BÖLÜM 80

YAĞ ASİDİ OKSİDASYON VE KARNİTİN METABOLİZMA BOZUKLUKLARI

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GİRİŞ

Mitokondriyal yağ asit β-oksidasyonu açlıkta, ateşli hastalıklar sırasında ve artmış kas aktivitesi sırasında dokuların enerji yokluğuna karşı geliştirdiği fizyolojik bir yanıttır.[1] Yağ asit oksidasyonu kalp için %80'e kadar enerji sağlarken, karaciğer fonksiyonlarının da devam etmesini sağlar.[2] Karaciğerde yağ asit oksidasyonu sonucunda keton cisimleri, 3-hidroksibütirat ve asetoasetat üretilir.[1] Bunlar da özellikle beyin gibi ekstrahepatik organlarda alternatif enerji kaynağı olarak kullanılır.[1]

Mitokondriyal yağ asit oksidasyonu üç basamakta meydana gelir.[3] Birinci basamakta uzun zincirli yağ asitleri mitokondriye girerler.[3] Yağ asitleri sitoplazmada koenzim A esterlerine aktive olur ancak iç mitokondriyal membrana taşınabilmek için karnitinlere ihtiyaç duyarlar.[3] Daha sonra mitokondri içinde tekrar koenzim A'ya transfer edilirler.[3] Karnitin palmitoil transferaz I, sitoplazmik malonil ko-A tarafından sitoplazmada yağ asitlerinin oksidasyonunda önemli rol oynar.[3] Orta ve kısa zincirli yağ asitleri ise mitokondriye karnitine ihtiyaç duymaksızın girerler ve mitokondriyal matrikste ko-A esterlerine aktive olurlar.[3] İkinci basamakta spiral yolak üzerinden β-oksidasyon gerçekleşmektedir.[3] Bu spiral yolaklarda dehidrojenasyon reaksiyonları flavin adenin dinükleotid (FAD) ve nikotinamid adenin dinükleotid (NAD) bağımlıdır.[3] Farklı uzunluklardaki yağ asitleri farklı enzimlerle katalizlenir.[3] Uzun zincirli yağ asitlerini katalizleyen enzimler membrana bağlı enzim ve mitokondrideki mitokondriyal trifonksiyonel protein tarafından gerçekleştirilir.[3] Orta ve kısa zincirli yağ asitlerini katalizleyen enzimler ise matrikste bulunur.[3] Riboflavin (B2 vitamini) flavin mononükleotid ve flavin adenin dinükleotidin prekürsörü olup bazı yağ asit oksidasyon defektlerinin tedavisinde kullanılmaktadır.[3,4] Yağ asit oksidasyonunda üçüncü basamak ise elektron transferidir.[3]

Elektronlar respiratuvar zincirden direkt veya taşıyıcı proteinler ile geçerler.[3] Mitokondriyal yağ asit oksidasyonundaki basamaklar şekil 1'de özetlenmiştir.[1,3]

Yağ asit oksidasyon bozuklukları enerji eksikliğine neden olarak erişkinlerde hafif hipotoni kliniğinden infantil dönemde ani bebek ölümüne kadar değişken yelpazede klinik bulgulara neden olur.[1]

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rocker-bottom ayaklar, hipospadias, serebral kortikal displazi, gliozis) görülebilir. Dismorfik özellikler olarak makrosefali, geniş ön fontanel, telekantus, kulaklarda malformasyonlar, geniş alın, düzleşmiş nazal köprü gibi bulgular görülür.[70] Erken başlangıçlı hipertrofik kardiyomiyopati ve ani ölüm gelişebilir.[70] Daha geç başlangıçlı glutarik asidüri tip 2'lerde dismorfik özellikler ve konjenital malformasyonlar görülmezken daha hafif seyirli bir klinik ve riboflavin yanıtlılığı dikkat çeker.[70] Hastalarda ataklar halinde kusma, dehidratasyon, hipoketotik hipoglisemi, asidoz, hepatomegali ve miyopati görülebilir.[70]

Anyon açığı artmış laktik asidoz, ılımlı hiperamonyemi, izovalerik aside bağlı "terli ayak" kokusu fark edilebilir.[70] Plazma açilkarnitin profilinde C4-C18 arası yaygın açilkarnitin yükseklikleri, idrar organik asit incelmesinde etilmalonik asit, glutarik asit, 3-hidroksiizovalerik asit, laktik asit, orta ve uzun zincirli dikarboksilik asitlerizovalerilglisin, izobütirilglisin artışı görülür.[70] Renal tübüler disfonksiyona bağlı jeneralize aminoasidüri diğer görülebilecek bir bulgudur.[70] Tedavide destek tedavisi ve riboflavin yanıtlı olgular için B2 vitamini verilmesi önerilir.[70]

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