МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ УЗБЕКИСТАН
ОБЩЕСТВЕННОЕ ОБЪЕДИНЕНИЕ НЕВРОЛОГОВ УЗБЕКИСТАНА

NEVROLOGIYA

НЕВРОЛОГИЯ

**Рецензируемый
научно-практический журнал
“НЕВРОЛОГИЯ”
Публикуется 4 раза в год**

2 (90), 2022

АДРЕС РЕДАКЦИИ:
Республика Узбекистан
100007, г. Ташкент, ул. Паркентская, 51.
Тел.: 268-27-50.

Макет и подготовка к печати
проводились в редакции журнала.
Подписано в печать: 01.06. 2022 г.
Формат: 60 x 90 1/8.
Усл. печ. л. 11,16. Уч. изд. л. 7,6.
Тираж: 400 экз. Цена договорная

Оператор:
Мирзамухамедов О. Д.

Отпечатано в
ООО “GLOSSA” SHK NIM
100015, г. Ташкент, ул. Авлиё ота 93.
Тел.: (+99898)281-39-98

Журнал зарегистрирован
в Управлении печати и информации
г.Ташкента Per. № 0129 от 06.11.2014 г.

Электронная версия журнала
на сайтах: **www.med.uz www.tipme.uz**

Издается при поддержке компаний:
СП ООО “ NOBEL PHARMSANOAT”
(генеральный партнер),
«BERLIN-CHEMIE», «АРТЕРИУМ»,
и представительство
«PRO.MED.CS Praha a.s..»

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UDK:616.8-085.851 616.8-085.2/.3 616.8-07

KATTALARDAGI BOSH OG‘RIG‘I KASALLIKLARIDA PRENATAL ESTROGEN-TESTOSTERON BALANSI XAVF OMILI SIFATIDA

Rahimova Sh.M., Saidvaliyev F.S., Rahimova D.M.
Toshkent tibbiyot akademiyasi

Kalit so‘zlar: prenatal jinsiy steroidlar, 2D:4D barmoqlar nisbati, migren, zo‘riqish bosh og‘rig‘i, abuzus bosh og‘rig‘i

Prenatal jinsiy steroidlar (ya’ni prenatal testosteron (PT), prenatal estrogen (PE)) ko‘pincha kasallikni etiologiyasi va kechishi bilan bog‘liq. Ular jinslar o‘rtasidagi farqlarni ko‘rsatadi (erkaklarda PT PE ga nisbatan yuqori konsentratsiyasi), homiladorlikning birinchi trimestri oxirida PT cho‘qqiga chiqadi va miya hamda boshqa organlar tizimlarida doimiy "tashkiliy" o‘zgarishlarni keltirib chiqaradi. PT va PE ning nisbiy darajalari tug‘ilish, tezlik, kuch, tajovuzkorlik, autizm, ko‘plab saraton va yurak kasalliklariga turli xil ta’sir ko‘rsatishi mumkinligi tahmin qilingan. Biroq, PT va PE ni aniqlash hamda tadqiq qilish qiyin bo‘lganligi sabab bu tahminlar o‘z isbotini topmagan. Ikkinchi va to‘rtinchi barmoqlarning nisbiy uzunligi (raqamlar nisbati (2D: 4D)) PT bilan salbiy va PE bilan ijobiy bog‘liqligi aniqlanishi, bizga bunday tadqiqotlarni amalga oshirishimizga imkon beradi. 2D:4D va jinsiy dimorfizmning ko‘plab belgilari o‘rtasidagi assotsiatsiyalar o‘rganilgan bo‘lsa-da, 2D:4D va PT va PE o‘rtasidagi rivojlanish munosabatlari hali ham munozarali.

Ko‘pgina tadqiqotchilar testosteronning erta ta’sirining keyingi rivojlanish natijalariga, ayniqsa xatti-harakatlariga ta’sirini aniqlashga qaratilgan tadqiqot dasturlarini olib bormoqdalar. Bularga hayvonlar modellari bilan eksperimental ishlar va inson psixologiyasi sohasidagi ko‘plab ishlar kiradi, ularda testosteronning erta ta’sirining xulq-atvor jinsini farqlashdagi roliga qaratilgan [1]. Xulq-atvor natijalari bo‘yicha uzoq muddatli ishlarga qo‘shimcha ravishda, yaqinda testosteron erta ta’sirining kattalar salomatligiga, jumladan tuxumdon polikistozi sindromi [2,3] va reproduktiv tizim saratoniga [4,5] ta’siri ko‘plab qiziqishlarni uyg‘otmoqda. "Erta ta’sir etuvchi testosteron" tushunchasi sut emizuvchilar uchun keng ma’noga ega, chunki prenatal (va ehtimol postnatal) davrda erkaklarda testosteronning yuqori ishlab chiqarilishi birlamchi reproduktiv to‘qimalarning differentsiatsiyasini rag‘batlantiradi, so‘ngra balog‘at yoshi boshlanishidan oldin uzoq muddat nisbiy moyak sustligi kuzatiladi. Shu bilan birga, testosteronni erta ishlab chiqarishning o‘ziga xos shakli va vaqti turlar bo‘yicha farq qiladi va bundan ham muhimi, potentsial maqsadli to‘qimalar rivojlanishining shakli va vaqti turlar va to‘qimalar turlari o‘rtasida sezilarli darajada farq qiladi. Misol uchun, kemiruvchilar ko‘proq potentsial ko‘rsatishini kutish mumkin. Postnatal va prenatal testosteron ta’sirining muqobil rivojlanish shakllari tufayli ta’siri,

erkak primatlar (shu jumladan odamlar) esa chaqaloqlik davrida ko'proq testosteron ishlab chiqarganligi sababli kuchli postnatal ta'sir ko'rsatishini kutish mumkin [6].

Erkaklarda prenatal testosteron ishlab chiqarish. Homila davrida erkaklarda testosteron ishlab chiqarishning eng yuqori cho'qqisi homiladorlikning 10- va 18- haftalari orasida sodir bo'ladi. Keyinchalik, turli sabablarga ko'ra, masalan, gipotalamus-gipofiz bezining teskari aloqasi, platsenta steroid kontsentratsiyasining oshishi va prolaktin ishlab chiqarishning ko'payishi tufayli testosteron darajasi pasayadi [7]. Tahminlarga ko'ra, homiladorlikning kechki davri moyaklar faolligining ancha pastligi bilan tavsiflanadi, bu past testosteron kontsentratsiyasida va kindik qonida topilgan jinsiy o'xshashlikda aks etadi [7-10], garchi tug'ilishdan oldingi haftalarda homila steroid profillari qoniqarsiz bo'lsa-da, tug'ilish LG ko'tarilishiga olib keladi va bir necha soatdan keyin testosteron ko'tariladi [11]. LG to'lqini proksimal sabablari oxirigacha o'rganilmagan, lekin bu plasentar steroidlar qayta aloqasi samarasini birdaniga yo'qolishi bo'lishi mumkin, o'g'il bolalar qon zardobidagi umumiy testosteron konsentratsiyasi tug'ilgandan keyin 1-2 haftada bolalik darajasigacha tushadi, keyin 8-hafta boshlanishida 2-postnatal pikkacha ko'tariladi, 4-6 oylarda esa yana bolalik darajasigacha tushadi [7]. Shunday qilib, insonda testosteron ishlab chiqarilishi 3 farqli piklardan iborat: homiladorlikning o'rta davridagi pik va postnatal davrdagi 2 pik. Har bir pikda zardobdagi umumiy testosteron darajasi katta yoshdagi erkaklardagi konsentratsiya oralig'ida yoki undan pastroq diapozonda oshadi. Tug'ilganda jinsiy gormonni bog'laydigan globulin kontsentratsiyasi juda past bo'ladi, lekin tez ko'tariladi, shuning uchun bog'lanmagan testosteron birinchi postnatal pikda yuqori, ikkinchi tug'ruqdan keyingi pikda esa past bo'ladi [7]. Bu esa bir haftalik yoshdagi chaqaloqlarning tupugida testosteronning yuqori konsentratsiyasida, so'ngra qonda topilgan eng yuqori piklarda past konsentratsiyalarda namoyon bo'ladi [12,13]. Aksincha, digidrotestosteron kontsentratsiyasi tug'ilgandan keyingi birinchi haftalarda past bo'ladi, ammo tug'ruqdan keyingi ikkinchi pikda juda yuqori bo'ladi [14]. Odamning prenatal testosteron ishlab chiqarishidagi uchta pikdan homiladorlikning o'rtadagi piki muhim biologik ta'sirga ega ekanligi ma'lum bo'lib, u ko'proq yoki kamroq to'g'ridan-to'g'ri tug'ilish paytida ko'rinadigan jinsiy farqlarni keltirib chiqaradi, ammo jinsiy farqlanish tug'ilgandan keyin ham davom etishi mumkin. Moyaklar chaqaloqlik davrida ayniqsa tez o'sadi, bu moyak faolligini va gonadotropin stimulyatsiyasini aks ettirishi mumkin [13,15]. Ba'zi dastlabki dalillar, shuningdek, tug'ruqdan keyingi testosteron ishlab chiqarish chaqaloqlarda jinsiy olatni normal o'sishi uchun zarur ekanligini ko'rsatadi [16].

Homilada testosteronni to'g'ridan-to'g'ri o'lchash. Ta'kidlanganidek, prenatal androgen ta'sirining har qanday tahminiy kattalar belgisini tasdiqlash uchun muhim to'siq bachadondagi homiladan periferik qon namunalarining yetishmasligi hisoblanadi. Shu bilan birga, homilalik androgen darajasini to'g'ridan-to'g'ri o'lchash uchun bir qator muqobil usullar foydali tadqiqot vositalari sifatida taklif qilingan va ulardan biri 2D: 4D ni tasdiqlash uchun qo'llanilgan.

Amniotik suyuqlik. Homiladorlikning o'rtalarida erkaklarda testosteronning ko'tarilishi amniotik suyuqlikda aniqlanishi mumkin [10, 17-21], ammo abortlarda o'lchanadigan jinsiy farqlar homila periferik qoniga qaraganda kichikroq va amniotik testosteron darajasi va periferik qon darajasi o'rtasidagi bog'liqlik past bo'ladi [22]. Prenatal testosteronni o'rganish uchun amniotik suyuqlikdan foydalanish amniosentezni klinik sharoitda qo'llash bilan bog'liq bir qator amaliy kamchiliklarga ham ega. Namunalar har doim opportunistikdir, homila yoshini diqqat bilan kuzatib bo'lmaydi va amniotik testosteronning haqiqiyligini tekshirish uchun namunalarni osongina yig'ib bo'lmaydi, oxirgi bunday test 20 yil oldin salbiy natijalar bilan o'tkazilgan [22]. Bir tadqiqotda sonlarning to'g'ri nisbatini tekshirish uchun amniotik testosteron ishlatilgan [23]. 29 nafar o'g'il va qizdan iborat guruhda amniotik suyuqlik testosteronining chap qo'lda emas, balki o'ngda salbiy nisbati, ikki yoshda 2D:4D va estradiolning ijobiy tomonga nisbatan kichik tendensiyalari aniqlandi. Amniotik suyuqlikdagi testosteronning estradiolga nisbati muhim bashoratchi bo'lib, 2D:4D o'ng qo'lidagi tafovutning 20% dan biroz ortiqligini tushuntirdi. Biroq, estrogen vositachiligi muhim rol o'ynaydigan suyak o'sishiga doir ma'lumotlarni hiosbga olmaganda, estradiolning biologik ahamiyati va testosteronning estradiolga nisbati prepubertal jinsiy farqlashdagi boshqa ma'lumotlar yetarlicha o'rganilmagan [24,25].

Yangi tug'ilgan chaqaloqning kindik qoni. To'g'ridan-to'g'ri o'lchashning ikkinchi yondashuvi prenatal ta'sirni o'rganish uchun testosteronning neonatal kindik qon kontsentratsiyasidan foydalanadi. Yuqorida aytib o'tilganidek, kindik qon testosteron darajasi juda past va muhim paytlarda testosteron darajasiga mos kelmaydi [7-10]. Barmoqlarning to'g'ri nisbatini tekshirish uchun kindik qoni hali qo'llanilmagan, chunki bu usulning samaradorligi past.

Homilador onaning qoni. To'g'ridan-to'g'ri o'lchash uchun uchinchi yondashuv, androgenlarning homilaga ta'sirini o'rganish uchun homilador onaning testosteron darajasini aniqlash usulini qo'llaydi. Bu yondashuv yanada munozarali, chunki ona va homila jinsiy steroid darajalari o'rtasidagi munosabatlar yaxshi o'rganilmagan. Gravida gormoni darajasi homila ishlab chiqarilishi haqida juda kam ma'lumot beradi [10, 26,27], ammo bir tadqiqot erkak homila tashuvchi ayollarda testosteron darajasining yuqori ekanligini aniqladi [28]. Aksincha, bilvosita dalillar onaning androgen ishlab chiqarishi ayol homilasiga sezilarli ta'sir ko'rsatishi mumkinligini ko'rsatadi [29,30]. Bu usul barmoqlarning to'g'ri nisbatlarini sinash uchun ishlatilmagan va ijobiy natijalar barmoqlar nisbatlarining haqiqiyligini qo'llab-quvvatlasa-da, salbiy natijalar barmoqlar nisbatidagi jinsiy farqlarda androgenlarning roliga qarshi dalil sifatida talqin qilinishi mumkin emas.

Homilaning androgenlarini o'lchashning to'g'ridan-to'g'ri usullarining ishonchliligi haqidagi muammolarni chetga surib qo'ysak, raqamli nisbatlar barcha to'g'ridan-to'g'ri usullarga nisbatan bir qator amaliy afzalliklarga ega va muhim qo'shimcha ko'rsatkich bo'lib xizmat qilishi mumkin. To'g'ridan-to'g'ri o'lchovlar chaqaloqlik va bolalik davridagi natijalarni o'rganish uchun foydali bo'lishi mumkin bo'lsa-da, ular saraton yoki yurak-qon tomir kasalliklari kabi kattalar natijalarini o'rganish uchun unchalik amaliy emas, bu juda uzoq va qimmat istiqbolli tadqiqotlarni talab qiladi. Raqamlar nisbatlarini ham oson va ishonchli tarzda o'lchash va qayta o'lchash mumkin. Barmoqlar nisbatini o'rganish amniotik testosteronni o'rganishga qaraganda ta'sirlarni aniqlash uchun ko'proq subyektlarni talab qilsa-da, barmoq nisbati o'lchovlari ko'plab subyektlardan, kattaroq yoshda va klinik bo'lmagan sharoitlarda osongina to'planishi mumkin, bu esa kattaroq, ko'proq nazorat qilinadigan va ko'proq vakillik namunalarini olish imkonini beradi.

Egizaklar va jinsiy gormonlar. Testosteronning erkak homilalardan qo'shni homilaga amniotik suyuqlik perfuziyasi orqali o'tishi kemiruvchilarda ko'rsatildi [31,32] va shunga o'xshash hodisa egizaklar homiladorligida ham sodir bo'ladi [33]. Ushbu da'voni tasdiqlovchi to'g'ridan-to'g'ri dalil yo'q. Perfuzion "yuqtirish" odamlarda sodir bo'lsa ham, ta'siri kichik, chunki erkak egizakli qizlarning sezilarli "erkaklashuvi" aniqlanmagan. Ammo ba'zi tadqiqotlar buni tasdiqlagan [34,35], lekin hammasi ham emas [36]. Yaqinda o'tkazilgan tadqiqotda chap va o'ng qo'l taqqoslandi. 2D:4D qarama-qarshi jinsli va bir xil jinsli 4 yoshdan 15 yoshgacha bo'lgan egizaklarda o'lchandi [37]. Ushbu tadqiqot erkak egizaklari bo'lgan qizlarning 2D:4D nisbati urg'ochi egizakli qizlarga qaraganda pastroq ekanligini aniqladi, lekin faqat chap qo'lda ushbu nisbat aniqlandi. Amniotik suyuqlik orqali testosteron ta'siri bu topilmani tushuntirishi mumkin.

Hayvon modellarida eksperimental tadqiqotlar. Hayvonlarda prenatal androgenlarning ta'siri bo'yicha eksperimental tadqiqotlar inson ta'siri haqida muhim ma'lumot manbai bo'ldi. Homiladorlikning o'rtasi va tug'ruqdan keyingi birinchi davrda erkaklarda testosteron ishlab chiqarilishi barcha o'rganilgan sut emizuvchilar uchun odatiy holdir [38]. Birinchi postnatal cho'qqi kalamushlarda

[39,40], sichqonlarda [41], otlarda [38], qo'ylarda [42] va paromlarda [43] tasvirlangan. Biroq, ko'plab tadqiqotlar uchun, masalan xulq-atvordagi jinsiy farqlar [1], metabolik rivojlanish [44] va metastatik prostata saratoni [45] va b.lar uchun eksperimental tadqiqotlar amalga oshirilishi to'liq yo'lga qo'yilmagan. Ba'zi muammolar solishtirma natijalari kuzatilmaganligidan, boshqa muammolar esa fiziologiya yoki rivojlanish vaqti va tabiatidagi farqlardan kelib chiqadi, bu esa etiologik taqqoslashni qiyinlashtiradi.

Sonlar nisbatidagi farqlar. Jinsiy steroidlar to'g'ridan-to'g'ri suyaklarning nisbiy uzunligiga ta'sir qilishi mumkin, bu (1) prenatal davrda falangalarning rivojlanishiga yoki (2) metafizlarning o'sishiga ta'sir qiladi. Ikkala holatda ham barmoqlarning qisqa suyaklari haqida aniq ma'lumotlar yo'q va tahminiy fiziologiya uzun suyaklarning fiziologiyasi bilan o'xshashlikka bog'liq. Jinsiy steroid retseptorlari turli xil homila qismlarida ifodalanadi [46]. Homilaga ta'sir qilish asosan homiladorlikning birinchi trimestrida, moyaklar rivojlanishi va erkak homilada androgen ishlab chiqarishning ko'payishi davrida sodir bo'ladi. Jinsiy steroidlar metafizar to'qimalarga asosan estrogen retseptorlari a va b [47-50] orqali ta'sir qiladi. O'smir o'g'il bolalarda uzun suyaklarga ta'siri testosteronning mahalliy aromatizatsiyasi orqali amalga oshiriladi [51]. Androgen retseptorlari o'sish jarayonida ishtiroki ma'lum bo'lsa-da [52], ammo androgen retseptorlarining suyak uzunligiga ta'siri noma'lum. Estrogen retseptorlari vositachiligining metafiz o'sishiga ta'sirining eng oddiy tushunchasi shundaki, ular gipertrofiyalangan xondrositlarning tezlashtirilgan degeneratsiyasi orqali o'sish plastinkasining sinteziga yordam beradi [49]. Bundan tashqari, jinsiy steroidlar estrogenik yo'l orqali [50], balog'atga yetishning dastlabki bosqichlari bilan bog'liq bo'lgan o'sish sur'atlarini keltirib chiqaradi. O'sish sur'ati balog'at yoshida o'sish omillari, ayniqsa IGF-1 sekretsiyasini oshirishda jinsiy steroidlarning tizimli roli natijasidir [53]. Estrogenlarning o'sishni ingibitsiyalash ta'siri ularning o'sishni rag'batlantiruvchi ta'siriga bog'liq ko'rinadi, chunki gipertrofiyalangan xondrositlar yuqori darajadagi estrogenlar bilan rag'batlantiriladi, ular kamayadi va natijada degeneratsiyalanadi [49] Estrogenlarning suyak o'sishiga ta'siri balog'at davridagi chiziqli o'sishning normal modelida, shu jumladan bo'yning o'sishida asosiy rol o'ynaydi. Erkaklar urg'ochilarga qaraganda balandroq bo'yga (va odatda uzunroq barmoqlarga) gipermorfoz orqali erishadilar. Estrogen retseptorlari yetishmovchiligi yoki aromataza yetishmovchiligi aniqlangan bir nechta erkaklar balog'at yoshidan va suyak mineral zichligi past bo'lgandan keyin ham bo'yi o'sishda davom etdilar [54]. Jinsiy steroidlarning primordiya yoki metafizar o'sishiga ta'siri barmoq suyaklarining nisbiy uzunligidagi kuzatilgan farqlarga turli yo'llar bilan ta'sir qilishi mumkin, jumladan (1) jinsiy steroidlarga suyak sezgirligidagi farqlar yoki (2) suyaklar orasidagi farqlar. Barmoqlar nisbatidagi jinsiy farqlar, agar turli barmoqlarning suyaklari jinsiy steroidlarni turlicha qabul qilsa, paydo bo'lishi mumkin (chunki ular retseptorlarning faolligi, aromataza faolligi bilan farqlanadi yoki steroid komplekslari va o'sish omillari o'rtasidagi o'zaro ta'sir qilish uchun turli xil sharoitlarni yaratadi). Jinslar o'rtasidagi farqlar turli barmoqlarning suyaklari jinsiy steroidlarga o'xshash javob bersa ham, ularning o'sish vaqtlaridagi farqlar tufayli ham paydo bo'lishi mumkin. Suyaklarning eng yuqori o'sish davri yoki xondrifikatsiya yoki ossifikatsiyaning boshlanishi vaqtlaridagi farqlar, steroid ishlab chiqarishdagi jinsiy farqlarning o'zgarishi bilan birga, sezgirlik va suyaklarga ta'sir qilishning o'xshash shakllariga qaramay, jinsiy steroidlarning turli xil ta'sirlariga olib kelishi mumkin. Shu bilan birga prenatal steroidlar turli to'qimalar rivojlanishiga ta'sir qilishi mumkin.

Shunday qilib, odamlarda endogen prenatal androgenlarning ta'sirini o'rganish usullari, 2D:4D, o'z qiymatini saqlab qoladi. 2D:4D ning haqiqiyligini tekshirish uchun insoniy bo'lmagan modellardagi tajribalardan foydalanish mumkinmi? Barmoqlarning rivojlanishidagi turlararo farqlar ham yuqorida aytib o'tilgan natijalarga o'xshash umumlashtirish muammolarini keltirib chiqarishi mumkin. Hatto primatlar orasida ham raqamli nisbatlar sezilarli darajada farq qilishi mumkin. Ammo agar boshqa turlarda gomologik jins farqlari aniqlansa, tajribalar ularning umumiy kelib chiqishini tasvirlashga yordam beradi. Bir tadqiqot shuni ko'rsatdiki, barmoqlar nisbatidagi o'xshash jinsiy farqlar sutdan ajratilgan va katta yoshdagi laboratoriya sichqonlarida [54] topilgan, bu jinsiy farqlar haqida gap ketganda taksonomik jihatdan keng gomolog tizimni ko'rsatishi mumkin. Xuddi shunday jinsiy farqlar Hamadryas maymunlarining metakarpal suyak nisbatida ham topilgan [55], ammo qarama-qarshi jinsdagi farqlar 2D:4D jonli Gvineya maymunlarida [56] qayd etilgan. Bir tadqiqotda kalamushlarda prenatal testosteron darajasini pasaytirishi ma'lum bo'lgan kalamush oyoq barmoqlari nisbatiga prenatal spirtning ta'siri o'rganildi [57].

2D:4D tadqiqoti tarixi. 2D:4D da jinsiy dimorfizm (odatda erkaklarda ikkinchi barmoqlariga qaraganda to'rtinchi barmoqlari uzunroq) birinchi martta 19-asrda qayd etilgan [58]. Biroq, faqat 1998 yilga kelib 2D:4D formati (i) oyoq-qo'l va genitouriya shakllanishida ishtirok etgan genlarga bog'liq bo'lib, (ii) PT bilan salbiy va PE bilan ijobiy bog'liq [59] deb tahmin qilina boshlandi. Ushbu takliflar 2D:4D va jinsiy dimorfizmni yanada chuqurroq o'rganishni talab qildi va 2D:4D ga oid tadqiqotlar yillik soni 1998-yildan 2007-yilgacha 1 tadan 51 taga ko'paydi va 2008-yildan 2010-yilgacha bu raqam yiliga o'rtacha 60 ta maqolani tashkil etdi.

Odamlarda ikkinchi (ko'rsatkich) barmoq uzunligining to'rtinchi (nomsiz) barmog'iga nisbati (2D:4D) erkaklarda ayollarga qaraganda pastroqdir (Ekker, 1875; Jorj, 1930; Manning), Scutt, Wilson, & Lewis-Jones, 1998), shuning uchun bu nisbat jinsiy dimorfizmdan dalolat beradi. Populyatsiyalar ichida 2D:4D nisbati sezilarli darajada farq qiladi. Ikkala jinsda ham ikkinchi barmoq to'rtinchi barmoqdan uzunroq yoki qisqaroq bo'lishi mumkin (Jones, 1944). Odatda jinsiy dimorfizm jinsiy gormonlar ta'siri ostida homilaning erta rivojlanishida o'rnatiladi va 2D:4D nisbati odatda homilaning erta bosqichlaridan keyin barqaror hisoblanadi (masalan, Garn, Burdi, Babler va Stinson, 1975; Manning va boshq., 1998; Felps, 1952) yoki ikki yoshdan keyin (Brown, Hines, Fane & Breedlove, 2002). Garn va boshqalar (1975) 56 ta odam homilasida 7 haftalik va undan katta yoshdagi homilaning o'rtacha falangeal va metakarpal o'lcham darajasi kattalarnikiga juda mos kelishini aniqladilar. Qo'l suyaklarining nisbiy o'lchamlari homiladorlikning boshida aniqlanganligi ma'nosida juda umumiy edi. Felps (1952) homilada 2D:4D nisbatini o'rganmagan, faqat kattalardagina o'rgangan va boshqa tadqiqotlarga tayanib, homilada 2D:4D nisbati birdan kichik, birdan katta va birga teng degan xulosaga kelgan. Malas, Dogan, Evcil va Desdicioglu (2006) tashqi anomaliyalari bo'lmagan 161 homilani o'rganishda ayol homilalarda erkak homilalarga qaraganda ancha yuqori 2D:4D nisbatini aniqladi.

Korrelyatsiya tadqiqotlari. 2D:4D nisbati va ularning jinsga bog'liq belgilar bilan o'zaro bog'liqligini tavsiflovchi tadqiqotlar olib borildi. Takrorlash sinovidan o'tgan dastlabki tadqiqotlar shuni ko'rsatdiki, 2D:4D nisbati jinsiy rivojlanishda etnik kelib chiqishiga ko'ra farq qiladi, ammo erkaklarda 2D:4D nisbati barcha etnik guruhlarda ayollarga qaraganda 2D:4D nisbatidan kamroq bo'ladi va buni o'ng qo'lda yaqqol kuzatish mumkin, [60]; umuman olganda 2D:4D nisbati barcha sutemizuvchilar uchun o'xshash jinsiy farqlarni ko'rsatadi [61]; 2D:4D da jinsiy dimorfizm homila rivojlanishining boshida sodir bo'ladi [62]; 2D:4D nisbati sport qobiliyati bilan [63] autizm [64] osteoartrit kabi ba'zi bir jinsga xos kasalliklar uchun biomarker bo'lishi mumkin [65]. Shunday qilib, ko'pchilik tadqiqotlar PT [66] bilan korrelyatsiyaga qaratilgan bo'lsa, ba'zilari PT va PE [67] ga qaratilgan. Birinchi taqdiqoqtda normal PT darajasini o'zgartiradigan belgilar bilan 2D:4D korrelyatsiyasi o'rtasidagi bog'liqlik o'rganiladi. Tug'ma buyrak usti bezlari displaziyasi yuqori prenatal androgenlar darajasi va past 2D:4D nisbatini o'zaro bog'liqligini ko'rsatuvchi belgilardan sanaladi (68,69 14,15). Bundan tashqari, testosteronning yuqori sezuvchanligi past 2D:4D nisbati bilan bog'liqligi haqida boshqa tadqiqotlarda ham ta'kidlab o'tilgan [70,71]. Biroq, boshqa tadqiqotlar 2D: 4D va androgen sezgirligi [72] o'rtasidagi korrelyatsiya tadqiqotlari bo'yicha salbiy natijalarni xabar qildi va 2D:4D va PT [73] o'rtasidagi korrelyatsiyani shubha ostiga qo'ydi.

Bu esa korrelyatsiya ma'lumotlari bilan bog'liq cheklovlardan alohidalashgan eksperimental tadqiqotlarga ehtiyoj tug'dirdi.

Eksperimental tadqiqotlar. PNAS (Proceedings of the National Academy of Sciences of the United States of America) da Zheng va Cohn [74] 2D:4D rivojlanishida PT va PE ning ta'sirini sichqonlarda eksperimental usulda aniqladilar.

Zheng va Cohnning eksperimental tadqiqotlari korrelyatsion tadqiqotlar keltirib chiqargan muammolarni hal etdi. Ularning tadqiqotlari shuni ko'rsatdiki, homila barmoqlarining rivojlanishi va PT hamda PE orasida uzviy bog'liqlik mavjud. Barmoq tog'aylarining rivojlanishi erta biologik markeri (Sox 9) dan foydalanib, sichqonlarda 12,5- va 17-embrional kunlarida homila jinsiy farqlanishini o'rgandilar. Qizig'i shundaki, insonlarda bu natija o'ng kaftda yaqqol namoyon bo'ladi. Keyin esa ular rivojlanayotgan barmoq kurtaklari androgen va estrogen retseptorlariga boy ekanligini va bu ayniqsa 4-barmoqda sezilarli darajada ekanligini aniqladilar. AR va ER ning inaktivatsiyasi va retseptorlari antagonistlarini (flutamid va fulvestrant), digidrotestosteron va estradioldan foydalanish 2D:4D ning to'rtinchi belgi bo'yicha ta'sir qiluvchi PT va PE muvozanati bilan aniqlanishini ko'rsatdi; ya'ni AR xondrositlar proliferatsiyasini oshirdi, ER esa to'rtinchi barmoqda xondrositlar proliferatsiyasini pasaytirdi. Shunday qilib, 2D:4D da jinsiy farqlar ayollarga nisbatan erkaklarda topilgan PE qiymatlariga nisbatan yuqori PTdan kelib chiqadi va bu ta'sir to'rtinchi barmoq uzunligidagi o'zgarishlar bilan bog'liq. Muhimi, retseptor antagonistlari va tug'ilgandan keyin berilgan gormonlar 2D:4D ga ta'sir qilmagan. Shunday qilib, 2D: 4D nisbati nafaqat PT tomonidan, balki PT va PEning muvozanati bilan ham belgilanadi. PE ta'sirini hisobga olmaslik, korrelyatsion tadqiqotlarning kuchsizligi bilan birga, homila jinsiy steroidlari va 2D:4D o'rtasidagi haqiqiy munosabatlarni chalkashtiradi. Zheng va Cohn [75] to'rtinchi barmoq falangalarini shakllanishida ishtirok etuvchi 19 ta PT yoki PEga sezgir genlar ro'yxatini taqdim etdi. 2D:4D bilan bog'liq bo'lgan skelet genlarining ushbu ro'yxatidan foydalangan holda, endi biz 2D:4D va jinsga bog'liq kasalliklarning etiologiyalari, immunitet tizimi kasalliklari, yurak-qon tomir kasalliklari va boshqa bir qator kasalliklar o'rtasidagi aloqalarni batafsil ko'rib chiqishimiz mumkin.

Migren va zo'riqish bosh og'rig'ida 2D:4D nisbati xavf omili sifatida: Migren nogironlikka olib keluvchi, qator turli murakkab simptomatika bilan kechuvchi keng tarqalgan birlamchi bosh og'rig'idir. Bu miya tizimining xulq-atvor va / yoki fiziologik jihatdan buzilishining asosiy sababidir [75]. Butun dunyo bo'ylab faol bosh og'rig'idan aziyat chekuvchilar 46%ni tashkil etsa, shundan 11%i migrenga to'g'ri keladi. Ayollarda migren erkaklarga qaraganda ikki-uch baravar ko'proq uchraydi [76]. Masalan Xitoyda epidemiologik tadqiqotlar migrenning bir yillik tarqalishi 9,3% (erkaklar: 5,9%, ayollar: 12,8%) ekanligini ko'rsatdi [77]. Shuni ta'kidlash kerakki, bolalarning 10 foizi migrendan aziyat chekmoqda. Bu shuni anglatadiki, ba'zi hollarda migren bolalik davrida hayot sifatiga ta'sir qiladi [78,79]. Shunga qaramay, yaqinda o'tkazilgan tadqiqotlar shuni ko'rsatdiki, migren hali yetarli darajada o'rganilmagan kasallik sifatida qolmoqda [80,81]. Migrenning patofiziologik mexanizmlarini o'rganish uning ko'p faktorli kasallik ekanligini tasdiqlamoqda [82-86]. Migren, albatta, genetik moslashuvchanlikka bog'liq [87-89], hurujlar turli endogen omillar va atrof-muhit omillari [90-93] bilan bog'liq bo'lishi mumkin. Ammo hozirgacha migrenda prenatal omillar keng o'rganilmagan [94- 96].

Prenatal davrda homila turli omillarga, shu jumladan gormonal kasalliklarga nisbatan sezgirdir [97-99]. Intrauterin gormonal muhit, ehtimol, kattalardagi migrenga ham ta'sir etishi mumkin. Migren keng tarqalgan sog'liqni saqlash muammosi bo'lib, erta ontogenezda allaqachon aniqlanishi mumkin, bu esa bolalar va o'smirlarning 10% iga ta'sir qiladi [78,79]. Inson qo'lidagi 2 va 4 barmoqlarining uzunligi (2D: 4D) nisbati intrauterin hayot davomida jinsiy steroidlarning nisbatlarini baholashning mashhur usuli hisoblanadi. Geshvind va Galaburd (1985) prenatal testosteronning bosh miya chap yarim sharning muayyan hududlarining o'sishini sekinlashtirishi va o'ng yarim sharning gomolog hududlarining o'sishiga yordam beradigan birinchi gipotezani ilgari surdi. Tadqiqotchilar autizm va migren [100] kabi etiologiyaga yuqori prenatal testosteron darajasini bog'lashdi. Geshvind va Galaburd prenatal testosteron migren va chapaqaylik [100] o'rtasida bog'liqlik borligini tahmin qildilar.

Jinsiy dimorfizmning migren tarqalishi va rivojlanishiga ta'sirida ko'plab tadqiqotchilar jinsiy gormonlar [101,102] ning muhim rolini ko'rsatadi. Biroq, prenatal bosqichda jinsiy steroidlarning roli to'liq o'rganilmagan. Yuqorida keltirilgan prenatal gormonal atrof-muhit sharoitlari Xie va boshq. testosteronning prenatal ustunligi ayollarda [94] ko'proq migren tarqalishiga olib kelishi mumkinligini ko'rsatdi. Xitoy populyatsiyasida 2D raqamining maskulinatsiyalangan nisbati bo'lgan ayollar: 4D R & L odatda migren va zo'riqish bosh og'rig'idan ko'proq azob chekishgan, ammo erkaklar bunday munosabatlarga ega emaslar [94]. Tadqiqot natijalari shuni ko'rsatadiki, jinsiy steroidlarning prenatal ta'siri ham ayollar, ham erkaklarda migren xavfiga ta'sir qiladi.

Manning & Peters (2009) tadqiqotlarida, past 2D:4D chap taraflama aniqlangan [103]. Chap qo'lning ustunligi ham migren [100] bilan bog'liq. 1982 yilda Geschwind va Begun migren bilan kasallanganlar [103] orasida chapaqaylarning yuqori chastotasini xabar qildi.

Migren va jinsiy gormonlar darajasi o'rtasidagi munosabatlar ko'plab epidemiologik tadqiqotlar tomonidan e'tirof etilgan. Ayniqsa, ayollarda estrogen darajasining o'zgarishi migren [102] uchun xavf omili sifatida aniqlanadi. Purabolgasem va boshq., migrenli ayollarda tuxumdonlar polikistozi sindromi (TPKS) bilan yuqori darajadagi erkak jinsiy gormonlar (asosan testosteron) migren hurujlarini kuchaytirishi haqida hech qanday dalil yo'qligini aytdi [104]. Glintborg va boshq. esa migren TPKS bo'lgan ayollarda ko'proq tarqalganligini xabar qildi [105]. Sirpeterman va boshq. TPKS bilan homilador ayollar orasida zardobdagi androgenlarning periferik kontsentratsiyasi sezilarli darajada oshganini va xomila [106] uchun ortiqcha miqdorda androgenlarning potentsial manbai ekanligini ko'rsatdi. Ilgari estrogen ayollarda [107] migren hujumining boshlanishiga ta'sir ko'rsatishi mumkinligi ko'rsatilgan. Yaqinda ayol jinsiy gormonlari estrogen darajasini oshirgan migrenli erkaklarga ham ta'sir ko'rsatdi - van Osterhaut migrenli erkaklarda (oyiga kamida 3 epizod bilan) estrogen darajasini (E2) va androgen yetishmovchiligini bir vaqtning o'zida (N=17) kuzatishdi [108]. Shilds va boshq. o'z tadqiqotida surunkali migrenli (N= 14) erkaklarda testosteron darajasi [109] ham kamayganligini xabar qildi.

Migren tarqalishining ortishi mumkin bo'lgan prenatal buzilishlarning hayotiy xavflarini baholashda foydali bo'lishi mumkin bo'lgan ko'rsatkichlarga ehtiyoj bor. Intrauterin gormonal muhit migren rivojlanishida muhim rol o'ynaydi, ammo bu yaxshi o'rganilmagan. Prenatal testosteron va estrogen darajalari bilvosita 2D:4D raqam nisbati bo'yicha baholanadi, har ikkala jins uchun ham bunday ko'rsatkichlardan biri sifatida qaralishi mumkin.

Migren va jinsiy gormonlar o'rtasidagi munosabatlar bir necha bor namoyon bo'lgan bo'lsa-da, bu munosabatlarning patofizologiyasi hali to'liq tushuntirilmagan. Migren rivojlanishida prenatal bosqichda jinsiy steroidlarning roli o'rganilmagan. Migren erkaklar va ayollarda intrauterin hayotda "jinsiy steroidlar bilan dasturlashtirilgan" bo'lishi mumkin. Ayollarda yuqori prenatal testosteron darajalari migren tarqalishi bilan sezilarli darajada bog'liq. Erkaklar qarama-qarshi korrelyatsiyani boshdan kechirdilar: testosteronning past darajasiga ega bo'lgan erkaklar prenatal hayotdagi bolalar kattalardagi migrenlardan azob chekish ehtimoli ko'proq deb tahmin qilinadi.

Ko'pgina ilmiy ma'lumotlar shuni ko'rsatadiki, jinsiy steroidlar migrenning patofiziologiyasida ishtirok etadigan miya va miya ustuniga murakkab dinamik ta'sir ko'rsatadi. Misol uchun, Endryu G. va boshqalar migren bilan bog'liq bo'lgan bir nechta neyrotransmitter tizimlari reproduktiv sikl davomida reproduktiv steroid darajasiga qarab o'zgarib turishini va estrogen

stabilizatsiyasiga sezgir ayollar uchun samarali davolanishni ta'minlashi mumkinligini aniqladi [110]. Pfaff D. va boshqalar estradiol retseptorlari serotoninergik hujayralarga tutashgan neyronlarda dorsal rafeda taqsimlanganligi va serotonin migrenning rivojlanishida ham, yengillashishida ham rol o'ynashi mumkinligini xabar qildi [111]. Boshqa jinsiy steroidlar ham migrenni tartibga solishi mumkin. Eikermann-Haerter K va boshqalar oilaviy gemiplegik migrenning (FGM) sichqon modelidan foydalangan holda, testosteron migren rivojlanishining muhim patofiziologik mexanizmlaridan biri hisoblangan kortikal tarqaladigan depressiyani (CRD) bostirishini aniqladilar [112].

Migren bilan birgalikda ZBO tarqalishida ham jinsiy farqlar muhim rol o'ynaydi. Jinsiy steroidlar ZBO patofiziologiyasiga ham ta'sir etishi mumkin [113,114]. Odamlarda 2D:4D nisbati jinsiy dimorfizmga ega [115]. U homila rivojlanishning birinchi trimestrining oxirigi vaqt oralig'ida aniqlanadi va keyingi o'sish davrida kam o'zgaradi [116,117]. 2D: 4D nisbati prenatal testosteronning salbiy korrelyatsiyasi va prenatal estrogenning ijobiy korrelyatsiyasi hisoblanadi [118]. Raqamlar nisbati etnik kelib chiqishi va mamlakatga bog'liq [119]. Keng ko'lamli tadqiqotlar 2D: 4D nisbati va so'nggi xulq-atvor va fiziologik natijalarni birlashtiradi. Bu nisbat bilan spermatozoidlar soni, autizm, miokard infarkti (MI), koronar qon tomir kasalliklari, miopiya, kattalardagi o'pka saratoni, yon tomonlama amiotrofik skleroz va boshqa bir qator kasalliklar bog'liqligi aniqlangan [120-122]. Biroq, 2D:4D nisbati va asosiy bosh og'rig'i o'rtasidagi munosabatlar hali to'liq o'rganilmagan.

Tadqiqotlar shuni ko'rsatdiki, 2D:4D nisbati migren va ZBO da salbiy korrelyatsiyalanadi. Bundan kelib chiqadiki, yuqori PT va past PE ayollardagi migren va ZBO bilan bog'liq. Ammo bu taqdqiqot natijalari migren va ZBO ni ayollarda ko'p uchrash bilan bog'liqligiga to'g'ri kelmaydi. Ushbu hodisani tushuntirish qiyin bo'lsa-da, ammo past darajadagi estrogen, migren patofiziologik jarayoni klinik ma'lumotlar bilan tobora ko'proq qo'llab-quvvatlanmoqda. Masalan Sances G va b. bergan ma'lumotlarga ko'ra homiladorlikning erta davrlarida estrogen darajasi oshadi, lekin tug'ruqdan keyin tez tushishi kuzatiladi. Migren homiladorlik vaqtida yaxshilanganini kuzatish mumkin. Tug'ruqdan keyin esa deyarli barcha ayollarda migren xurujlari takrorlangan. [123]. Calhoun AH oral kontraseptiv vosiatalarni qo'llashgan, ular 20 mkg etinilestradiol saqlovchi preparatni xayzning 1-kunidan 21-kuniga qadar, qo'shimcha 0.9 mg conjugated equine estrogens ni 22-kunidan 28-kunigacha 11 ta xayz sikliga bog'liq migren bilan kasallangan ayollarga berishdi. Ular deyarli barcha bemorlar sikldagi bosh og'rig'i kunlarining kamida 50% kamayishiga erishganligini aniqladilar [124]. Ushbu natijalar bu hodisani tushuntirishda hizmat qilishi mumkin.

Faqat fiziologik omillar emas, balki psixologik omillar ham migren va ZBO [114] mexanizmida muhim rol o'ynashi mumkin. Migrenli bemorlar odatda migren bo'lmagan odamlarga qaraganda neyrotizm yoki salbiy ta'sirga nisbatan ko'proq sezuvchanlikni ko'rsatadilar [125]. Cao va boshq. aurasiz migrenli bemorlar, shuningdek, ZBO bilan og'rigan bemorlar nazorat guruhiga qaraganda yuqori nevrotizmga ega bo'lgan degan xulosaga kelishdi [126]. Ba'zi tadqiqotlar nevroz bilan migren va ZBO o'rtasida ba'zi aloqalar mavjudligini aniqlaganlar. Shu bilan birga, Hermann VM va boshq. estrogen Aizen modeliga ko'ra, neyrotizmning pasayishiga olib kelishi mumkinligi aniqlandi [127]. Bir qator olimlar migren va ZBO hurujlarini, ular bilan kechuvchi nevrozni prenatal jinsiy gormonlar nisbatiga bog'liq deb tahmin qilishmoqda.

Xulosa. 2D:4D nisbati va prenatal jinsiy testorteron va estrogen balansi orasidagi bog'liqlik ko'plab kasalliklar bo'yicha o'rganilgan bo'lsa-da, aynan bosh og'rig'i kasalliklarida keng yoritilmagan. Shu vaqtgacha faqat birlamchi bosh og'riqlari va prenatal testosteron va estrogen balansi orasidagi aloqalar o'rganilgan bo'lib, biz ushbu taqdqiqotlarni ikkilamchi bosh og'rig'i, yani abuzus bosh og'riqli bemorlarda o'rganishni rejalashtirdik. Bundan tashqari bu usul har bir populyatsiyada o'ziga xos natijalarga ega bo'lib, ushbu tadqiqot tadqiqot guruhlarini kengaytirish va turli populyatsiyalarda korrelyatsiyalarni tahlil qilish orqali davom ettirilishi kerakligini o'z ichiga oladi.

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УДК: 616.89-008.434:376.3-085-053.2

НАРУШЕНИЯ РАЗВИТИЯ РЕЧИ ПРИ НЕВРОЛОГИЧЕСКИХ ЗАБОЛЕВАНИЯХ У ДЕТЕЙ

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Ключевые слова: речевая деятельность, неврологическая заболевания, дети

Речевая деятельность представляет собой особую и наиболее совершенною форму общения, присущею только человеку.

Речь у ребёнка играет исключительно важную роль в формировании высших корковых и психических функций (ВПФ), она является базовой для формирования мышления, обеспечивает возможность планирования и регуляции поведения, влияет на развитие личности в целом [1] детей раннего возраста с тяжелой перинатальной патологией головного мозга на фоне терапии Кортексином [2] В осуществлении речи принимают участие речевые зоны коры головного мозга, расположенные в доминантном полушарии (у правшей – в левом, левшей – в правом). Речеслухо-