

ÇOCUKLARDA HIPOGLİSEMİYE YAKLAŞIM

Yazar

Cumali ALAN

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Çocuk Metabolizma Hastalıkları Yan Dal Uzmanı



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BÖLÜM 1

GLİKOZ HOMEOSTAZININ ENDOKRİN VE METABOLİK DÜZENLENMESİ VE MOLEKÜLER MEKANİZMALAR

GİRİŞ

Metabolik homeostaz, organizmanın enerji alımı ile harcaması arasındaki dengeyi değişken fizyolojik gereksinimlere uyum sağlayacak biçimde sürekli yeniden düzenleyen çok katmanlı bir biyolojik sistemdir. Bu sistem, termodinamiğin birinci yasası doğrultusunda alınan enerjinin metabolik faaliyetler ve ısı üretimi için kullanılması ya da glikojen ve trigliserid depoları şeklinde saklanması ilkesine dayanmaktadır (1). Güncel yaklaşımlar metabolik dengeyi yalnızca besin alımı ve enerji tüketimi üzerinden değil; sinir sistemi, endokrin sistem ve bağışıklık sistemi arasındaki bütünlük iletişim ağı çerçevesinde değerlendirmektedir (2). Bu düzenleyici ağın merkezinde yer alan hipotalamus, periferik dokulardan gelen hormonal ve sinirsel sinyalleri entegre ederek iştahı, bazal metabolik hızı ve enerji substratlarının dokular arasındaki dağılımını koordine etmektedir.

Hücresel düzeyde enerji durumunun izlenmesi, metabolik denge- nin sürdürülmesinde belirleyici öneme sahiptir. AMPK, ATP düzeyle- rindeki düşüşe yanıt olarak aktive olan temel enerji sensörüdür. AMPK aktivasyonu, enerji tüketen anabolik süreçleri baskımlarken katabolik yolları uyarak hücresel enerji ekonomisini yeniden düzenlemektedir (20). Bu mekanizma, yalnızca hücresel uyumu sağlamakla kalmayıp obezite ve tip 2 diyabet gibi metabolik hastalıkların patofizyolojisinde de merkezi bir rol oynamaktadır.

duyarlılığını artıran ajanlar, dokuya özgü AMPK aktivatörleri ve çoklu reseptör agonistleri gibi yenilikçi tedaviler diyabet ve obeziteyi yalnızca yönetilebilir kronik hastalıklar olmaktan çıkararak hücresel düzeyde geri çevrilebilir metabolik süreçler haline getirebilir. ADA'nın 2026 kılavuzlarında da vurgulandığı üzere, bireyin sosyal belirleyicileri, teknoloji okuryazarlığı ve hedef organ hasarı riski tedavi başarısının temel belirleyicileri olacaktır (13). Bu bütüncül perspektif, metabolik sağlığın korunmasında daha hassas, daha proaktif ve daha insan merkezli bir klinik yaklaşımın habercisi olarak değerlendirilmektedir.

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BÖLÜM 2

HİPOGLİSEMİ RİSKİ ALTINDAKİ ÇOCUKLARIN YÖNETİMİ

HİPOGLİSEMİNİN TANIMLANMASI

Tek bir glikoz değeri kullanarak yenidoğan hipoglisemisini tanımlamak zordur (1). Doğumdan sonraki ilk 48 ila 72 saat içinde, bebekler hipoglisemi belirtileri geliştirebilir, kan şekeri normal yetişkin seviyelerinden önemli ölçüde düşük seviyelerde olabilir. Yetişkinlerde veya daha büyük çocuklarda, Whipple triadı (hipoglisemi belirtileri, düşük serum glikoz seviyesi yanında belirti ve semptomların glikoz verilmesi ile düzelmesi) kullanılabilir. Ancak bu genellikle yenidoğanda pratik değildir. Yenidoğan hipoglisemisinin sıklıkta klinik belirtileri: jitteriness / tremors, siyanotik ataklar, konvülsiyonlar, aralıklı apne atakları veya takipne, zayıf veya tiz sesli ağlama, uyuşukluk, beslenme güçlüğü, ani solgunluk, hipotermi, kalp durması ve yetmezliği olabilir (Tablo 1). Diğer bazı durumlar (menenjit veya hipoglisemi ilişkisiz nöbetler) bu söz konusu klinik bulguları gösterebildiğinden, hipoglisemiye belgelemek ve kan şekerini normal seviyelere çıkarmak için yeterli glikoz uygulanarak belirtilerin kaybolup kaybolmadığını doğrulamak önemlidir (2).

Teşhis veya terapötik amaçlar için tanımlanan normal değer aralıkları, bebeğin büyüklüğüne, gebelik yaşına, önceki hipoglisemi öyküsüne, mevcut klinik durumuna, enerji kaynaklarının mevcudiyetine ve devam eden enerji gereksinimlerine bağlıdır. Hipoglisemi tanımları, tüm bu faktörleri kapsayacak kadar esnek olmalıdır.

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HİPERİNSÜLİNİZM

GİRİŞ

Hiperinsülinemik hipoglisemi (HH), düzensiz insülin salgılanmasıyla ilişkili klinik, genetik ve morfolojik olarak heterojen bir grup bozukluğu ifade eder. Yenidoğanlarda ve bebeklerde kalıcı hipoketotik hipogliseminin en yaygın nedenidir ve kalıcı beyin hasarı riskiyle ilişkilidir. Bu nedenle, epilepsi, serebral palsi ve nörogelişimsel yetersizlikler gibi komplikasyonları önlemek için hızlı bir tanı koymak ve derhal tedaviye başlamak esastır (1).

İnsülinin glikoz ve yakıt metabolizması üzerindeki metabolik etkisi nörolojik hasar riskini artırır. İnsülin, periferik tüketimini artırarak kan glikoz seviyesini düşürür, glikojen sentezini uyarır ve glikojenolizi ve glukoneogenezi inhibe eder. Öte yandan, insülinin yağ dokuları üzerinde anabolik bir etkisi vardır. Lipogenezi uyarır, serbest yağ asidi salınımını ve beta-oksidasyonunu inhibe eder ve böylece keton cismi oluşumunu engeller. Bu, hipoketotik duruma neden olur ve serebral metabolizma için alternatif yakıtların kullanılabilirliğini azaltır (2). Yenidoğan ve bebeklerin beyni, yetişkinlere kıyasla daha yüksek oranda glikoz tükettiği için hipoglisemik beyin hasarına karşı daha savunmasızdır. HH tipik olarak yenidoğan döneminde şiddetli hipoglisemi ile ortaya çıkar, ancak değişken şiddet ve etiyoloji ile bebeklik, çocukluk ve hatta yetişkinlik döneminde de ortaya çıkabilir (3, 4).

HH, doğum asfiksisi, intrauterin büyüme geriliği, maternal diyabetes mellitus (5) gibi bazı risk faktörleri nedeniyle geçici olabilir veya

taların bu olanaklara erişebilmesi için yeni, rutin olarak kullanılabilen görüntüleme teknikleri geliştirilmelidir.

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BÖLÜM 4

HİPOGLİSEMİDE PERİOPERATİF YAKLAŞIM

Hipoglisemi tanısı ve tedavisi acil olan en önemli bulgulardandır. Hiperglisemiden daha nadir görülmesine rağmen hipogliseminin değerlendirilmesi daha komplekstir. Glukoz ihtiyacının sürekli olarak karşılandığı anne rahmindeki dönemden glukoz alımının dalgalanmalar gösterdiği doğum sonrası hayata geçiş çeşitli adaptasyonlara ihtiyaç gösterir. Bu geçiş tamamlandığında glukoz homeostaz mekanizması yaşam boyu aynı kalmasına rağmen yenidoğanlar ve küçük çocuklar, erişkinlere göre açlık durumunda yeterli yakıt ihtiyacının karşılanması için glikojenolize, glukoneojenezise ve yağ asidi oksidasyonuna daha fazla bağımlılık gösterirler. Geç bebeklik döneminde beslenme aralıklarının artması ile birlikte bu mekanizmalarda meydana gelen bir bozukluk hipoglisemiye yol açabilir (1-6). Gecikmiş tanı ya da yetersiz yönetim sonucu gelişen tekrarlayan hipoglisemiler gelişmekte olan beyine zarar verici olmaktadır. Beyin gelişiminin hızlı olduğu özellikle süt çocukluğu döneminde tekrarlayan hipoglisemiler nörolojik sekellere (konvülsiyon, mental ve motor retardasyon) yol açabilir. Bu nedenle bebeklik ve çocukluk döneminde görülen hipoglisemi ivedilikle araştırılması ve tedavi edilmesi gereken tıbbi bir acildir. Hipogliseminin sebebi önceden bilinmiyorsa etiyojolojiyi ortaya koyma anlamında kritik önem taşıyan kan ve idrar örnekleri alınmalıdır (Tablo 1) (1).

Bebeğin gelecekteki yaşam kalitesinin sağlanması santral sinir sistemi bütünlüğünün korunmasına bağlıdır. Cerrahi girişim birçok hipoglisemik darbeye dayanmaya çalışan beyni korumak için acil bir durumdur. Anestetik yönetim güvenlik için diğer monitörizasyonlara ek olarak biyokimyasal dikkatli takibi gerektirir. Seçilmiş hastalarda hipoglisemi izlem için epidural anestezinin uygulanması tercih edilebilir ancak pediatrik olgularda bu yöntem pratikte pek uygulanabilir değildir. Cerrahi sırasında oynak insülin seviyelerine rağmen hafif hiperglisemi sağlamak önemli bir sorundur (10,15,16). Intraoperatif süreçte glisemik kontrolün sağlanmasında verilen anestezi tipinin ne olduğu ve eğer genel anestezi ise verilen anestetik maddenin ne olduğu önemlidir. Anestetik gazlardan enfluran ve halotan pankreatik insülin salınımını inhibe ederek hiperglisemiye sebep olabilir. Gingerich ve ark. (15) 0,33 mM (1,5 MAC) konsantrasyonundaki halotanın ratların pankreas hücrelerinden %33 oranında insülin salgısını azalttığını belirtmişlerdir. Ewart ve ark. (16) da ratlarda glukozun uyardığı insülin salınımında doz bağımlı olarak bir azalmaya sebep olduğunu göstermişlerdir. Gerçekte 1,18 MAC (0,47 mM) enfluran dozunda %50 oranında insülin salınımında bir azalma görülmektedir. Bu anestetik maddelerin insülinomalara tam olarak etkisi bilinmemektedir. Yukarıda belirtilen çalışmalar göstermiştir ki insülinomalı olgularda enfloran daha fazla insülin salgılanmasını baskılayıcı özelliği nedeniyle halotana tercih edilebilir. Sonuç olarak; persistan hiperinsülinemik olguların peri ve postoperatif izlemleri hipo ve hiperglisemi açısından dikkatli yapılmalıdır.

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İNFANT VE ÇOCUKLARDA HİPOGLİSEMİ

Geç infantil dönem ve çocukluk çağı boyunca hipoglisemi hiperglisemiden daha az görülmekle birlikte, bu dönemdeki hipoglisemiler daha karmaşıktır. Gelişmekte olan beyin hipoglisemik hasara yatkındır ve tanının gecikmesi veya yetersiz tedavi gelişmekte olan beyin için daha zararlıdır. Nedeni bilinmeyen hipoglisemi tablosunda ayırıcı tanı için acilen kan ve idrardan “kritik örnek” alınması önemlidir (Tablo 1).

HİPOGLİSEMİ TANIMI

Hipoglisemi plazma glukozunun 50 mg/dl'nin altında olmasıdır. Tam kan glukozu plazmadan %10-15 daha düşüktür. Hipoglisemi tedavisi esnasında kabul edilebilir en düşük glukoz düzeyi 70 mg/dl'dir ve plazma glukozu 70 ile 100 mg/dl arasında tutulmalıdır. Glukoz ölçümünde glukometrelerin kullanılması hiperglisemi tedavisinde uygun olmakla birlikte, hipogliseminin tanısında önerilmez. Tarama testi olarak kullanılsa da 60 mg/dl'den daha düşük bir glukometre ölçümü, kan veya plazmanın laboratuvarında ölçümü ile doğrulanmalıdır (1-4).

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NEONATAL HIPOGLİSEMİ

Fetal ve neonatal dönem büyüme, farklılaşma ve dolayısıyla metabolizmanın en hızlı olduğu yaşam dönemidir. Bu da organizmanın en önemli substratlarından biri olan glukoz ilgili aksaklıkların önemini artırır. Normal kan şekeri aralığının yenidoğanlar için bir farkı bulunmamaktadır.

Normal bir yenidoğanda ilk 1-2 saatteki kan şekeri düşüşünü izleyen bir yükselme başlar ve bundan sonra şeker normal düzeylerde seyredererek devam eder. Ancak yenidoğan dönemi gibi hem hastalık riski ve sıklığının arttığı, hem de bunlara sekonder metabolik dekompanseasyonun daha kolay geliştiği bir dönemde hipoglisemiye yatkınlığın artması da beklenen bir durumdur (1).

Neonatal hipoglisemi : Yenidoğanda kan şekerinin 40 mg/dl nin altında olması genel olarak hipoglisemi olarak tanımlanmaktadır. Kapiler ölçümle saptanan hipogliseminin venöz plazma örneğinde doğrulanması gerekmektedir. Ancak uzlaşır raporlarında hipogliseminin tanım veya tedavisi açısından tatmin edici bir noktaya gelinmediği vurgulanmaktadır. Kabul gören bir eşik tanımı da 47 mg/dl dir. Kesin bir tanımın olmaması çalışmalarda kabul edilen patolojik düzeyin farklı olması, olguların değişen hipoglisemi süreleri ve eşlik eden tabloların farklılığı, kontrol gruplarının olmaması, olgu sayılarının sınırlılığı gibi nedenlere dayanmaktadır. Beslenme şekli de önemlidir. Anne sütü ile beslenenlerde kan şekerleri daha düşük, keton düzeyleri daha yüksek ve beyin zedelenmesi riski daha azdır (2,3,4,5,6,7).

Aslında erişkine oranla yenidoğan beyninin hipoglisemiye karşı belirgin bir toleransı vardır. Bunun bilinen nedenleri şunlardır ; 1) akson,

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DİYABETİK ANNE ÇOCUĞU

Diabetes Mellitus (DM) gebelik süresince fetal gelişimi olumsuz etkileyen ve yenidoğanda önemli metabolik bozukluklara yol açan bir hastalıktır. Günümüzde özellikle gebelik öncesi veya gebeliğin ilk haftalarında diabetin tanımlanması ve hipergliseminin kontrol altına alınmasıyla, hastalığın neden olduğu konjenital anomaliler azalmış, uygun perinatal ve neonatal yaklaşımlarla fetal-perinatal ölümler %3'ün altına düşürülmüştür (1-4).

Maternal hipo-hiperglisemi, ketoasidoz, preeklampsi, üriner sistem enfeksiyonu, hipertansiyon ve hidromnios diabetik gebelerde sık görülmekte ve fetusu olumsuz etkilemektedir. Erken devrede görülen maternal hipoglisemi fetusu etkilemez. Hiperglisemi ise 24-28. gebelik haftasından başlayarak belirginleşir, fetal kayıplar bu devreden sonra artar. Ölüm nedeni açık değildir. Diabetik gebelerde yükselen HbA_{1c}'nin oksijen taşıma kapasitesinin az oluşuna bağlı olarak gelişen doku hipoksisi, maternal metabolik asidoz ve hiperglisemi sorumlu tutulmaktadır (2,5)

Gebelikte Tip 1 diabet %0.1-0.5, gestasyonel diabet %3-12 oranında görülürken, diabetik anne bebeği (DAB) ne 1000 canlı doğumda 1 olarak rastlanılmaktadır (Diabetin fetus üzerindeki en önemli etkisi “macrosomia” (irilik)tir. Vasküler komplikasyonlu diabetli gebelerde plasental yetersizliğe bağlı olarak intrauterin gelişme geriliği (small for gestational age=SGA) görülürken, bunun dışındaki diabetik gebelerde %20-40 oranında fetus gelişimi gebelik yaşına göre fazladır. Fetal macrosomia “Pederson hipotezi” ile açıklanmak istenmektedir: Annede insülin yetersizliğine veya etkisizliğine bağlı olarak gelişen hiperglisemi, plasentadan kolaylaştırılmış diffüzyon yoluyla fetusta hiperglisemiye

(%0.5-11), anormal glukoz torelans testi ise %8-27 oranında saptanmaktadır. Eğer baba diabetli ise risk üç kat artar. Neonatal macrosomianın ileride obesiteye yol açabileceği gösterilmiştir. Men tal gerilik görülme sıklığı normal popülasyonla aynı olmasın karşın, serebral palsy, epilepsi ve psikomotor gelişim bozukluğu insidansı daha yüksektir. Anne yaşı ve diabetin kontrolü, maternal ketozis, vasküler komplikasyonlar, intrauterin gelişme geriliği, prematürelilik ve perinatal olaylar bebeğin ilerdeki nörolojik durumunu etkileyen başlıca etmenlerdir (23,24). Gebelikte dikkatli medikal ve obstetrik bakım ve uygun neonatal yaklaşım ile DAB'nde görülebilecek çoğu komplikasyonları önlemek, normal bir bebek ağırlığı ve postnatal metabolik adaptasyonu sağlamak olasıdır. Çoğu merkezlerde perinatolojistler mümkünse gebelik esnasında tüm kadınların diabet yönünden taranmasını, hiç olmazsa aşın kilo alımı, evvelce iri veya ölü bebek doğum öyküsü, pozitif aile öyküsü ve 25 yaş üstü tüm gebelerde bu taramanın yapılması gerektiği konusunda uzlaşmış görünmektedir.

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YENİDOĞAN VE PEDIATRİK YAŞ GRUPLARINDA HIPOGLİSEMİYE METABOLİK YAKLAŞIM

GİRİŞ

Hipoglisemi, yenidoğan ve çocukluk çağında en sık karşılaşılan metabolik acillerden biridir. Özellikle yenidoğan döneminde glukoz homeostazının fizyolojik adaptasyon süreci, prematürite, intrauterin büyüme geriliği, perinatal stres ve beslenme yetersizlikleri nedeniyle hipoglisemi sıklıkla görülmektedir. Bununla birlikte, tekrarlayan, persistan, ağır veya beklenmedik klinik koşullarda ortaya çıkan hipoglisemi, altta yatan bir kalıtsal metabolik hastalığın ilk ve bazen tek belirtisi olabilir.

Kalıtsal metabolik hastalıklarda hipoglisemi; hepatik glikojen depolarının kullanılamaması, glukoneogenez bozuklukları, yağ asidi β -oksidasyonundaki yetersizlik, ketogenez kusurları, mitokondriyal enerji metabolizmasının bozulması veya bazı metabolitlerin glukoz üretimi üzerindeki inhibitör etkileri sonucunda gelişebilir.

Hipogliseminin metabolik kökenli olduğunun erken tanınması üç temel nedenle önem taşır:

1. Akut dönemde nöroglükopenik beyin hasarı, nöbet, ensefalopati ve kardiyorespiratuvar komplikasyonların önlenmesi.
2. Tekrarlayan hipoglisemik ataklar sırasında gelişebilecek karaciğer, kalp ve iskelet kası hasarının azaltılması.
3. Hastalığa özgü beslenme, açlıktan korunma ve metabolik dekom-pansasyon yönetiminin erken başlatılması.

Özellikle hipoglisemi sırasında keton yanıtının değerlendirilmesi, metabolik ve endokrin nedenlerin ayırıcı tanısında temel basamaklar-

SONUÇ

Yenidoğan ve çocukluk çağında hipogliseminin metabolik kökenli olduğunun erken tanınması, geri dönüşümsüz nörolojik hasarın ve yaşamı tehdit eden metabolik krizlerin önlenmesi açısından kritik öneme sahiptir.

Persistan veya tekrarlayan hipoglisemi, açlık ve enfeksiyonla tetiklenen ataklar, uygunsuz keton yanıtı, hepatomegali, laktik asidoz, hipera-monyemi, kardiyomiyopati ve rabdomiyoliz kalıtsal metabolik hastalık açısından temel uyarıcı bulgulardır.

Tanısal yaklaşımın merkezinde, hipoglisemi sırasında alınan kritik örneğin doğru yorumlanması yer alır. Özellikle β -hidroksibütirat ve serbest yağ asitlerinin birlikte değerlendirilmesi; hiperinsülinizm, yağ asidi oksidasyon bozuklukları, ketogenez kusurları ve ketotik hipoglisemi nedenlerinin ayırımında yüksek klinik değer taşır.

Metabolik hipoglisemi şüphesi bulunan hastalarda erken enerji desteği, katabolizmanın önlenmesi, hastalığa özgü biyokimyasal ve genetik incelemelerin planlanması ve multidisipliner yönetim, prognozu belirleyen temel unsurlardır.

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