

i skustva i novi ni od svetot

**REHABILITACIJA NA AUTIZMOT
SO IMMUNOMODULACIJSKIM
TERAPIJAM**

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Rezi me

Avtoimunitetot može da ima ključna uloga
vo patogenezata na autizam, so ranopostupak
na narušavanje na razvojni centralni
nervni sistem. Virusite, kako što se virusot
na morbilite, bi možele da predizvikaat
avtoimunitet, kako što e evidentirano so
silna korelacija na mozgane avtoantitela
i antitelata na morbilite. Decata so
autizam, isto taka, imaat specifični
avtoantitela na mozokot i podignati
ni vo avtoimunitet – specifični citokini
interleukin-12 i gama-interferon. Vsu
nost, postoji silna pričina da se veruva
deka vo autizam se vključeni imunoaktivacija
i avtoimunitet kaj mozokot, a pacienti
te pokažuvaat odgovor na terapijate
na imunomodulacijata. Ponatamu, so
cel da se identifikuva avtoimuno-
autistično narušavanje (AAN) se
razviva protokol za testiranje na
avtoimunitetot. Vo ovoj napisovite
istražuvani razvoji se opišani za da
sugeriraat deka avtoimunitetot e
mnogubitna celost koja treba da se
koristi za da ponudi rehabilitacija
na autističnim pacijentima preku
imunoterapija.

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world experience and current events

**REHABILITATION OF AUTISM WITH
IMMUNE MODULATION THERAPY**

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Abstract

Autoimmunity may play a key role in the
pathogenesis of autism, an early-onset disorder
of the developing central nervous system. Vi-
ruses such as measles virus might induce au-
toimmunity as evidenced by a strong correlation
of brain autoantibodies and measles antibodies.
Autistic children also harbor brain-specific
autoantibodies and elevated levels of autoim-
munity-specific cytokines interleukin-12 and
interferon-gamma. Collectively, there is com-
pelling reason to believe that autism involves
immune activation and autoimmunity to brain
and patients show responsiveness to immune
modulation therapy. Furthermore, for the pur-
pose of identifying Autoimmune Autistic Dis-
order (AAD), a protocol for testing autoimmu-
nity is developed. In this article, novel research
developments are described to suggest that
autoimmunity is a very important target that
should be used to offer rehabilitation to autistic
patients through immune therapy.

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Klu-ni zborovi: autizam; avtoimunitet, imunoterapija; avtoantitela; virusi; citokini; CNS-naru{ uvawa

Voved

Autizmot e biologsko naruzuvawe { to ja o{ tetuva funkcijata na centralniot nerven sistem (CNS). Toj manifestira razurnuva~ki nevrolo{ki, kako i psihijatriski rezultati kaj zabolento lice. Dijagnozata se pravi ranoto detstvo, pred voзраст od 34 meseci, no nevoljata prodol`uva do zrela voзраст, stanuvaj}i do`ivotna pre~ka (invalidnost). Vo posledno vreme autizmot ne se definira spored etiologijata ili patologijata, tuku spored prisustvoto na poseben model na karakteristiki na vladeewa { to sledat poseben razvoen tek so indikacija za odlou`uvawe ili devijanten razvoj vo prvite tri godini od`ivotot. Autisti~nite vladeewa { to go karakteriziraat naruzuvaweto, vkladuvaat "kvalitativni deficiti" vo ~etiri glavni kategorii: **deficiti na razvojnite stapki i/ili sekvencii** i **deficiti na reakcija na senzornite stimulansi**; **deficiti na govor, jazyk i kognitivni kapaciteti**; **kako i deficiti na socialni interakcii ili na~ini vo odnos so drugite lu|e**. Do neodamna za~estenosta na autizmot be{e 4-5 na sekoj 10.000 ra|awa, no brojot na autisti~nite slu~ai nagloraste (1). Denes se veruva deka autizmot e najbrzo raste~ka razvojna pre~ka kaj decaata so presmetana za~estenost od 1 vo 125 do 1 vo 500 ra|awa.

Autizmot e najprominentno mozo~no naruzuvawe od celiot spektar na autisti~ni naruzuvawa (SAN) { to vkladuva grupa na razvojni naruzuvawa. **Toa e kompleksno i heterogeno naruzuvawe**. Mnogokratni faktori mo`e da bidat involvirani vo patogenezata na naruzuvaweto (2, 3). I ako nema nekoj genidentifikovan specifi~no za autizmot, deset ili pove}egeni se presmetani i poso~eni za spektarot na autisti~nite naruzuvawa (4).

Key words: Autism; Autoimmunity; Immunotherapy; Autoantibodies; Viruses; Cytokines; CNS disorders

Introduction

Autism is a biological disorder that impairs the function of the central nervous system (CNS). It manifests devastating neurological as well as psychiatric outcomes in the affected individual. The diagnosis is made during early childhood before the age of 34 months but the affliction continues well into the adulthood, becoming a life-long disability. Currently, autism is defined not by etiology or pathology but by the presence of a particular pattern of behavioral characteristics that follow a particular developmental course with evidence of delay or deviant development within the first three years of life. Autistic behaviors that characterize the disorder include "qualitative deficits" in **four** main categories: **deficits of developmental rates and/or sequences; deficits of responses to sensory stimuli; deficits of speech, language, and cognitive capacity; and deficits of social interactions or ways in relating to other people**. Until recently, the incidence of autism was 4-5 in every 10,000 births but the number of autistic cases is rising sharply (1). Today, autism is believed to be the fastest growing developmental disability in children with an estimated incidence of 1 in 125 to 1 in 500 births.

Autism is the most prominent brain disorder of all autistic spectrum disorders (ASD) that include a group of developmental disorders. **It is a complex and heterogeneous disorder**. Multiple factors might be involved in the pathogenesis of the disorder (2, 3). While no single gene has been identified specifically for autism, an estimated ten or more genes have been proposed for autistic spectrum disorders (4).

I ako baraweto na genetski te faktori se favorizira, se o~ekuva deka genetski te faktori pokrivaat ne pove}e od 10% kaj autisti~nata populacija; drugi te 90% na autisti~nata populacija se objasnuva so negenetski faktori. Tie vku~uvat faktori na sredinata, imunofaktori te, nevrohemiski te faktori i drugi, se u{ te, nepoznati faktori. Pred nekolku godini nie imavme hipotezi deka imunoaktivacijata vodi kon avtoimunitet i inflamacijata na mozokot { to mo`e da odigra va`na uloga vo patogenezata na autizmot (5). A sega inflamacijata na mozokot e najdena i kaj autizmot (6). Ovoj nau~en napis gi opi{uva istra`uvaki te razvoji { to mo`e da se koristat za rehabilitacija na autizmot so imuno-modulacijska terapija (IMT).

Avtoimuna teorija za autizmot

Autizmot e mnogu kompleksno nevrolo{ko naru{uvawe. Nie autizmot go prou~uvavme kako edno avtoimuno naru{uvawe, kade {to virusno-avtoimune interakcii mo`e da vodat kon patolo{ki promeni vo CNS. [pekuliravme deka edna virusno predizvikana avtoimuna reakcija na mielinot na mozokot vo razvoj mo`e da go o{teti anatomski ot razvoj na nervnite pati{ta kaj decata so autizam (5). Ova e mnogu va`no kaj mozokot vo razvoj ednostavno bi deji brzinata na transmisijata na nervniot impuls bitno zavisi od strukturnite osobini na izoliraweto na mielinската obvika, povrzuvajji gi nervnite vlakna i dijametralnata oska. Nakuso, napravivme hipoteza deka edna avtoimuna reakcija na mozo~nite strukturi, osobeno na mielinската obvika, ima kriti~na uloga vo predizvikuvaweto na nevrolo{ki te o{tetuvawa kaj pacienti so autizam. Postavivme deka edno imuno o{tetuvawe po prirodната infekcija ili vakcinacija mo`e da predizvika "zaseci" ili mali promeni kaj mielinската obvika. Ovie anatomski promeni mo`e ul timati vno da vodat kon do`ivotni naru{uvawa na povi{soki mentalni funkcii, kako {to se

While the search for genetic factors is favored, genetic factors are expected to account for no more than 10% of the autistic population; the remainder 90% of the autistic population will be explained by non-genetic factors. They include environmental factors, immune factors, neurochemical factors and other as yet unknown factors. Several years ago, we hypothesized that immune activation leading to autoimmunity and inflammation in the brain may play an important role in the pathogenesis of autism (5). And now the inflammation of the brain has been found in autism (6). The present scientific article describes research developments that can be used to rehabilitate autism with immune modulation therapy (IMT).

Autoimmune Theory for Autism

Autism is a very complex neurological disorder. We studied autism as an autoimmune disorder, in which viral-autoimmune interactions may lead to pathological changes in the CNS. We speculated that a virus-induced autoimmune response to developing brain myelin may impair anatomical development of neural pathways in autistic children (5). This is very important in the developing brain simply because the speed of nerve-impulse transmission depends essentially on structural properties of the insulating myelin sheath, connecting nerve fibers, and axon diameter. Briefly, we hypothesized that an autoimmune reaction to brain structures, in particular myelin sheath, plays a critical role in causing neurological impairments in patients with autism. We postulated that an immune insult after a natural infection or vaccination might cause "nicks" or small changes in the myelin sheath. These anatomical changes could ultimately lead to life-long disturbances of higher mental function such as learning,

u-eweto, pameteweto, komuniki jata, social na interakcija itn. Identifikavme nekoj virusni, nevralni i avtoimuni faktori { to ne vodea da razvime spekulativen "neuroavtoimuniteten model na autizmot", koj neodamna be{ e objaven (3, 7). Smetame deka autizmot mo` e uspe{ no da se tretira koristej{i nekoj od terapiite { to se poka`aa efikasni pri lekuwane na drugi avtoimuni bolesti. Konova, me|utoa, kompletna identifikacija i karakterizacija na avtoimunata patologija kaj autizmot e od najgolemva`nost deneska.

Avtoimuna hipoteza kaj autizmot

Faktori na sredinata (virus) →
Pogre{no i muno regulirawe →
Avtoimunitet na mozokot →
Autizam

Avtoimunitetot se misli deka e "sr`#na problemot kaj autizmot. Avtoimunitetot e abnormalna imunoreakcija, vo koja imunolo{ki ot sistem stanuva glaven vo reakcijata protiv organite na teloto, a vistski ot rezultat e avtoimuna bolest. Klini~kata prezentacija na avtoimunitete bolesti opfa}a nekolku faktori: faktori na sredinata, genetskata povrzanost osobeno na genite za imunolo{ki ot odgovor, imunoabnormalnostite na imunoregulatornite T-kletki { to poteknuvaat od timusot, avtoantitelata, osobeno organsko specifi~ni avtoantitela, faktorot na polot za pogolema za~estenost kaj ma{-ki ot ili kaj`enski ot pol, hormonski te faktori i reakcijata na imunomodulacijskata terapija (2, 3). Virusite se smetaat za aktivira~ki pottiknuva~i na avtoimunitete bolesti, koi op{ to se povrzuvaat so IR-genite, na primer: HLA-alelite, haplotipite ili Gmizotipovite, locirani na hromozomot 6 kaj ma`ite. Kako { to e izlo`eno vo Tabela 1, mnogu od ovie parametri se identifikuvani sega kaj decata so autizam.

memory, communication, social interaction, etc. We have identified certain viral, neural, and autoimmune factors that led us to develop a speculative "Neuroautoimmunity Model of Autism" that was recently published (3, 7). We think that autism can be treated successfully using some of the therapies proven effective in treating other autoimmune diseases. To that end, however, the complete identification and characterization of autoimmune pathology in autism is of utmost importance today.

Autoimmune Hypothesis in Autism

Environmental Factors (virus) →
Faulty Immune Regulation →
Autoimmunity to Brain →
Autism

Autoimmunity appears to be the "core" of the problem in autism. Autoimmunity is an abnormal immune reaction in which the immune system becomes primed to react against body organs, and the net result is an autoimmune disease. The clinical presentation of autoimmune diseases involves several factors: environmental factors, genetic link especially of immune response (IR) genes, immune abnormalities of thymus-derived immunoregulatory T cells, autoantibodies especially organ-specific autoantibodies, gender factor for greater prevalence in males or females, hormonal factors, and response to immune modulation therapy (2, 3). Viruses are commonly considered as trigger agents for autoimmune diseases, which are generally linked to IR genes, for example HLA allele, haplotypes or Gm isotypes, located on chromosome 6 in man. As summarized in Table 1, many of these parameters have now been identified in autistic children.

Tabela 1. Avt oimuni abnormalnost i kaj aut izmot

1. Autizmot poka`uva mikrobiološki povznanosti na nekoi virusi, kako { to se morbilite (8, 9), rubeolata (10) i CMV (11, 12).
2. Autizmot poka`uva zgolemena frekventnost na genetski odgovori za imunološki odgovor, na primer: HLA-antigeni, C4B-nulti ot al el, haplotipot B44-SC30-DR4, HLA-C i HLA-B1 (13-15).
3. Autisti~nite pacienti imaat o{ tetuvava na celularni ot i humoralni ot imunitet: namaluvawe na IgA; zgolemuvawe na IgG3, anti nuklearni antitel a i imunokompleksi; namaluvawe brojot na limfocitite, CD4 + T-kletki { to pomagaa i kletki-prirodni ubijci (KPU); zadu{ en celularen imunitet kako reakcija na namalena mitogeno predizvikan a limfocitna stimulacija i namalena KPU-kletno-aktivnost (16-19).
4. Decata so autizam poka`uvaat nesoodvetna imunoreakcija na osnovni ot protein na mielinot (20) i vakcinata protiv morbil i-zau{ ki-rubeola (MPR) (21).
5. Autizmot go opfa}a faktorot na polot i ma{ ki ot pol zaboluva ~etiri pati pove}e odo{ to `enski ot (3).
6. Autizmot ~esto se javuva vo vrska so semejnata istorija na avtoimuni bolesi, na primer: pove}ekratna skleroza, revmatoiden artritis, tip II dijabetes (22).
7. Autizmot, isto taka, gi opfa}a i hormonalni te faktori, na primer: sekretin, beta-endorfin i taka natamu (2).
8. Autisti~nite pacienti imaat organsko specifi~ni avtoantitel a za mozo~nite antigeni, kako { to se mielin bazi~ni ot proteina (MBP) (3, 5), neuron-akson filamentozni proteini (NAFP) (3, 23), proteini te na serotonin receptorot (24), galaktocerebrozidi te (3) i proteini te na nucleus caudatus (25).
9. Autisti~nite pacienti poka`uvaat imunofunkcija kako reakcija na T-kletno-nata aktivacija (26, 27), poka~uvawe

Table 1. Autoimmune Abnormalities in Autism

1. Autism shows microbial associations of certain viruses such as measles (8, 9), rubella (10) and CMV (11, 12).
2. Autism displays increased frequency of immune response (IR) genes, for example HLA antigens, C4B null allele, haplotype B44-SC30-DR4, HLA-C and HLA-B1 (13-15).
3. Autistic patients have impairments of cellular and humoral immunity: decrease of IgA; increase of IgG3, antinuclear antibodies and immune complexes; decrease of lymphocyte count, CD4+ T helper cells and natural killer (NK) cells; and suppressed cellular immunity as reflected by decreased mitogen-induced lymphocyte stimulation and reduced NK cell activity (16-19).
4. Autistic children show inappropriate immune reaction to myelin basic protein (20) and measles-mumps-rubella (MMR) vaccine (21).
5. Autism involves a gender factor affecting males about four times more than females (3).
6. Autism often occurs in conjunction with a family history of autoimmune diseases, for example, multiple sclerosis, rheumatoid, type II diabetes and arthritis (22).
7. Autism also involves hormonal factors, e.g., secretin, beta-endorphin, etc. (2).
8. Autistic patients have organ-specific autoantibodies to brain antigens such as myelin basic protein (MBP) (3, 5), neuron-axon filament proteins (NAFP) (3, 23), serotonin receptor proteins (24), galactocerebroside (3), and caudate nucleus proteins (25).
9. Autistic patients show immune activation as reflected by T cell activation (26, 27), elevation

na avtoimunetiški te specifi~ni citokini (7, 28) i inflamaciija na mozokot (6).

10. Autisti~nite pacienti dobro reagiraat na avtoimunata terapija so oralni avtoantigeni (3), transfer-faktor { to poteknuva od leukocitite (29) i intravenozni te immunoglobulini (19).

of autoimmunity-specific cytokines (7, 28) and inflammation of the brain (6).

10. Autistic patients respond well to autoimmune therapy with oral autoantigen (3), leukocyte-derived transfer factor (29) and intravenous immunoglobulin (19).

Kaj avtoimunata patologija, edna od istaknate karakteristiki, se organsko-specifi~nite avtoantitela. Vo slu~ajot na autizam, tie }ebidat mozo~no-specifi~ni avtoantitela. Sekako, zna~itel en broj na decata so autizam imaat avtoantitela za nekolku mozo~ni antigeni. Odsite ispitani mozo~ni avtoantigeni, najza~esteno se javuva MBP na mielinskata obvika, { to sugerira {e da zaklu~ime deka avtoimunata reakcija kon MBP se javuva kaj autizmot (3, 5). I ako ne e poznat precizniot aktivi~ra~ki mehanizam za avtoimunitetot. Nie istra`uvavme dve mo`nosti: (I) vi rusno predizvika avtoimuna reakcija i (II) avtoimuna reakcija predizvika od `iva. Neodamna izvedovme serolo{~ka studija za vi rusni antitela i antitela predizvikani od `iva. Najprvin ja izme~rime vi rusnata serologija kaj vi rusot na morbilitate (VM), vi rusot na zau{kite (VZ), vi rusot na rubeolata (VR), citomegalovirusot (CMV) i ~ove~kiot vi rus na herpesot-6 (^VH-6). Otkrivme deka decata so autizam imaat zna~itel no povi soki od normalni te nivoa na antitela samo kaj vi rusot na morbilitate, no nivoto na antitela kaj drugite ~etri virusi zna~itel no ne se razlikuvame }u decata so autizam i normalni te deca. Spored toa, sugeriravme deka infekcijata od morbilitate bi mo`ela etiolof ki da se povrze so avtoimunitetot kaj autizmot (3, 9). Vtoro, bi dej}i autizmot i izlo`uvaweto na `iva mo`e da go opf atati avtoimunitetot, `ivata delumno se smeta kako rizi~en faktor kaj autizmot. Taka, postavivme hipoteza deka ako autizmot opfa}a vraska me }u izlo`uvaweto na `iva i avtoimunitetot, toga { decata so autizam bi trebalo da imaat

For autoimmune pathology, one of the salient features is the organ-specific autoantibodies. In case of autism, they would be brain-specific autoantibodies. Indeed, a significant number of autistic children harbor autoantibodies to several brain antigens. Of all the brain autoantigens tested, the most common one appears to be the MBP of the myelin sheath, which led us to postulate that an autoimmune response to MBP is involved in autism (3, 5). Although the precise trigger mechanism for autoimmunity is not known we investigated two possibilities: (I) virus-induced autoimmune reaction, and (II) mercury-induced autoimmune reaction. We recently conducted serological study of viral antibodies and mercury-induced antibodies. First, we measured virus serology to measles virus (MV), mumps virus (MuV), rubella virus (RV), cytomegalovirus (CMV), and human herpesvirus-6 (HHV-6). We found that autistic children harbored significantly higher than normal levels of antibodies to measles virus only, but the level of antibodies to other four viruses did not significantly differ between autistic and normal children. Accordingly, we postulated that a measles infection might etiologically be linked to autoimmunity in autism (3, 9). Secondly, because both autism and mercury exposure could involve autoimmunity, mercury has been anecdotally proposed as a risk factor in autism. So, we hypothesized that if autism involved a connection between mercury exposure and autoimmunity then autistic children should harbor

povisoki nivoa na avtoimuni markeri predizvikani od `iva, imeno, antinukleolarni te antitelai antilamininski antitelai. Neodamna izvedovme laboratoriska studija na ovie dva avtoimuni markera kaj decata so autizam i normalnite deca. Rezultate od ovaa studija poka`aa deka distribucijata na ovie dva markera ne se smeni kaj decata so autizam.

Taka, `ivata ne se javi kako rizi~enfaktor za avtoimunitet kaj autizot (30). Ponatamu, odkrivme deka ogromen broj deca so autizam poka`aa serolo{ka povrzanost me|u virusot na morbiliti i MBP-antitelai, t.e. kolku {to e povi soko nivo to na antitelata kaj virusot na morbiliti, tolku e pogolema i promenata na MBP-antitelata. No, ovaa povrzanost ne be{e odkriena kaj drugite virusi i/ili drugite mozo~ni avtoantitelai {to gi prou~uvame. Jasno e deka ova e eksperimenten dokaz za etiolo{kata povrzanost kaj virusot na morbiliti so avtoimunitet kaj autizot (3, 8, 9).

I zvorot na virusot na morbiliti kaj decata so autizam ne e dobro poznat. Bidej{itie nemaat istorija za isipuvawe na germanski te morbiliti, ottuka ne e verojatna infekcijata na morbiliti od burentip. Sepak, ima mo`nost od pojava na "atipina ili asimptomati~na# infekcija na morbiliti vo otsustvo na tipina noto isipuvawe na morbiliti. Takvata infekcija bi mo`ela da se javi ili od varijatna infekcija na morbiliti ili bi mo`ele da se dobie od imuni zacija so MPR-vakcina. Edna atipina infekcija na morbiliti vo otsustvo na isipuvawe i nevoobi~aeni nevrolo{ki simptomi neodamna bea opi{ani i sugeriraa prisustvo na varijanten virus na morbiliti kaj ma`i (31). Vo na{atalaboratorija neodamna sobravme eksperimenten dokaz koj potvrduva deka mnogu deca so autizam imaat abnormalni ili nesoodvetni antitelai na MPR-vakcinata, no ne i za drugite vakcini, kako {to e difterija-tetanus-pertusis (DTP) ili difterija-tetanus (DT). I ovie antitelai bea osobeno protiv podgrupata na morbiliti na MPR-

elevated levels of mercury-induced autoimmune markers, namely the antinucleolar antibodies and antilaminin antibodies. We recently conducted a laboratory study of these two autoimmune markers in autistic children and normal children and the results of this study showed that the distribution of these two markers did not change in autistic children.

Thus mercury does not appear to be a risk factor for autoimmunity in autism (30). Furthermore, we found that a vast majority of autistic children showed a serological association between measles virus and MBP autoantibodies, i.e., the higher the measles virus antibody level the greater the chance of MBP autoantibody. But this association was not found for other viruses and/or other brain autoantibodies that we studied. Clearly, this is an experimental evidence for an etiological link of measles virus to autoimmunity in autism (3, 8, 9).

The source of measles virus in autistic children is not well known. Because they do not have a history of a German measles rash hence a wild type measles infection is rather unlikely. But there exists a possibility of an "atypical or asymptomatic" measles infection in the absence of a typical measles rash. Such an infection could occur either by a variant measles infection or it could be acquired from immunization with MMR vaccine. An atypical measles infection in the absence of a rash and unusual neurological symptoms has recently been described to suggest the existence of a variant measles virus in man (31). In our own laboratory, we have recently gathered experimental evidence that shows that many autistic children have abnormal or inappropriate antibodies to MMR vaccine, but not to other vaccines like diphtheria-tetanus-pertussis (DPT) or diphtheria-tetanus (DT). And these antibodies were specifically directed against the measles subunit of the MMR

vakcinata (9, 21). U{ te pove}e, ima{ e silna serolo{ ka korelacija me|u MPR-antitelata i MBP-antitelata, sugeriraj-}i slu-ajna povrzanost na MPR-vakci nata so autizmot ili so autisti ~nata regresija { to se javuva po MPR-imunizacijata kaj deca (21). Sepak, potrebni se pove}e istra`uvawa na ova tema. Zatoa razmi sluvame deka edna atipi~na infekcija na morbili mo`e etiolo{ ki da bide povrzana so mozo~niot avtoimunitet kaj autizmot. Vo vrska so ova, drugi studii za avtoimunitetot { to proizveduva citokini, isto taka, se relevantni: (1.) decata so autizam imaat zna~itelno zgol emuvawe na avtoimunitetot, { to pobudiva citokini, kako { to se interleukin-12 (IL-12) i interferon-gama (IFN-gama) vo polza na Th-1 imunolo{ki ot odgovor (7, 28); i (2.) vakcinacijata za morbili so MPR-vakcina glavno pottiknuva IFN-gama za Th-1 tip na imunoreakcijata (32). Ova otkritie bi mo`elo indirektno da ja objasni slu-ajната vrska me|u MPR i autizmot (9, 21). Jasno e deka ovi e otkritija se va`ni za da se razbere osnovni ot mehanizam na avtoimunitetot kaj autizmot, no potrebni se pove}e istra`uvawa za da se razbere ni vnata precizna uloga kaj patogenezata na ova naru{ uvawe.

Studii za citokinite kaj autizmot

Pred nekolku godini predlo`ivme da ja prou~uvame regulacijata na citokinite kaj autizmot, no poradi nedostig od finansiska poddr{ka ne bevme vo mo`nost podetalno da ja prou~uvame ova tema. Zatoa, pak, realiziravme po~etni studii i napravivme nekoi klu~ni opservacii. Studii te za citokinite mo`e da se izvedat so tri razli~ni metodi: (1.) Citokinite mo`et da bidat izmereni vo biolo{ki fluidi, kako { to se serumot, plazmata ili cerebrospinalni ot fluid, { to pretstavuva endogeno (ili *in vivo*) proizvedeni cirkuliraj~ki citokini;

vaccine (9, 21). Moreover, there was a strong serological correlation between MMR antibodies and MBP autoantibodies, suggesting a causal association of MMR vaccine with autism or autistic regression that has been described after the MMR immunization in children (21). While more research is necessary on this topic, we speculate that an atypical measles infection may etiologically be linked to brain autoimmunity in autism. In this respect, other studies of autoimmunity-producing cytokines are also quite relevant: (1.) autistic children have significant increases of autoimmunity-inducing cytokines such as interleukin-12 (IL-12) and interferon-gamma (IFN-gamma) in favor of a Th-1 immune response (7, 28); and (2.) measles vaccination with MMR vaccine mainly induces IFN-gamma for Th-1 type of immune response (32). This finding could indirectly explain a causal link between MMR and autism (9, 21). Clearly, these findings are important for understanding the basic mechanism of autoimmunity in autism but more research is needed to understand their precise role in the pathogenesis of the disorder.

Cytokine Studies in Autism

Several years ago, we propose to study cytokine regulation in autism but due to lack of funding support we have not been able to study this topic in a greater detail. But we have carried out initial studies and made some key observations. Cytokine studies can be performed by three different approaches: (1.) Cytokines can be measured in biological fluids such as serum, plasma or cerebrospinal fluid, which represents endogenously (or *in vivo*) produced circulating cytokines;

(2.) Proizvodstvoto na citokini te mo`e da se prou~uva preku periferne krvne mononuklearne kletke (PKMNC) po mitogenska stimulacija *in vitro*; i (3.) Citokinskoto specifi~no iRNA izrazuvawe mo`e da se meri so PKMNC po mitogenska stimulacija. Nie na po~etokot go zedovme prvi ot metod, bi dej}i toj pretstavuva *in vivo* sostojba i gi izmerivme cirkuiraj~ki te ni voa na citokini te kaj decata so autizam. Otkrivme deka ni voto na serumot na samo tri citokini (IL-2, IL-12 i IFN-gama) be}e zna~itelno krenato kaj decata so autizam, a ni voto na serumot na drugite }est citokini (IL-1, IL-4, IL-6, IL-10, IFN-alfa i TNF-alfa) zna~itelno ne se razlikuvame |u normalnite i decata so autizam (7, 26, 28). Poradi specifi~noto zgolemuwane na IL-12 i IFN-gama sugeriravme deka autizmot ja opfa}a Th-1 imunolo}ki ot odgovor (7, 28). Posledovatelno, izvedovme studija za proizvodstvoto na IL-2, IL-6 i TNF na PKMNC. Otkrivme deka proizvodstvoto na IL-2 be}e zna~itelno zgolemen kaj decata so autizam. Proizvodstvoto na IL-6 i TNF na PKMNC kaj decata so autizam be}e umereno povi soko otkolku kaj normalnite deca, a razlikata nema}e nikakva statisti~ka zna~ajnost (7). Na}iot rezultat za proizvodstvoto na TNF kaj decata so autizam i ednakov na prethodni ot izve}taj (33). Naodamna dve drugi grupi istra`uva~i upotrebi}a alternativni metodi i otkri}a deka PKMNC kaj decata so autizam proizveduva poka~eno ni voa na IL-12 i IFN-gama ili izrazuva povi soki od normalni ni voa na iRNA za IFN-gama (za citirawe videte vo literatura #7). Ovie otkritija go poka`uvaat postoeveto na Th-1 tipot na imunolo}ki odgovor kaj decata so autizam i toa, isto taka, }e bide ednakvo so avtoimunata patologija kaj autizmot, bi dej}i IL-2, IL-12 i IFN-gama citokini te se dobro poznati pottiknuva~i na avtoimunitete bolesti (34). Vo pogled na patogenezata na imunoposreduvanite bolesti, imunolo}ki aktivacijata e eden od primarnite nastani kaj avtoimunitetot, inflamacijata i virusnite

(2.) Cytokine production can be studied by peripheral blood mononuclear cells (PBMC) after mitogen stimulation *in vitro*; and (3.) Cytokine-specific mRNA expression can be measured in PBMC after mitogen stimulation. We initially took the first approach because it represents an *in vivo* state and measured circulating levels of cytokines in autistic children. We found that the serum level of only three cytokines (IL-2, IL-12 and IFN-gamma) was significantly elevated in autistic children but the serum level of six other cytokines (IL-1, IL-4, IL-6, IL-10, IFN-alpha and TNF-alpha) did not significantly differ between normal children and autistic children (7, 26, 28). Because of a specific increase of IL-12 and IFN-gamma, we suggested that autism involves Th-1 immune response (7, 28). Subsequently, we conducted a study of IL-2, IL-6 and TNF production by PBMC. We found that the IL-2 production was significantly increased in autistic children. The production of IL-6 and TNF by PBMC of autistic children was moderately higher in autistic children than the normal children but the difference did not attain statistical significance (7). Our result of TNF production in autistic children is consistent with a previous report (33). Recently, two other groups of researchers took alternative approaches and found that PBMC of autistic children produce elevated levels of IL-12 and IFN-gamma or express higher than normal levels of mRNA for IFN-gamma (for citations see ref. #7). Taken together, these findings demonstrate the existence of Th-1 type of the immune response in autistic children and that would also be consistent with autoimmune pathology in autism because the IL-2, IL-12 and IFN-gamma cytokines are well known inducers of autoimmune diseases (34). Regarding the pathogenesis of immune-mediated diseases, immune activation is one of the primary events in autoimmunity, inflammation and viral infections.

infekcii. Imunoaktivacijata vodi kon spontana proliferacija na perifernite krvni mononuklearni kletki, zgolemen i zraz na aktivacijske markeri na perifernite krvni mononuklearni kletki i zgolesena akumulacija na rastvorlivi antigeni dobieni od krvnata mononuklearna kletka, glavno, citokinite, citokinski receptori i adheziivnite molekuli. Vrz osnova na ovie razmisluvawa, imunoaktivacijata se javuva prirodno kaj decata so autizam, bidej{ti tie imaat podignati nivona imunoaktivacijski antigeni, kako { to se: sCD8, IL-2, IL-12 i IFN-gama (26, 28) i nivnata krv so dr` i aktivirani T kletki (26, 27). Taka, razumno e da se zaklu`deka zgolemuvaweto na IL-12 kaj decata so autizam uk`uva na antigena stimulacija na Th-1 kletkite, koi via INF-gama mo`e da pottikne avtoimunitet (7). IL-12 citokinet selektivno go pomaga razvojot na Th-1 kletkite (35) i Th-1 kletkite iniciraat patogenoza na organsko specifi~nite avtoimuni bolesi (34).

Testirawena avtoimunitetot kaj autizmot

Neodamne{nite otkritija jasno poka`uvaat deka avtoimunitetot ima mnogu v`na uloga vo patogenezata na nevrolo{ki tenaru{uvawa, vkluvaj}i go autizmot (2, 3). Bidej{ti mozokot e zaboleno ot organ, avtoimunata reakcija }e bide protiv mozokot. Avtoimunitetot obi~no se manifestira so izvesni avtoimunitet faktori { to gi identifikuvavme kaj deca so autizam. Ovie faktori se va`ni za da ja identifikuvaat mozo~nata avtoimuna reakcija. So ispituvawe na krvta mo`e da odredime dali eden pacient poka`uva avtoimunitet na mozokot, dali toj ili taa e kandidat za eksperimentna imunomodulacijska terapija, i dali reakcijata na terapijata e efektivna. Taka, ovoj tip imunoevaluacijata e krajno va`en za rehabilitacija na pacienti so autizam. Specifi~ni testovi se navedeni podolu:

Immune activation leads to spontaneous proliferation of peripheral blood mononuclear cells, increased expression of activation markers on peripheral blood mononuclear cells, and increased accumulation of blood mononuclear cell-derived soluble antigens, mainly cytokines, cytokine receptors, and adhesion molecules. Based on these considerations, immune activation occurs naturally in autistic children because they have elevated levels of immune activation antigens such as sCD8, IL-2, IL-12 and IFN-gamma (26, 28) and their blood contains activated T cells (26, 27). Thus it is reasonable to conclude that the increase of IL-12 in autistic children points to antigenic stimulation of Th-1 cells, which via INF-gamma may induce autoimmunity (7). The IL-12 cytokine selectively promotes the development of Th-1 cells (35) and Th-1 cells initiate the pathogenesis of organ-specific autoimmune diseases (34).

Testing for Autoimmunity in Autism

Recent advances have clearly shown that autoimmunity plays a very important role in the pathogenesis of neurological disorders, including autism (2, 3). Since brain is the affected organ, the autoimmune response will be directed against the brain. Autoimmunity is commonly manifested by certain autoimmune factors that we have identified in children with autism. These factors are important for identifying a brain-specific autoimmune response. By performing blood tests we can determine if a patient shows autoimmunity to brain, if he or she is a candidate for experimental immune modulation therapy, and if the response to therapy is effective. Thus, this type of immune evaluation is extremely important in rehabbing patients with autism. The specific tests are listed below:

1. **Profil na mozo~ni avtoantitela:** Ovoj test gi otkriva antitelata kaj dva mozo~ni proteina-MBP i NAFF. Otkrivme deka MBP-antiteloto kaj autisti~nata populacija e zabele`itelno povi-soko otkolku kaj normalnata populacija; ottuka, toa slu`i kako primaren marker na avtoimunata reakcija kaj autizmot. Sprotivno na toa, NAFF-antiteloto kaj autisti~nite pacienti e samo marginalno pivisoko otkolku normalnite kontroli, pravej}i go vtor marker za izbor. Sepak, se prepore~uva ovie dva avtoimuni markera da se testi raat istovremeno (3).

2. **Virusno-serolo{ki profil:** Ovoj test go meri nivoto na antitela vo virusite, kako {to se: morbilite, zau{kite, rubeolata, CMV ili ^VH-6. Prika`avme deka nivoto na antiteloto kaj morbilite e zgolemeno kaj mnogu deca so autizam. Toa mo`e da bide znak za infekcija, minata infekcija ili imunoreakcija na MPR-vakcinata (3, 9).

3. **Vakcino-serolo{ki profil:** Ovoj test gi otkriva antitelata na vakcinite, vkluvaj}i gi MPR i DTP. Poka`avme deka zna~itelen broj deca so autizam, none i normalnite deca, zadr`uvaat edinstven tip antitelo na morbilina MPR-vakcinata. Ova antitelo bi mo`elo da pretstavuva abnormalna ili nesoodveten imunolo{ki odgovor na ovaa vakcina i bi trebalo da se testira vo vrska so avtoimunitetot kaj autizmot (3, 21).

4. **Citokinski profil:** Dva citokina IL-12 i IFN-gama, imaat mnogu va`na patogenetska uloga kaj avtoimunitete bolesti, odnosno tie ini ci raat avtoimuna reakcija preku pottiknuvawe na Th-1 tip na belite krvni kletki. Otkrivme deka ovie dva citokena selektivno se podignati kaj decata so autizam, {to sugerira pottiknuvawe na avtoimunitetot preku Th1- kletkite kaj autizmot. Zatoa, tie treba da se merat kako znak za o{teten kletoen avtoimunitet kaj pacienti so autizam (7, 28).

1. **Brain autoantibody profile:** This test detects antibodies to two brain proteins, namely the MBP and NAFF. We have found that the incidence of MBP autoantibody in the autistic population is markedly higher than that of the normal population; hence, it serves as a primary marker of the autoimmune reaction in autism. In contrast, the incidence of NAFF antibody in autistic patients is only marginally higher than the normal controls, making it a secondary marker of choice. It is however recommended that these two autoimmune markers be tested simultaneously (3).

2. **Virus serology profile:** This test measures level of antibodies to viruses such as measles, mumps, rubella, CMV or HHV-6. We have shown that the level of measles antibody is elevated in many autistic children, which could be a sign of a present infection, past infection, or immune reaction to MMR vaccine (3, 9).

3. **Vaccine serology profile:** This test detects antibodies to vaccines, including MMR and DTP. We showed that a significant number of autistic children, but not the normal children, harbor a unique type of measles antibody to MMR vaccine. This antibody might represent an abnormal or inappropriate immune reaction to this vaccine and should be tested in relation to autoimmunity in autism (3, 21).

4. **Cytokine profile:** Two cytokines namely IL-12 and IFN-gamma play a very important pathogenic role in autoimmune diseases, i.e., they initiate an autoimmune reaction via induction of Th-1 type of white blood cells. We have found that these two cytokines are selectively elevated in autistic children, suggesting the induction of autoimmunity via Th-1 cells in autism. Therefore they should be measured as a sign of impaired cellular autoimmunity in patients with autism (7, 28).

5. **Serotonski profil:** Ovoj test go meri nivoto na serumot ili plazmata na serotoni not. Otkrivme deka paci enti te so autizam i maat abnormal no ni vo na serotoni n, { to bi trebal o da se testi ra pred da se dade tretmanot so terapija na selekti ven serotonski inhi bi tor na povtorno vruvawe (SSRI). Ni voto na zgol emeni ot serotoni n kaj autizmot mo`e, isto taka, da bi de povrzano so avtoimunata reakcija na serotonski te receptori vo mozokot (21).

6. **Avtoimni markeri pottiknati od `iva:** Ovoj test ja analizi ra avtoimunata reakcija na izlo`uvawe na `iva (ili te{ ki metali). Ovie markeri opf a}aat nuklearni anti tela sproti nuklearni te antigeni i antilamininski te anti tela sproti proteini te na bazalnata membrana. Otkrivme deka samo mal broj na deca so autizam se poziti vni na ovie anti tela, no ni voto na ovie anti tela zna~itel no ne se razli kuva{ e od normalni te deca (30).

Subjekt i (pacient i) i laboratoriski proceduri vo na{ et o ist ra` uvawe

Vo na{ eto eksperimentno istra`uvawe prou-uvavme deca so autizam, normalni deca, bra}a ili sestri na deca so autizam, deca so drugi bolesti, a retko i vozrasni. Vo istra`uvaweto edi nstveno vkl u~ivme deca so autizam so cvrsta dijagnoza na autizam, a gi iskl u~ivme drugi te dijagnozi, kako { to se: pervazivni razvojni naru{ uvawa (PRN), pervazivni razvojni naru{ uvawa-nespecificirani na drug na~in (PRN-NDN) i Aspergeroviot sindrom. Subjekti te bea grupi rani spored vozrast i pol kade { to be{ e mo`no, a nikoj ne be{ e iskl u~en od u~estvo vo studijata poradi faktor na rasa, vozrast ili pol, osven onie { to ne bea cel na na{ ata istra`uva~ka programa. Klini~kata dijagnoza na autizmot be{ e bitno napravena spored *Dijagnosti~ki i stati sti~ki pri ra~nik za mentalni naru{ uvawa, ~etvrto izdani e* (DSM-IV).

5. **Serotonin profile:** This test measures serum or plasma level of serotonin. We have found that the patients with autism have abnormal level of serotonin, which should be tested before administering the treatment with selective serotonin reuptake inhibitor (SSRI) therapy. Elevated serotonin level in autism might also be related to autoimmune reaction to serotonin receptors in the brain (21).

6. **Mercury-induced autoimmune markers:** This test assays for autoimmune reaction to mercury (or heavy metals) exposure. These markers include antinuclear antibodies against nucleolar antigens and antilamin antibodies against basement-membrane proteins. We have found that only a small number of autistic children are positive for these antibodies but the level of these antibodies did not differ significantly from the normal children (30).

Subjects and Laboratory Procedures in Our Research

In our experimental research, we studied autistic children, normal children, siblings of autistic children, children with other diseases and rarely adults also. In our research, we only included autistic children with a firm diagnosis of autism but excluded other diagnosis such as pervasive developmental disability (PDD), pervasive developmental disability-not otherwise specified (PDD-NOS), and Asperger's syndrome. The subjects were matched for age and gender whenever possible but no one was denied participation in the study because of the race, age or gender factors, except those beyond the scope of our research program. The clinical diagnosis of autism was essentially according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).

Normalni deca bea oni e { to imaat cvrsto fizi~ko zdravje bez nikakov znak na mozo~na bolest ili, pak, mentalna bolest ili nekoja druga poznata medicinska sosto~nja. Pred da se zemat primeroci krv od licata, obezbedi vme soodvetna dozvola od Institucionalni ot revizijski odbor (IRO) na Dr`avni ot univerzitet vo Jutai pred toa od univerzitet vo Mi~igen. Sé na sé, gi iskoristi vme prethodno sobrani te serumski primeroci skladi rani vo zamrznata sosto~nja vo zamrznava~na -20° C, odr`uvaj}i go ciklusot na zamrznava~e i rastopuvava~e na mi ni mum. Detal i te od razli~ni laboratorijski proceduri i metodi na analiza se opi {ani vo na {ite publikacii (3, 5, 7-9, 21, 23-25, 28, 30).

Immunomodulacijska terapija (IMT) kaj autizmot

Laboratorijski te otkritija jasno ja poka`uvaat ulogata na avtoimunitetot vo patogenezata na autizmot. I dejata deka autizmot e avtoimuno naru {uvawe dopolnitelno e zacvrstena od faktot deka autisti~nite pacienti reagiraat dobro na rehabilitacijata so imunomodulacijski te lekovi (2, 3, 7, 19, 29). Imunointervencijete mo`e da predizvikaat imunomodulacijsko sosto~nja na spre~uvawe ili stimulacija. Bidej}i autisti~nite pacienti ne poka`uvaat klasi~na primarna imunodeficiencija, ne e dobra strategijata ednostavno da zajakne nivni ot imunitet. Sepak, tie, imaat imunopatologija i zatoa, zavisno od prirodata na imunopatologijata, celta na IMT treba da se normalizira ili povtorno da se vospostavi imunofunkcija. Ova }e dozvoli pobalansirana imunoreakcija, odbegnuvaj}i gi glavni te fluktuacii na o~iglednata imuna aktivnost, {to mo`e da bide {tetna za pacientot. IMT sekoga {treba da se dava vo konsultacija so lekar, najdobro so klini~ki imunolog, alergolog ili hematolog. Sledni ot spisok na imunomodulacijski te terapii (IMT) treba da se razgledaat kaj autizmot:

Normal children were those having a firm physical health without any sign of brain disease or mental illness or any other known medical condition. Before drawing blood samples of human subjects, we obtained proper permission of the Institutional Review Board (IRB) at Utah State University and formerly at the University of Michigan. By and large, we employed previously collected serum samples that were stored frozen in a freezer at -20°C while keeping the freezing-thawing cycle to a minimum. The details of various laboratory procedures and assay methods are described in our publications (3, 5, 7-9, 21, 23-25, 28, 30).

Immune Modulation Therapy (IMT) in Autism

Laboratory findings clearly demonstrate the role of autoimmunity in the pathogenesis of autism. The idea that autism is an autoimmune disorder is further strengthened by the fact that autistic patients respond well to rehabilitation with immune modulating drugs (2, 3, 7, 19, 29). Immune interventions can produce immune modulation—a state of suppression or stimulation. Since autistic patients do not show a classical primary immunodeficiency, simply boosting their immunity is not a good strategy. However, they do have immune abnormalities and therefore depending on the nature of the immune abnormality the goal of IMT should be to normalize or reconstitute the immune function. This will permit a more balanced immune response, avoiding major fluctuations of overt immune activity, which could be detrimental to the patient. The IMT should always be given in consultation with a physician, preferably a clinical immunologist, allergist or hematologist. The following list of immune modulation therapies (IMT) should be considered for autism:

1. **Steroidna terapija:** Steroidi te, kako { to se Predni zon i/ili ACTHvoobi ~aeno se upotrebuvaat kako prv lek pri tretmanot na pacienti so avtoimuni bolesi. Osven za izve{taite za slu~ai { to poka`uvaat pozitivni reakcii na steroidi (36), ne se izveduvala klini~ki obidi. A sepa, mnogu semejstva davaat sopstveni izve{tai za klini~ko podobruvawe na autisti~nite karakteristiki koga ni vni te deca primaat steroidi za medicinski sostojsi poinakvi od autisti~noto naru{uvawe.

2. **Terapija so transfer faktor:** Transfer factor (TF) e imunomodulator za kontrola na kletotimot na T-limfocite, osobeno v tekot na patogeno infekcii. Za da bide efikasna, TF normalno se pravi od leukocitili od strogo selektirani donatori na krv. So koristevana ovoj tip na TF, edna otvorena studija poka`uva klini~ko podobruvawe na autisti~nite simptomi kaj nekoi deca (29). Isto taka, postoji komercialen brend na TF koj po definiciji ne e TF, tuku e produkt na govedski kolostrom; negovoto koristevanje vo lekuvaweto na autisti~nite pacienti ne e nau~no dokumentirano.

3. **Imunoglobulinska terapija** Ova metoda za rehabilitacija ve}e se praktikuva za rehabilitacija na autisti~ni pacienti so avtoimuni problemi. Otvoreni obidi na intravenozno imunoglobulin (IV-Ig) poka`aa deka pove}eto, ne site deca so avtoimuni reagi raat pozitivno na ovoj tretman (19). Klini~ki, taka tretani te deca poka`aa podobruvawe vo jzikot, komunikacijata, socijalna interakcija i raspon na vnimanje. Pred nekolku godini, go predlo`ivme koristeweto na "Oral-Ig" kako alternativna metoda na IV-Ig. Oral-Ig poznato e deka dava znatno podobruvawe na autisti~nite simptomi kaj SAN-pacienti. Toj rezultat e re~isi ist kako IV-Ig, ili ponekoga{duri i podobar od IV-Ig.

4. **Autoantigen terapija:** Rehabilitacija na pacienti te so avtoimuni bolesi

1. **Steroid therapy:** Steroids such as Prednisone and/or ACTH are commonly used as the first course of treatment for patients with autoimmune diseases. Except for case reports showing positive responses to steroids (36), the clinical trials have not been conducted. And yet many families anecdotally report clinical improvement of autistic characteristics when their children were given steroids for medical conditions other than the autistic disorder.

2. **Transfer factor therapy:** Transfer factor (TF) is an immune modulator for controlling cellular immunity of T lymphocytes, especially during pathogenic infections. To be effective, TF is normally made from the leukocytes of highly select blood donors. By using this type of TF, an open-label study has shown clinical improvement of autistic symptoms in some children (29). Also, there is a commercial brand of TF which by definition is not a TF but simply a bovine colostrums product; its usefulness in treating autistic patients has not been scientifically documented.

3. **Immunoglobulin therapy:** This approach to rehabilitation is already in practice for rehabilitating autistic patients with autoimmune problems. Open-label trials of intravenous immunoglobulin (IV-Ig) have shown that most but not all autistic children respond favorably to this treatment (19). Clinically, children so treated have shown improvements in language, communication, social interaction and attention span. Several years ago, we suggested the use of "Oral-Ig" as an alternative approach to IV-Ig. The oral-Ig has now been shown to produce significant improvement of autistic symptoms in ASD patients, and the outcome is either about the same as IV-Ig or sometimes even better than the IV-Ig.

4. **Autoantigen therapy:** Rehabilitation of patients with autoimmune diseases is also carried

isto taka, se realizirajo oralna prijava avtoantigeni. Ova, isto taka, je priljubena za avtizmo. Ovoj modalitet se potrjuje vrzefaktot deka avtizmo opfajava avtoimuna reakcija na mozokot MBP. Ova odkritie otvori tesen pogled kon monosta za rehabilitacijo na avtisti~ni pacienti so dodatoci vo ishranata { to sodrat mozen MBP ili melin, na primer: sfingolin (3).

5. **Glutatinska terapija:** Glutathionot, tripeptid { to sodri tri amino-kiselini, je prirodni imunomodulator, antioksidant i detoksifikator. Zaradi ovie tri biolo{ki funkcii, glutathionot je najpotencijalen za{titnik na telo od infekcii, avtoimuni problemi i drugi abnormalnosti, vklju~vaji go i oksidativni stres (37). Taka, glutathionot se koristi za rehabilitacijo na imunoproblemi kaj deca so avtizam so klini~ko podobravawe.

6. **Plazmaferezisna terapija:** Ova procedura se koristi za lekuvawe na pacienti so infekcii, avtoimuni boleti i imunokompleksni boleti. Dodeka procedurata uspe{no se koristi za lekuvawe na pacienti so nevrolo{ki naru{uvawa, kako { to se opsesi vno-kompulzivno naru{uvawe (38). Taa dosega ne se koristela za rehabilitacijo na pacienti so avtizam.

Zaklu~oci

Na{eto istra~uvawe poka`a deka avtoimunitetot je srcevi na na problemot kaj mnोजना pacienti so avtizam. Avtoimunitne abnormalnosti i reakcijata na pacienti te na tretaman so imunomodulacijska terapija, ja zacvrsti i dejata deka avtizmo je avtoimuno naru{uvawe. Avtoimuna reakcija, najverojatno, je nasodena kon melinskata obivka na mozokot, a mo`e isto taka da bidat opfateni i drugi nevralni strukturi dlaboko vo mozokot. Neodamna odkrivme (8) deka nucleus caudatus je involviran vo nevropatologijata na avtizmo - novo odkritie od potencialno golema klini~ka i terapevtska vavnost.

out by oral administration of autoantigens. This is also applicable to autism. This modality relies on the fact that autism involves autoimmune reaction to brain MBP. This finding has opened up a narrow window of opportunity for rehabilitating autistic patients with nutritional supplements containing brain MBP or myelin, for example the sphingolin (3).

5. **Glutathione therapy:** Glutathione, a tripeptide containing three amino acids, is a natural immune modulator, antioxidant and detoxifier. Owing to these three biological functions, glutathione is the body's most potent protector against infections, autoimmune problems and other abnormalities including oxidative stress (37). Thus glutathione has also been used to rehab immune problems in autistic children with clinical improvement.

6. **Plasmapheresis therapy:** This procedure is used for managing patients with infections, autoimmune diseases and immune complex diseases. While the procedure has been successfully used to treat patients with neurological disorders such as obsessive-compulsive disorder (38) but it has so far not been used to rehab patients with autism.

Conclusions

Our research has shown that autoimmunity is the core of the problem in many patients with autism. The existence of autoimmune abnormalities and the patient responsiveness to treatment with immune modulation therapy strengthens the idea that autism is an autoimmune disorder. Autoimmune response is most likely directed against myelin sheath in the brain but other neural structures deep in the brain might also be involved. We recently [8] found the involvement of caudate nucleus in the neuropathology of autism - a novel finding of potentially great clinical and therapeutic significance.

Nucleus caudatus e mnogu va` en mozo`en centar za kontrola na dvi` eweto i kognitivnoto procesui rawe, koi se abnormalni kaj decata so autizam. Bidej}i tri ~etvrtini od autisti ~nata populacija ima avtoimuni problemi, mislime deka najgolembroj autisti ~ni pacienti bi mo`ele direktno da imaat polza od avtoimunotistra` uvawe denes. Ovaa podgrupa, verojatno, e "dobi ena#forma in i cira na od virus, verojatno od virusot na morbilite, ta treba da se ispitaat i drugi etiolo{ki faktori. Vo 2002 ja ozna`ivme ova podgrupa kako "Avtoimuno autisti ~no naru{uvawe (AAN)# - termin koj ja opi{uva avtoimunata podgrupa na autizam (39). Zaklu`ivme deka istra` uvawata za avtoimunitetot imaat globalen pridones za rahabilitacija na autizam vo svetot. Zatoa doktorite i istra` uva`ite treba da mu posvetat pove}e vni manie na avtoimunotistra` uvawe i imunomodulaci skata terapija kaj autizmot.

Priznanie

D-r Singimiska` uva ogromna blagodarost na semejstvata {to u`estvuvaa vo negovoto istra` uvawe. Toj bi sakal da imzablagodari na nekol kumi na studenti i tehni`ari za nivnata pomo{ vo laboratoriskata rabota. Negovoto istra` uvawe be{e poddr`ano bez ni kakov konflikt na interesi so privatni grantovi od Institutot za istra` uvawe na autizmot, Fondacijata Dudley T. Aougherty, Fondacijata BHARE, Fondacijata Yorio i Fondacijata Forrest Lattner Jr.

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The caudate nucleus is a very important brain center for controlling movement and cognitive processing, which are abnormal in autistic children. Since up to three-quarter of the autistic population has autoimmune problems, we think that a major proportion of autistic patients could benefit directly from autoimmunity research today. This subset is likely an "acquired" form triggered by a virus, possibly measles virus but other etiological factors should also be explored. In 2002, we designated this subset as an "Autoimmune Autistic Disorder (AAD)" – a term coined to describe the autoimmune subset of autism (39). We conclude that the autoimmunity research has a global impact for rehabbing autism worldwide hence the physicians and researchers should pay closer attention to autoimmunity research and immune modulation therapy in autism.

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