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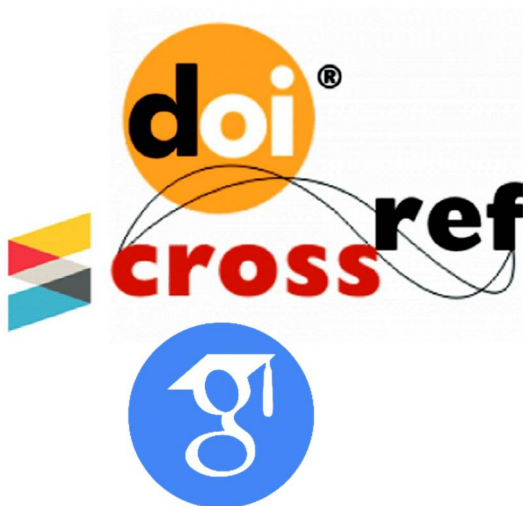
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STAGE-BY-STAGE DIAGNOSIS OF EXUDATIVE OTITIS MEDIA IN CHILDREN BASED ON TRANSFERRIN AND CERULOPLASMIN LEVELS IN ORAL FLUID

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ABSTRACT

This study examined the diagnostic significance of transferrin and ceruloplasmin levels in oral fluid (OF) for diagnosing the secretory stage of exudative otitis media (EOM) in children aged 1–5 years. The study included 77 children with EMA and chronic adenoiditis (main group), 60 children without EMA and without adenoid hypertrophy (comparison group), and 35 healthy children (control group). It was found that in the main group, the level of transferrin in the middle ear fluid was 4 times higher than normal (12.4 ± 1.1 mg/L), and the level of ceruloplasmin was also 4 times higher (4.8 ± 0.5 mg/L). A strong positive correlation ($r = 0.74$; $p < 0.01$) was identified between transferrin levels and exudate viscosity. When transferrin levels >12 mg/L are combined with sIgA <0.12 g/L, the risk of developing “sticky ear” increases 4.5-fold. These data allow for the implementation of a non-invasive diagnostic algorithm based on oral fluid biomarkers in clinical practice.

Keywords: exudative otitis media, children, oral fluid, transferrin, ceruloplasmin, sIgA, oxidative stress, non-invasive diagnosis, mucosal immunity.

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OG'IZ BO'SHLIG'I SUYUQLIGIDA TRANSFERRIN VA CERULOPLAZMIN KO'RSATKICHLARI ASOSIDA BOLALARDA EKSSUDATIV O'RTA OTITNI BOSQICHMA-BOSQICH TASHXISLASH

ANNOTATSIYA

Ushbu tadqiqotda 1–5 yoshli bolalarda ekssudativ o'rta otit (EO'O) sekretli bosqichini tashxislashda og'iz bo'shlig'i suyuqligidagi (OBS) transferrin va ceruloplazmin ko'rsatkichlarining diagnostik ahamiyati o'rganilgan. Tadqiqotga EO'O va surunkali adenoiditi bo'lgan 77 nafar bola (asosiy guruh), adenoid giperfiasiz EO'Osi bo'lmagan 60 nafar bola (qiyosiy guruh) va 35 nafar sog'lom bola

(nazorat guruhi) jalb etilgan. OBSda transferrin darajasi asosiy guruhda me'yordan 4 barobar yuqori ($12,4 \pm 1,1$ mg/l), seruloplazmin esa 4 barobar yuqori ($4,8 \pm 0,5$ mg/l) ekanligi aniqlandi. Transferrin darajasi va eksudatning qovushqoqligi o'rtasida kuchli to'g'ri korrelyatsiya ($r=0,74$; $p<0,01$) topildi. Transferrin >12 mg/l va sIgA $<0,12$ g/l birga bo'lganda «yopishqoq quloq» rivojlanish xavfi 4,5 barobar ortadi. Ushbu ma'lumotlar OBSning biomarkerlari asosida noinvaziv tashxis algoritmini klinik amaliyotga joriy etish imkonini beradi.

Kalit so'zlar: eksudativ o'rta otit, bolalar, og'iz bo'shlig'i suyuqligi, transferrin, seruloplazmin, sIgA, oksidativ stress, noinvaziv tashxis, mukozal immunitet.

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ПОЭТАПНАЯ ДИАГНОСТИКА ЭКССУДАТИВНОГО СРЕДНЕГО ОТИТА У ДЕТЕЙ НА ОСНОВЕ ПОКАЗАТЕЛЕЙ ТРАНСФЕРРИНА И ЦЕРУЛОПЛАЗМИНА В РОТОВОЙ ЖИДКОСТИ

АННОТАЦИЯ

В данном исследовании изучена диагностическая значимость показателей трансферрина и церулоплазмينا в ротовой жидкости (РЖ) для диагностики секреторной стадии экссудативного среднего отита (ЭСО) у детей в возрасте 1–5 лет. В исследование были включены 77 детей с ЭСО и хроническим аденоидитом (основная группа), 60 детей без ЭСО с отсутствием аденоидной гипертрофии (группа сравнения) и 35 здоровых детей (контрольная группа). Было установлено, что в основной группе уровень трансферрина в РЖ был в 4 раза выше нормы ($12,4 \pm 1,1$ мг/л), а уровень церулоплазмينا — также в 4 раза выше ($4,8 \pm 0,5$ мг/л). Выявлена сильная прямая корреляция ($r=0,74$; $p<0,01$) между уровнем трансферрина и вязкостью экссудата. При сочетании показателей трансферрина >12 мг/л и sIgA $<0,12$ г/л риск развития "клеякого уха" увеличивается в 4,5 раза. Эти данные позволяют внедрить в клиническую практику алгоритм неинвазивной диагностики на основе биомаркеров ротовой жидкости.

Ключевые слова: экссудативный средний отит, дети, ротовая жидкость, трансферрин, церулоплазмин, sIgA, окислительный стресс, неинвазивная диагностика, мукозальный иммунитет.

KIRISH Ekssudativ o'rta otit (EO'O) bolalar otorinolaringologiyasining ijtimoiy ahamiyati jihatidan eng dolzarb muammolaridan biri bo'lib, 5 yoshgacha bo'lgan bolalarning 80–90% dan ortig'i kamida bir marta shu kasallikdan aziyat chekadi [1]. Kasallik cho'qqisi (30–35%) boladagi nutq shakllanishining kritik davriga (1–5 yosh) to'g'ri kelishi uni alohida klinik muhimlikka ega qiladi [2]. Kasallikning seroze bosqichidan mukoze shakliga o'tishi, ikki tomonlama zararlanishning yuqori chastotasi (86% gacha) va qaytmas eshitish zaifligining shakllanishi — bularning barchasi kasallikni erta aniqlash va faol davolash taktikasini tanlashga zaruratni tug'diradi. Zamonaviy orinolingologiyada EO'Oni tashxislashning asosiy instrumental usullari sifatida timpanometriya, otomikroskopiya va akustik refleksometriya qo'llaniladi. Biroq ushbu usullarning cheklangan imkoniyatlari (subyektiv talqin, yosh bolalarda texnik qiyinchiliklar, eksudatning qovushqoqligini baholay olmaslik) yangi ob'ektiv va noinvaziv biomarkerlarni izlashni taqozo etadi [3, 4]. Og'iz bo'shlig'i suyuqligi (OBS) — so'lak va qon plazmasining transsudat komponentlaridan iborat murakkab biologik suyuqlik bo'lib, nazofarinks va o'rta quloqda kechayotgan patologik jarayonlarning mahalliy «ko'zgusi» hisoblanadi. Bubotubal tizimning shilliq qavati va nazofarinks bitta mukosal immunitet tizimining funktsional-struktura birligi sifatida harakat qilishi OBSni EO'Oni noinvaziv monitoring qilishning istiqbolli ob'ekti sifatida ko'rib chiqish imkonini beradi [5].

Transferrin — temirni tashuvchi asosiy plazma glikoproteini bo'lib, kapillyar

o'tkazuvchanligi ortganda to'qima suyuqliklariga o'tadi va mahalliy yallig'lanish intensivligining nisbiy markeri bo'lib xizmat qiladi [6]. Seruloplazmin — mis tashuvchi ferroferoksidaza fermenti bo'lib, oksidativ stressdagi o'tkir faza oqsillaridan biri hisoblanadi; uning miqdori yallig'lanish jarayonida jadal ortadi [7]. Ushbu ikki biomarkerning OBSdagi dinamikasi EO'Oda bugungi kunga qadar yetarlicha tadqiq etilmagan.

Ushbu tadqiqotning maqsadi — 1–5 yoshli bolalarda EO'O sekretli bosqichida OBSda transferrin va seruloplazmin ko'rsatkichlarining diagnostik hamda prognostik ahamiyatini baholash, shuningdek ushbu biomarkerlar asosida kasallik bosqichini noinvaziv aniqlash algoritmini asoslashdan iborat.

MATERIAL VA METODLAR Tadqiqot 2021–2024 yillarda Qashqadaryo viloyati Kitob shahar bolalar ko'p tarmoqli shifoxonasi bazasida olib borildi. Jami 172 nafar 1–5 yoshli bola kuzatuvga jalb etildi. Guruhlar taqsimoti quyidagicha:

1-jadval. Tadqiqot guruhlarini tarkibi

Guruh	n	O'g'il/Qiz	O'rtacha yosh (yil)	Asosiy klinik diagnoz
Asosiy guruh (A+B)	77	44/33	3,2 ± 1,1	EO'O sekretli bosqichi + surunkali adenoidit
Qiyosiy guruh	60	34/26	3,8 ± 1,3	Surunkali adenoidit, EO'Osiz
Nazorat guruhi	35	20/15	3,5 ± 1,0	LOR organlari sog'lom

Barcha bemorlar Samarqand davlat tibbiyot universiteti etika qo'mitasi tomonidan tasdiqlangan standartlarga muvofiq ota-onalarning yozma roziligidan so'ng kuzatuvga olingan. OBS namunalari ertalab ovqatlanmasdan oldin, og'izni yuvmasdan, passiv oqish usulida steril idishlarga yig'ildi (5 ml). Namunalar 4°C da 30 daqiqa davomida markazdan qochma kuchda (3000 rpm) aylantirib, supernatant ajratildi va -70°C da saqlandi. Transferrin miqdori immuno-turbidimetrik usulda (Beckman Coulter reagentlari, AQSh), seruloplazmin faolligi esa Ravin usulining modifikatsiyasi bilan aniqlandi. sIgA darajasi ELISA usulida (Orgentec Diagnostika, Germaniya) baholandi. Neyrofillar faolligi miyeloperoksidaza aktivligi orqali baholandi. Klinik tashxislash majmuasi quyidagilarni o'z ichiga oldi: videoendoskopiya, timpanometriya (A/B/C tipi), ipsilateral akustik refleksi, otoakustik emissiya (OAE) va qisqa latentli chaqirilgan eshitish potentsiallar (KLCHP). Statistik tahlil SPSS v.26 dasturida amalga oshirildi. Guruhlar orasidagi farqlar Student t-mezoni (sIgA, transferrin) va Mann–Whitney U-mezoni (seruloplazmin) bilan baholandi. Korrelyatsion tahlil Spirmen koeffitsienti orqali o'tkazildi. Farqlar $p < 0,05$ bo'lganda statistik ahamiyatli deb qabul qilindi.

TADQIQOT NATIJALARI Kuzatuvga qabul qilish paytida OBSning immuno-biokimyoviy profili guruhlar o'rtasida statistik jihatdan sezilarli farqlarni ko'rsatdi (2-jadval).

2-jadval. Tekshirilayotgan guruhlar bo'yicha OBSning dastlabki ko'rsatkichlari ($M \pm m$)

Ko'rsatkich	Asosiy guruh (n=77)	Qiyosiy guruh (n=60)	Nazorat guruhi (n=35)	p*
sIgA, g/l	0,12 ± 0,02*#	0,21 ± 0,03*	0,32 ± 0,04	<0,001
Transferrin, mg/l	12,4 ± 1,1*#	6,2 ± 0,8*	3,1 ± 0,4	<0,001
Seruloplazmin, mg/l	4,8 ± 0,5*#	2,9 ± 0,3*	1,2 ± 0,2	<0,001
Neyrofillar faolligi	Yuqori	O'rtacha	Past	<0,05

Izoh: * — nazorat guruhi bilan solishtirganda $p < 0,05$; # — qiyosiy guruh bilan solishtirganda $p < 0,05$.

Asosiy guruhda transferrin darajasi ($12,4 \pm 1,1$ mg/l) me'yordan 4 barobar yuqori bo'lib, bu o'rta quloq shilliq qavati kapillyarlaridan plazma oqsillarining jadal ekssudatsiyasini tasdiqlamoqda. Seruloplazmin ($4,8 \pm 0,5$ mg/l) esa me'yordan 4 barobar yuqori bo'lib, faol oksidativ stressning ob'ektiv ko'rsatkichi hisoblanadi. Shilliq qavatlarning to'siq funksiyasining asosiy markeri sifatida qaraganda, sIgA darajasi asosiy guruhda $0,12 \pm 0,02$ g/l gacha kritik pasayishni ko'rsatdi — bu nazorat ko'rsatkichidan 2,7 barobar past. Spirmen korrelyatsion tahlili OBSdagi transferrin darajasi va no'gora bo'shlig'i ekssudatining qovushqoqligi o'rtasida kuchli to'g'ri statistik bog'liqlikni aniqladi ($r = 0,74$; $p < 0,01$). Qovushqoqlik ball tizimida raqamlashtirildi: 1 ball — seroz ekssudat, 2 ball — shilliq, 3 ball — yopishqoq/gelsimon. Muhim prognostik topilma sifatida quyidagi kombinatsiya aniqlandi: transferrin > 12 mg/l + sIgA $< 0,12$ g/l bo'lganda «yopishqoq quloq» (adhesiv o'zgarishlar) shakllanish xavfi 4,5 barobar ortadi. Bu ma'lumot davolash taktikasini o'z vaqtida korreksiya qilish uchun prognostik prediktor vazifasini bajaradi.

Shuningdek, seruloplazmin darajasi timpanogramma turi bilan statistik jihatdan bog'liq ekanligi aniqlandi: B tipdagi timpanogramma (no'gora bo'shlig'ida suyuqlik) bo'lgan bolalarda seruloplazmin C tipdagi bolalarga nisbatan sezilari yuqori ($p < 0,05$).

3-jadval. Akustik impedansometriya natijalari guruhlar bo'yicha

Timpanogramma turi	Klinik ahamiyati	Asosiy guruh (n=77)	Qiyosiy guruh (n=60)	Nazorat
A tipi	Normal	0%	100%	100%
B tipi	O'rta quloqda suyuqlik	74%	0%	0%
C tipi	Manfiy bosim (naydisfunksiyasi)	26%	0%	0%
Akustik refleks yo'qligi	Suyuqlik to'sig'i belgisi	95%	0%	0%

Asosiy guruhda OAE bolalarning 92% da qayd etilmadi («Refer» natijasi) — bu kochlear buzilishlar bilan emas, balki no'gora bo'shlig'idagi ekssudatning tovush o'tkazuvchi to'siq yaratishi bilan bog'liq. KLCHP da V cho'qqi qayd etish bo'sag'alari 35–40 dB ga ko'tarilishi aniqlandi — bu «mass-effekt»ning klassik audiologik belgisi hisoblanadi. Asosiy guruh davolash taktikasiga ko'ra ikki kichik guruhga ajratildi: A kichik guruhi (n=40) — past intensivlikli lazer nurlanishi (PILN) + topik immunokorrektorlar + o'yin autoinsufflyatsiyasi; B kichik guruhi (n=37) — standart davolash (kutish taktikasi, dekonjestantlar).

4-jadval. Davolash yakunida OBSning biokimyoviy ko'rsatkichlari dinamikasi (M±m)

Ko'rsatkich	A kichik guruhi (n=40)	B kichik guruhi (n=37)	Nazorat guruhi (n=35)	p (A vs B)
sIgA, g/l	$0,28 \pm 0,03^*$	$0,15 \pm 0,02$	$0,32 \pm 0,04$	$<0,05$
Transferrin, mg/l	$3,8 \pm 0,5^*$	$8,4 \pm 0,9$	$3,1 \pm 0,4$	$<0,001$
Seruloplazmin, mg/l	$1,4 \pm 0,2^*$	$3,1 \pm 0,4$	$1,2 \pm 0,2$	$<0,001$
Neyrofillar faolligi	$6,5 \pm 0,8^*$	$14,6 \pm 1,2$	$4,2 \pm 0,5$	$<0,01$

Izoh: * — dastlabki ko'rsatkichlar bilan solishtirganda farqlar statistik ahamiyatli ($p < 0,05$).

A kichik guruhida transferrin konsentratsiyasi 3,2 barobar kamayib, $3,8 \pm 0,5$ mg/l ga tushdi — bu shilliq qavat kapillyar o'tkazuvchanligining tiklanishini ob'ektiv tasdiqlaydi. Seruloplazmin me'yorgacha tushishi oksidativ stress muvaffaqiyatli bostirganini ko'rsatadi. sIgA darajasi 2,3 barobar ko'tarilib ($0,28 \pm 0,03$ g/l), deyarli sog'lom bolalar ko'rsatkichiga yaqinlashdi. Aksincha,

B kichik guruhida transferrin yuqori darajada saqlanib qoldi ($8,4 \pm 0,9$ mg/l) — bu tomir o'tkazuvchanligining persistensiyasini va kasallikning qaytalanish xavfini ko'rsatmoqda. 6 oy o'tgach laboratoriya monitoringi A kichik guruhida erishilgan natijalarning barqarorligini tasdiqladi: transferrin ($3,9 \pm 0,4$ mg/l) va seruloplazmin ($1,5 \pm 0,2$ mg/l) fiziologik me'yor doirasida saqlanib qoldi. B kichik guruhida esa yallig'lanish profiliga qaytish tendensiyasi kuzatildi — transferrin $7,8 \pm 1,1$ mg/l, seruloplazmin $3,4 \pm 0,5$ mg/l. Klinik natijalar: A kichik guruhida qaytalanish chastotasi 7,5 barobar kamaydi (18,9% dan 2,5% ga), adenotomiyaga ehtiyoj esa 5% ga tushdi (B guruhida — 24,3%). A guruhida timpanogramma A tipiga 92,5% bolalarda qaytdi, B guruhida esa faqat 62,2% da ($p < 0,05$).

MUHOKAMA Olingan natijalar EO'O patogenezida mukozal immunitet va oksidativ stressning markaziy o'rni haqidagi zamonaviy g'oyalarni tasdiqlaydi. OBSdagi transferrin darajasining asosiy guruhda me'yordan 4 barobar ortishi o'rta quloq shilliq qavatida yallig'lanish bilan bog'liq kapillyar giperpermabilitetsiyasini — plazma oqsillarining transsudatsiyasini aks ettiradi [8]. Bu mexanizm bir necha jihat orqali izohlash mumkin. Birinchidan, faol yallig'lanish o'chog'idagi neytofillar va makrofaglar tomonidan transferrinni mahalliy sarflash kuchayadi. Ikkinchidan, EO'Oning asosiy sabablari qatoriga kiruvchi Porphyromonas gingivalis va boshqa gram-manfiy patogenlar transferrin retseptorlaridan foydalangan holda temir «o'g'irlash» strategiyasini amalga oshiradilar — bu jarayon mahalliy transferrin zaxiralarini kamaytiradi va OBSdagi darajasining kamayishiga sabab bo'ladi. Uchinchidan, intensiv oksidativ stress natijasida transferrin o'zi ham oksidlanib inaktivatsiyaga uchraydi [9]. Seruloplazmining ortishi «o'tkir faza javobi» mexanizmi orqali tushuntiriladi: yallig'lanish mediatorlari (IL-1 β , IL-6, TNF- α) jigarida seruloplazmining sintezini faollashtiradi. Mahalliy jihatdan seruloplazmin Fe²⁺ ni Fe³⁺ ga oksidlash orqali Fenton reaksiyasini inhibe etadi va shu bilan erkin radikallar hosil bo'lishiga to'sqinlik qiladi [10].

Transferrin >12 mg/l + sIgA $<0,12$ g/l kombinatsiyasida «yopishqoq quloq» xavfining 4,5 barobar ortishi muhim klinik-prognostik topilma hisoblanadi. Bu, Buzatto G. (2021) tomonidan nazofaringsdagi mediatorlar profili va otit kechishining og'irligi o'rtasida aniqlangan bog'liqlik bilan hamohang [11]. Bogomilskiy M.R. va boshq. (2022) tomonidan ta'kidlanganidek, EO'Oni faqat mexanik obstruksiya (adenoid giperfiya) bilan izohlash etarli emas — shilliq qavat immuniteti va oksidativ stress ham hal qiluvchi rol o'ynaydi [12]. Qiyosiy guruhda (adenoidit, EO'Osiz) transferrin va seruloplazminning ham oshgan bo'lishi (lekin asosiy guruhdan sezilarli past) nazofaringsdagi surunkali yallig'lanish o'rta quloq shilliq qavati holatiga bevosita ta'sir qilishini ko'rsatadi. Aynan shu sababli OBSning biokimyoviy profili adenoid o'lchamiga nisbatan kasallik rivojlanishini aniqroq bashorat qiluvchi mezon bo'lib chiqdi.

A kichik guruhida PILN + topik immunokorreksiya + o'yin autoinsufflyatsiyasi kombinatsiyasi transferrin va seruloplazminning tez me'yorlashuvini ta'minladi. PILN yallig'lanish shishini bartaraf etib, eshituv nayi o'tkazuvchanligini tikladi; topik lizatlar mukozal immunitetni faollashtirdi; autoinsufflyatsiya esa no'gora bo'shlig'i aeratsiyasini mexanik ta'minladi — bu uch komponentning sinergizmida eksudatning tez evakuatsiyasi ro'y berdi.

XULOSA

1. EO'O sekretli bosqichida OBSdagi transferrin darajasi ($12,4 \pm 1,1$ mg/l) va seruloplazmin ($4,8 \pm 0,5$ mg/l) me'yordan 4 barobar yuqori bo'lib, kapillyar giperpermabilitetsiya va faol oksidativ stressni ob'ektiv tasdiqlamoqda ($p < 0,001$).

2. OBSdagi transferrin darajasi va no'gora bo'shlig'i eksudatining qovushqoqligi o'rtasida kuchli to'g'ri korrelyatsiya aniqlandi ($r = 0,74$; $p < 0,01$), bu ushbu biomarkerni eksudatning reologik xususiyatlarini baholashda ishonchli noinvaziv vosita sifatida belgilaydi.

3. Transferrin >12 mg/l + sIgA $<0,12$ g/l kombinatsiyasi «yopishqoq quloq» va adhesiv eshitish zaifligining rivojlanish xavfini 4,5 barobar oshiradi — bu davolash taktikasini o'z vaqtida o'zgartirish uchun prognostik prediktor sifatida qo'llanilishi mumkin.

4. Optimallashtirilgan davolash sxemasi (PILN + topik immunokorreksiya + autoinsufflyatsiya) A kichik guruhida transferrinni 3,2 barobar kamaytirdi, seruloplazmini me'yorlashtirdi va sIgA ni 2,3 barobar oshirdi — bu B standart guruhiga nisbatan sezilari afzallik

($p < 0,05$).

5. OBSdagi transferrin va seruloplazmin ko'rsatkichlari dinamikasi 6 oy davomida kuzatuvda erishilgan natijalarning barqarorligini ob'ektiv baholash uchun noinvaziv monitoring mezoni sifatida tavsiya etilishi mumkin.

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