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THE SIGNIFICANCE OF THE INTESTINAL MICROBIOTA IN THE DEVELOPMENT OF AUTISTIC SPECTRUM DISEASES

Annotation

Autistic spectrum disorders (ASD or Russian RAS) have been widely researched as one of the diseases associated with the gut microbiome of the nervous system. Using the knowledge of microbes helps to understand this disease in a comprehensive way. Interestingly, researchers have also attracted the attention of the mother's oral cavity and vaginal microbiome as an important factor in the etiopathology of autism spectrum disorders (ASD). Thus, this review attempts to summarize knowledge about the microbiome and its relationship to the hypothesized etiology of ASK and related diseases. Effects of diet, prebiotics, probiotics, antibiotics, and fecal microbe transplantation on ASK have also been analyzed. Among them, the use of diet and probiotics is the most promising and advanced means due to the fact that they do not have side effects and are easy to take. Current gaps in knowledge and research call for larger and bolder investigations into the relationship between autism and the microbiome.

Key words: Autistic spectrum disorders, gut microbiome, prebiotics, probiotics, neuroendocrine and neuroimmune systems.

ЗНАЧЕНИЕ КИШЕЧНОЙ МИКРОБИОТЫ В РАЗВИТИИ ЗАБОЛЕВАНИЙ АУТИСТИЧЕСКОГО СПЕКТРА

Аннотация

Расстройства аутистического спектра (по англ. ASD или по русс. РАС) широко исследуются как одно из заболеваний нервной системы, связанных с кишечным микробиомом. Использование знаний о микробиомах помогает комплексно понять это заболевание. Интересно, что исследователи также привлекли внимание ротовой полости матери и вагинального микробиома как важного фактора этиопатологии расстройств аутистического спектра (РАС). Таким образом, в этом обзоре предпринята попытка обобщить знания о микробиоме и его связи с предполагаемой этиологией АСК и связанных с ним заболеваний. Также было проанализировано влияние пребиотиков, пробиотиков и трансплантации фекальных микробов на РАС. Среди них использование диеты и пробиотиков является наиболее перспективным и современным средством в связи с тем, что они не имеют побочных эффектов и их легко принимать. Текущие пробелы в знаниях и исследованиях требуют более масштабных и смелых исследований взаимосвязи между аутизмом и микробиомом.

Ключевые слова: Расстройства аутистического спектра, кишечный микробиом, пребиотики, пробиотики, нейроэндокринная и нейроиммунная системы.

ICHAK MIKROBIOTASINING AUTISTIK SPEKTR KASALLIKLARI RIVOJLANISHIDAGI AHAMIYATI

Аннотация

Autistik spektrdagi buzilishlar (ing. ASD yoki rus. RAS) asab tizimining ichak mikrobiomi bilan bog'liq holda yuzaga keladigan kasalliklardan biri sifatida keng tadqiq qilingan. Mikroblar haqidagi bilimlardan foydalanish ushbu kasallikni har tomonlama tushunishga yordam beradi. Qizig'i shundaki, tadqiqotchilar e'tiborini onaning og'iz bo'shlig'i va vaginal mikrobiomi ham autistik spektr kasalliklari (ASK) etiopatologiyasidagi muhim omil sifatida o'ziga jalb qilgan. Shunday qilib, ushbu obzorda mikrobiom va uning ASK va u bilan bog'liq kasalliklarning gipotetik etiologiyasi bilan aloqasi haqidagi bilimlarni umumlashtirishga harakat qilinadi. Parhez, prebiotiklar, probiotiklar, antibiotiklar va fekalniy mikroblari transplantatsiyasining ham ASK ga ta'siri tahlil qilingan. Ular orasida parhez va probiotiklardan foydalanish nojo'ya ta'sirlarga ega emasligi, qabul qilish usuli osonligi tufayli eng istiqbolli va ilg'or vositalardir. Bilimlar va tadqiqotlardagi mavjud bo'shliqlar autizm va mikrobiom orasidagi aloqadorlikni aniqlashda yanada kengroq va dadilroq izlanishlarni talab qiladi.

Kalit so'zlar: Autistik spektr kasalliklari, ichak mikrobiomi, prebiotiklar, probiotiklar, neuroendokrin va neyroimmun tizimlari.

Kirish. Kasalliklar, jarohatlar va xavf omillari global yuklamasi (Global Burden of disease (GBD)) tomonidan 2016 yilda o'tkazilgan so'nggi tadqiqot natijasiga ko'ra dunyoda 62,2 mln. odamda ASK mavjud [4].

Autizmining etiologiyasi geterojen bo'lib, irsiy, ekologik omillar va ularning kompleksi ta'sirida kelib chiqadi. Ko'pchilik tadqiqotlarda ichak va miya orasida "ichak-miya o'qi" nomi bilan ma'lum ikkiyoqlama aloqa mavjudligini aniqlangan. Ichak mikrobiotasi va autizm orasidagi bog'liqlik mikrobiomni tadqiq qilish sohasining asosiy jihatlaridan biri hisoblanadi. Bilamizki, odamlar ichak tarkibidagi moddalarni hayot faoliyatini mahsuloti sifatida qarashgan, ammo texnologiyalar rivojlanishi bilan biz tushundik-ki, ichak murakkab asab tizimiga ega va u miya bilan to'g'ridan-to'g'ri ta'sirlashadi va axborotning ikkiyoqlama uzatilishi amalga oshadi. Ushbu o'zaro ta'sir hatti-harakatlar, kayfiyat va bilishga intilishga bizdagi oshqozon-ichakning ichidagi suyuqlik ta'sir ko'rsatishidan dalolat beradi [5].

ASK bilan bir vaqtda bemorlarda tutqanoq, tashvishlanish, depressiya, Tik kasalliklari, Turett sindromi, ovqat hazm qilish yo'li muammolari, aqliy zaiflik kuzatiladi [6, 7]. Ular orasida qorinda og'riq, ich qotishi va ich ketishi kabi ovqat hazm qilish tizimi bilan bog'liq muammolar ASK bo'lgan bemor bolalarning 9%-idan 70% igacha qismida qayd qilinadi. Ushbu oshqozon-ichak muammolarini davolash qiyin, shuningdek ko'p hollarda ularga standart terapiya ham ta'sir ko'rsatolmaydi [8]. Ushbu muammolar ichak bakteriyalari bilan aloqador bo'lishi mumkin. Ichak-miya o'qi markaziy asab tizimi va ichakda yashovchi bir necha trillion mikroorganizmlar orasidagi o'zaro aloqadorlikni va ichak mikrobiotasidagi o'zgarishlar miyaning faoliyati va rivojlanishiga ta'sir qilishini ifodalaydi [9]. Shu tufayli, ichak mikrobiotasi tarkibi va funktsiyalari ASK davolashda muhim bo'lishi mumkin. Ushbu sharhda biz ASK tashxislangan bemorlar ichak mikrobiotasi tarkibining o'ziga xos xususiyatlari va probiotiklarning ichak-miya o'qi orqali ta'sir qilib oshqozon-ichak kasalliklari va ASK simptomlariga ta'sir qilishiga oydinlik kiritishni maqsad qilib qo'ydik.

Mavzuga oid adabiyotlarning tahlili. Ichak mikrobiotasi disbiozi va ASK. Ko'pchilik ma'lumotlarga ko'ra, ASK bo'lgan bolalar ich qotishidan aziyat chekishadi, ichak mikrobiotasi tarkibida *Escherichia/Shigella* va *Clostridium* klasteri XVIII, Fusobacteriales tartibi, Actinomycetaceae oilasi, *Fusobacterium*, *Barnesiella*, *Coprobacter*, *Olsenella*, and *Allisonella* avlodlari vakillari sonining nisbiy ortishi, *Faecalibacterium prausnitzii*, *Bacteroides eggerthii*, *Bacteroides uniformis*, *Oscillospira plautii* va *Clostridium (C.) clariflavum* sonining kamayishi kuzatiladi [10, 11, 12]. Bundan tashqari, lactobatsillalar sonining kamayishi bemorlardagi ich qotishi bilan bog'liq bo'lishi mumkin, chunki ularning kamayishi ASK bo'lmagan sog'lom bolalarda ham surunkali ich qotishiga sabab bo'ladi [13, 14]. Allergiyasi bo'lgan ASK bo'lgan bemorlar axlatida autoimmun kasalliklar kelib chiqishiga sabab bo'luvchi *Proteobacteria* tipiga mansub bakteriyalarning nisbiy soni yuqoriligi qayd qilingan [15]. Shuningdek, OHQY simptomlariga ega ASK bemorlarda *Turicibacter sanguinis*, *C. lituseburensis*, *C. disporicum*, *C. aldenense* va *O. plautii* soni ham yuqoriligi qayd qilingan. Yaqinda olimlar ASK bo'lgan bemorlar ichagida toksin ishlab chiqaruvchi bakteriyalar sifatida ma'lum *C. histolyticum* guruhi mikroorganizmlar soni yuqori ekanligini aniqlashdi [16].

ASK larida ichak-miya o'qidagi salbiy o'zgarishlar. Gipotalamus-gipofiz-buyrak usti bezi o'qi, adashgan nerv, neyroendokrin va neyroimmun tizim sifatida ma'lum bo'lgan simpatik va parasimpatik nerv va ichak nerv tizimi ichak va miya o'rtasidagi ikki yo'nalishga ega biokimyoviy signal yo'li hisoblangan ichak-miya o'qini tashkil qiladi [17]. Ko'plab tadqiqotlarda ushbu omilning ASK etiologiyasidagi ahamiyati o'rganilgan [18]. Ichak mikrobiotasi neyroendokrin, neyroimmun va vegetative asab tizimi orqali miyaning funktsiyalariga ta'sir ko'rsatadi [19].

ASK da ichak disbiozi va immun tizimining boshqarilishi buzilishi. Autizm da ichak mikrobiotasi disbiozi immunitetning buzilishiga olib keladi [20]. Interleukin-1 (IL-1), interleukin-6 (IL-6), interferon (IFN) va shish nekrozi omili (ShNO) faol immune tizimi tomonidan ajratiladigan xemokinlar va sitokinlar bo'lib, ular gemoensefalitik to'siq orqali o'ta oladi. Ushbu mediatorlar (vositachilar) bosh miyaning endothelial hujayralariga yopishadi va immunologik reaksiyalarni chaqiradi [21]. Tadqiqotlar ASK guruhi qoni plazmasida IL-1, IL-6 va IL-8 miqdori nazorat guruhidagi normal rivojlangan odamlar qon plazmasidagi ushbu sitokinlarga nisbatan yuqori ekanligi ko'rsatilgan [22]. Bundan tashqari ushbu immun tizimining 80% I ichak shilliq qavatida va uning atrofida joylashadi [23].

Probiotiklar ASK ichak-miya o'qini regulatsiyalash orqali ta'sir qilishi. Ichak mikrobiotasi-miya o'qini probiotiklar yordamida modulyatsiyalash ASK davolash va OHQT dagi buzilishlarni yengillashtirishda samarali strategiya bo'lishi mumkin. ASK bo'lgan bemorlarda olib borilgan probiotiklarni qo'llashga oid klinik tadqiqotlar *Clostridium* avlodiga mansub toksin ishlab chiqaruvchi turlarni probiotiklar yordamida kamaytirishga qaratildi. Probiotiklar ASK da qo'shimcha va muqobil terapiya sifatida tavsiflanadi [24]. 3 oy davomida probiotik qo'shimchalar olgan 5-9 yoshli, ASK bo'lgan bolalarda OI mikrobiotasi, OI simptomlari yaxshilanishi, ASK simptomlarining og'irlik darajasi kamayishi, xulq-atvor va faoliyatda ijobiy o'zgarishlar qayd qilindi [25]. Shuningdek, 12 yoshli bolaga 4 oy davomida kiritilgan 10 ta probiotikdan iborat multishtamm jamlanma ta'sirida ASK da kuzatiladigan oshqozon-ichak bilan bog'liq simptomlar kamayishi va yaxshilanishi qayd qilingan [26].

Probiotiklarning depressiya va tashvishlanish kabi belgilarga ta'siri yaxshi ma'lum. Og'iz orqali bo'lishi vankomitsin va *Bifidobacterium* qo'shimchalarini olgan autist bolalarda 3-(3-gidroksifenil)-3-gidroksiuron kislotasi, 3-gidroksifenilsirka kislotasi, va 3-gidroksigippur kislotaning siydikdagi miqdori sezilarli kamayadi [27]. 3-(3-gidroksifenil)-3-gidroksiuron kislotasi miyada katexolaminlar miqdorini kamaytirish orqali autizm belgilari yuzaga kelishiga sabab bo'ladi [28]. Shunday qilib, ushbu metabolitlar miqdorining kamayishi autist bolalarda ko'z kontakti tiklanishi va ich qotish belgilari kamayishiga olib keladi [27].

Probiotiklar ASK belgilarini kamaytiruvchi birikmalarni modulyatsiyashi mumkin. Irsiy va atrof-muhitning xavfli omillari birlashib glutamat (Glu) bilan bog'liq qo'zg'atuvchi va γ -aminobenzoy kislotaga bog'liq tormozlovchi neyrotransmitter autizm orasidagi muvozanatni buzadi [29]. Probiotiklar γ -aminobenzoy kislotasi, glutamat va 5-GT (5-gidroksitriptamin) kabi neyrotransmitterlarga ta'sir qila oladi [30]. Tabouy va boshq. (2018) Shank3 mutant sichqonlarida *L. reuteri* bilan davolash takrorlanuvchi odatlar kamayishi va gippokamp va prefrontal po'stloqda γ -aminobenzoy kislotasi retseptorlari genlari (GABRA1, GABRA1 va GABRB1) ekspressiyasi va oqsil miqdori ortishini qayd qilgan [31]. Bundan tashqari, *Lactobacillus* bilan davolash miya va ichakni bog'lab turuvchi adashgan nerv vositasida sichqonlarning emotsional va γ -aminobenzoy kislotasi retseptorlari ekspressiyasini boshqarishi ko'rsatilgan [32].

Tadqiqot metodologiyasi. So'nggi yillarda ichak mikrobiotasini o'rganishda MALDI-TOF mass-spektrometriya, *in situ* flyuoesent gibridizatsiya, real vaqt rejimida ishlaydigan miqdoriy PZR, immunoferment tahlil va keyingi avlod sekvenirlash kabi molekulyar genetik usullardan foydalanilmoqda [33].

Qator tadqiqotlarda real vaqt rejimida ishlaydigan miqdoriy PZR autizmi bo'lgan bolalar ichak mikrobiotasi tarkibidagi turli guruhga mansub mikroorganizmlarni miqdoriy o'rganishda foydalanish haqida ma'lumotlar berilgan. Real vaqt rejimida ishlaydigan miqdoriy PZR oddiy PZR ga nisbatan qator afzalliklarga ega. U oxirgi mahsulotning ko'pligiga emas mahsulot to'planishining logarifmik fazasiga yo'naltiriladi. Shu tufayli undagi natijalar aniq, chunki unga amplifikatsiyaning samaradorligi yoki reagentning kamayishi kam ta'sir ko'rsatadi.

Tahlil va natijalar. Shunday qilib, ASK ichak mikrobiotasi uchun xos bo'lgan xususiyatlarni o'rganish dolzarb hisoblanadi, chunki hozirgi paytgacha olingan ma'lumotlar autizm belgilari rivojlanishida ichak disbiozining ehtimoliy etiopatogenetik roli katta ta'sir ko'rsatishidan darak beradi. Shuningdek, ASK tushunchasi qamrab oladigan holatlarning geterogenligi, ushbu holatlar etiologiyasining ko'p omilli ekanligi murakkab dizaynli va biologik ko'rsatkichlar va psixopatologik simptomlarini baholashning maksimal standartlaridan foydalanadigan keng ko'lamli tadqiqotlarni talab qiladi.

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