlemesi durdurabilir veya yavaşlatabilir, ancak hastalığı tamamen veya kısmen tersine çevirme olasılığı düşük olduğundan erken tanı her zamankinden daha da önemlidir. Yenidoğan tarama panellerine bazı lizozomal bozuklukları ekleyen ülkeler vardır.[112]

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