BÖLÜM

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KOAH'da Duman Maruziyeti Modelleri

Patrick Geraghty, PhD and Robert Foronjy, MD
Çeviri: Uz. Dr. Fatih Seğmen

ÖNEMLİ NOKTALAR

1. KOAH dünya çapında yaygın bir ölüm nedenidir ve etkili tedavi eksikliği ile yaygın sigara kullanımının sürmesi göstermektedir ki, bu durum gelecek yıllarda doktorları uğraştıracak önemli bir kamu sağlığı sorunu olacaktır.
2. KOAH, YBÜ girişlerinin sık rastlanan sebeplerinden biridir ve YBÜ hastalarında KOAH tanısı YBÜ deliryumu, ARDS, hastanede ve taburcu işlemi sonrasında mortalite riskini yükseltmektedir.
3. KOAH'nin patogenezi hakkındaki sınırlı bilgimiz bu hastalığın tedavisinde ilerleme gösterilmesini engellemiş ve daha fazla temel ve klinik araştırma yapılması gereğini vurgulamıştır.
4. KOAH'nin hayvan modelleri, özellikle sigara dumanı maruziyet modeli, bu hastalığın başlıca özelliklerini yeniden ele alarak, göreceli olarak daha kısa bir zaman çerçevesinde hastalığa dair temel kavramların kazanımına fırsat sunmaktadır.
5. Hayvan modellerinden elde edilen bulgular bu hastalığın fizyopatolojisinde enflamasyonun, proteazların, oksidanların ve apoptosis'in önemini belirlemiştir. Buna ek olarak, bu çalışmalar KOAH'da akciğerlerde aktive olan anahtar onarım mekanizmalarını saptamıştır.
6. Bu çalışmalardan elde edilen bulgular, bu hastalıkta yıkıcı hasar yanıtlarını bloke edecek ve koruyucu akciğer onarım yanıtlarını artıracak 'hedef stratejiler' geliştirilmesine öncülük edebilir

KRONİK OBSTRÜKTİF AKCİĞER HASTALIĞININ ÖNEMİ

Kronik obstrüktif akciğer hastalığı (KOAH) tam olarak reversibl olmayan hava akımı kısıtlanması ile karakterize bir hastalık durumu olarak tanımlanmaktadır.[1] Hava akımı kısıtlamasına solunum yolu enflamasyonu[2], akciğer elastisitesi kaybı[3], akciğer dokusu yıkımı[4], ve küçük havayollarının kapanması neden olur.[5,6] Hava yolu kısıtlaması zamanla ilerler ve akciğerdeki fonksiyonu kaybı, bireylerin gündelik rutin aktivitelerini gerçekleştirme yeteneğini engelleyerek ölüm risklerini büyük ölçüde artırır. Nitekim KOAH günümüzde Birleşik Devletler'de başlıca ölüm sebepleri arasında üçüncü sırada yer almakta ve gelecek 20 yıl içinde tüm dünyada üçüncü ölüm sebebi olacağı öngörülmektedir.[7,8] Kardiyovasküler hastalıklarda yaşa göre düzeltilmiş mortalite geçen otuz yılda anlamlı bir düşüş göstermiş olsa da KOAH için yaşa göre düzeltilmiş mortalite bu sürede artarak[9] daha etkin tedaviler[10,11] ve daha fazla KOAH araştırması gereğinin altını çizmiştir. Gayet iyi bilinmektedir ki sigara dumanı maruziyeti ister aktif, ister pasif olsun bu hastalıkla ilişkilendirilen başlıca etiyolojik faktördür. Sigara içiciliğinin azaltılması yolunda aşama kaydedilmiş olsa da ABD'de 43.8 milyon kişi ya da nüfusun % 19'u (18 yaş ve

olarak, araştırmacılar sigara dumanı maruziyetinin yıkıcı etkilerinden akciğerin korunmasını sağlayan önemli enflamasyon mekanizmalarını belirlemiştir. Bu araştırmalardan elde edilen bilgilerin hastalığın seyrini önleyecek ya da tersine çevirecek etkin tedavilere dönüştürülme potansiyeli mevcuttur. Buna ek olarak, artık klinik insan deneyleri öncesinde potansiyel yeni tedavilerin test edilebilmesi için iyi yapılandırılmış duman maruziyet modelleri bulunmaktadır. Ancak, bu çalışmaların gerçekte tam olarak ne anlam ifade ettiği bazı nedenlerle tam olarak anlaşılmamıştır. Birincisi, KOAH uzun yıllar boyunca gelişen kompleks bir hastalıktır. Hastalığın ilk ya da erken aşamalarında uygulanan tedaviler ileri aşamadaki hastalara uygulandığında etkili olmayabilir. Bu durum KOAH açısından iç karartıcı bir sorundur çünkü bu hastalık ne yazık ki tanı konulamayan rahatsızlıklardandır ve çoğu zaman hastalık iyice ilerleyinceye dek tesbit edilememektedir.[156] Maalesef fare duman maruziyet modelini kullanan çoğu araştırma duman maruziyetinden ya da akciğer hasarı oluşmadan önceki dönemi ele almaktadır.[157] Açıkça görülmektedir ki tanısı yeni konan bir hasta için durum böyle değildir. Üstelik maruziyetin erken dönemlerinde bazı süreçlerin inhibe edilmesi hastalığı önleyebilir ancak ileri aşamalarda aynı yolağın bloke edilmesi ihtiyaç duyulan telafi edici mekanizmaları engelleyebilir. O hâlde bilim camiası hastalığın tedavisinden çok başlangıcını önlemek için çalışıyor olabilir. Hayvan modellerinde KOAH'ı önleyen[158,159] ancak klinik insan deneylerinde etkisiz hatta potansiyel olarak zararlı olan TNF-α antagonistlerindeki durum böyle olabilir.[160,161] Gelecekte hayvan maruziyet araştırmalarının hastalık oluşmuş durumdayken yürütülmesi gerekmektedir. A/J ırkı fareler bu araştırmalara çok uygundur çünkü yalnızca iki aylık duman maruziyetinden sonra anlamlı düzeyde amfizem geliştirmektedirler. Böylece müdahaleye, potansiyel faydasının ölçülebileceği bu zaman zarfında başlanabilir. Araştırma tasarımında değişimler işe yarayacak olsa da, fare duman maruziyet modelinin sınırlamaları da göz önünde bulundurulmalıdır. Çok açıktır ki, fareler insan değildir. Yaşam süreleri kısadır, daha az submukozal bezleri ve insanlara göre daha fazla havayolu makrofajları vardır.[162,163] Bu ve diğer biyolojik farklar düşünüldüğünde fare modeli insan akciğerinde olanlarla tam olarak örtüşmeyebilir. O halde bu modelle alınan gelecek vaad eden sonuçların, dikkatle yürütülen korelatif insan araştırmalarıyla doğrulanması gereklidir. İstatistikçi George E.P. Box bir zamanlar şöyle yazmıştı, "Bütün modeller yanlıştır, ama bazı modeller kullanışlıdır."[164] Duman maruziyet modeli, tanımı gereği, insan akciğerinde olan bitenin bir benzeridir. Faydalı öngörüler sağlayabilir, ancak dikkatsizce kullanılırsa gerçeği perdeleyebilir. Yola devam eden araştırmacılar için zorluk, fizyolojik, biyolojik ve yapısal bitiş noktalarını entegre eden maruziyet araştırmaları yürütmek ve bu bulguları insan üzerinde eşlenik in vitro ve in vivo modeller ve araştırmalarla doğrulamaktır. Sadece duman maruziyet modelinin sonuçlarına dayanarak ilaç geliştirme ya da test aşamasına geçmekte acele etmek, özellikle de modelin sınırlamaları göz önünde bulundurulduğunda, çok kullanışlı olmayacaktır. Bununla beraber, akıllıca kullanılırsa, bu model bu hastalık için gereken çok yönlü bir araştırma yaklaşımının önemli bir bileşeni olabilir.

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