iskustva i novini od svetot

REHABILITACIJA NA AUTIZMOT SO IMUNO-MODULACISKA TERAPIJA

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Rezime

Avtoimunitetot mo`e da ima klu~na uloga vo patogenezata na autizmot, so ran po~etok na naru{uvawe na razvojniot centralen nerven sistem. Virusite, kako {to se virusot na morbilite, bi mo`ele da predizvikaat avtoimunitet, kako {to e evidentirano so silna korelacija na mozo~nite avtoantitela i antitelata na morbilite. Decata so autizam, isto taka, imaat specifi~ni avto-antitela na mozokot i podignati nivoa na avtoimunitet – specifi~ni citokini interleukin-12 i gama-interferon. Vsu{nost, postoi silna pri~ina da se veruva deka vo autizmot se vklu~eni imunoaktivacija i avtoimunitet kaj mozokot, a pacientite poka`uvaat odgovor na terapijata na imunomodulacijata. Ponatamu, so cel da se identifikuva avtoimuno-autisti~no naru{uvawe (AAN) se razviva protokol za testirawe na avtoimunitetot. Vo ovoj napis novite istra`uva~ki razvoi se opi{ani za da sugeriraat deka avtoimunitetot e mnogu bitna cel {to treba da se koristi za da ponudi rehabilitacija na autisti~nite pacienti 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. Viruses such as measles virus might induce autoimmunity as evidenced by a strong correlation of brain autoantibodies and measles antibodies. Autistic children also harbor brain-specific autoantibodies and elevated levels of autoimmunity-specific cytokines interleukin-12 and interferon-gamma. Collectively, there is compelling reason to believe that autism involves immune activation and autoimmunity to brain and patients show responsiveness to immune modulation therapy. Furthermore, for the purpose of identifying Autoimmune Autistic Disorder (AAD), a protocol for testing autoimmunity 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 biolo{ko naru{uvawe {to ja o{tetuva funkcijata na **c**entralniot **n**erven **s**istem (CNS). Toj manifestira razurnuva~ki nevrolo{ki, kako i psihijatriski rezultati kaj zabolenoto lice. Dijagnozata se pravi ranoto detstvo, pred vozrast od 34 meseci, no nevoljata prodol`uva do zrela vozrast, 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 odlo`uvawe ili devijanten razvoj vo prvite tri godini od `ivotot. Autisti~nite vladeewa {to go karakteriziraat naru{uvaweto, vklu~uvaat "kvalitativni deficiti#vo **~etiri** glavni kategorii: **deficiti na razvojnite stapki i/ili sekvenci i deficiti na reakcija na senzornite stimulansi**; **deficiti na govor, jazik i kognitiven kapacitet**; **kako i deficiti na socijalni interakcii ili na~ini vo odnos so drugite lu|e**. Do neodamna za~estenosta na autizmot be{e 4-5 na sekoi 10.000 ra|awa, no brojot na autisti~nite slu~ai naglo raste (1). Denes se veruva deka autizmot e najbrzo raste~ka razvojna pre~ka kaj decata so presmetana za~estenost od 1 vo 125 do 1 vo 500 ra|awa.

Autizmot e najprominentno mozo~no naru{uvawe od celiot spektar na autisti~ni naru{uvawa (SAN) {to vklu~uva grupa na razvojni naru{uvawa. **Toa e kompleksno i heterogeno naru{uvawe**. Mnogukratni faktori mo`e da bidat involvirani vo patogenezata na naru{uvaweto (2, 3). Iako nema nekoj gen identifikuvan specifi~no za autizmot, deset ili pove}e geni se presmetani i poso~eni za spektarot na autisti~nite naru{uvawa (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).

Iako baraweto na genetskite faktori se favorizira, se o~ekuva deka genetskite faktori pokrivaat ne pove}e od 10% kaj autisti~nata populacija; drugite 90% na autisti~nata populacija se objasnuva so negenetski faktori. Tie vklu~uvat faktori na sredinata, imunofaktorite, nevrohemiskite faktori i drugi, sé u{te, nepoznati faktori. Pred nekolku godini nie imavme hipotezi deka imuno-aktivacijata 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`uva~kite razvoi {to mo`e da se koristat za rehabilitacija na autizmot so imuno-modulaciska 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-avtoimunite 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 anatomskiot razvoj na nervnite pati{ta kaj decata so autizam (5). Ova e mnogu va`no kaj mozokot vo razvoj ednostavno bidej}i brzinata na transmisijata na nervniot impuls bitno zavisi od strukturnite osobini na izoliraweto na mielinskata obvivka, povrzuvaj}i gi nervnite vlakna i dijametralnata oska. Nakuso, napravivme hipoteza deka edna avtoimuna reakcija na mozo~nite strukturi, osobeno na mielinskata obvivka, ima kriti~na uloga vo predizvikuvaweto na nevrolo{kite o{tetuvawa kaj pacienti so autizam. Postavivme deka edno imuno o{tetuvawe po prirodnata infekcija ili vakcinacija mo`e da predizvika "zaseci# ili mali promeni kaj mielinskata obvivka. Ovie anatomski promeni mo`e ultimativno da vodat kon do`ivotni naru{uvawa na povisoki 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, komunikacijata, socijalna interakcija itn. Identifikuvavme nekoi virusni, nevralni i avtoimuni faktori {to né vodea da razvieme spekulativen "nevroavtoimuniteten model na autizmot#, koj neodamna be{e objaven (3, 7). Smetame deka autizmot mo`e uspe{no da se tretira koristej}i nekoi od terapiite {to se poka`aa efikasni pri lekuvawe na drugi avtoimuni bolesti. Kon ova, me|utoa, kompletnata identifikacija i karakterizacija na avtoimunata patologija kaj autizmot e od najgolem va`nost deneska.

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.

Avtoimuna hipoteza kaj autizmot

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

Autoimmune Hypothesis in Autism

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

Avtoimunitetot se misli deka e "sr`# na problemot kaj autizmot. Avtoimunitetot e abnormalna imunoreakcija, vo koja imunolo{kiot sistem stanuva glaven vo reakcijata protiv organite na teloto, a vistinskiot rezultat e avtoimuna bolest. Klini~kata prezentacija na avtoimunite bolesti opfa}a nekolku faktori: faktori na sredinata, genetskata povrzanost osobeno na genite za imunolo{kiot 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{kiot ili kaj `enskiot pol, hormonskite faktori i reakcijata na imunomodulaciskata terapija (2, 3). Virusite se smetaat za aktivira~ki pottiknuva~i na avtoimunite bolesti, koi op{to se povrzuvaat so IR-genite, na primer: HLA-alelite, haplotipite ili Gm-izotipovite, 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.

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. *Avtoimuni abnormalnosti kaj autizmot*

1. Autizmot poka`uva mikrobiolo{ki povrzanosti 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 imunolo{kiot odgovor, na primer: HLA-antigeni, C4B-nultiot alel, haplotipot B44-SC30-DR4, HLA-C i HLA-B1 (13-15).
3. Autisti~nite pacienti imaat o{tetuvawa na celularniot i humoralniot imunitet: namaluvawe na IgA; zgolemuvawe na IgG3, antinuklearni antitela i imunokompleksi; namaluvawe brojot na limfocitite, CD4 + T-kletki {to pomagaat i kletki-prirodni ubijci (KPU); zadu{en celularen imunitet kako reakcija na namalena mitogeno predizvikana limfocitna stimulacija i namalena KPU-kleto~na aktivnost (16-19).
4. Decata so autizam poka`uvaat nesoodvetna imunoreakcija na osnovniot protein na mielinot (20) i vakcinata protiv morbili-zau{ki-rubeola (MPR) (21).
5. Autizmot go opfa}a faktorot na polot i ma{kiot pol zaboluva ~etiri pati pove}e odo{to `enskiot (3).
6. Autizmot ~esto se javuva vo vrska so semejnata istorija na avtoimuni bolesti, na primer: pove}ekratna skleroza, revmatoiden artritis, tip II dijabetes (22).
7. Autizmot, isto taka, gi opfa}a i hormonalnite faktori, na primer: sekretin, beta-endorfin i taka natamu (2).
8. Autisti~nite pacienti imaat organsko specifi~ni avtoantitela za mozo~nite antigeni, kako {to se mielin bazi~niot protein na (MBP) (3, 5), nevron-akson filamentozni proteini (NAFP) (3, 23), proteinite na serotonin-receptorot (24), galaktocerebrozidite (3) i proteinite na nucleus caudatus (25).
9. Autisti~nite pacienti poka`uvaat imunoaktivacija kako reakcija na T-kleto~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), galactocerebrosides (3), and caudate nucleus proteins (25).
9. Autistic patients show immune activation as reflected by T cell activation (26, 27), elevation

na avtoimunitetskite specifi~ni citokini (7, 28) i inflamacija 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 imunoglobulini (19).

Kaj avtoimunata patologija, edna od istaknatite karakteristiki, se organsko-specifi~nite avtoantitela. Vo slu~ajot na autizam, tie }e bidat mozo~no-specifi~ni avtoantitela. Sekako, zna~itelen broj na decata so autizam imaat avtoantitela za nekolku mozo~ni antigeni. Od site ispitani mozo~ni avtoantigeni, najza~esteno se javuva MBP na mielinskata obvivka, {to sugerira{e da zaklu~ime deka avtoimunata reakcija kon MBP se javuva kaj autizmot (3, 5). Iako ne e poznat precizniot aktivira~ki mehanizam za avtoimunitetot. Nie istra`uvavme dve mo`nosti: (I) virusno predizvikana avtoimuna reakcija i (II) avtoimuna reakcija predizvikana od `iva. Neodamna izvedovme serolo{ka studija za virusni antitela i antitela predizvikani od `iva. Najprvin ja izmerivme virusnata serologija kaj virusot na morbilite (VM), virusot na zau{kite (VZ), virusot na rubeolata (VR), citomegalovirusot (CMV) i ~ove~kiot virus na herpesot-6 (^VH-6). Otkrivme deka decata so autizam imaat zna~itelno povisoki od normalnite nivoa na antitela samo kaj virusot na morbilite, no nivoto na antitelata kaj drugite ~etiri virusi zna~itelno ne se razlikuvaa me|u decata so autizam i normalnite deca. Spored toa, sugeriravme deka infekcijata od morbilite bi mo`ela etiolo{ki da se povrze so avtoimunitetot kaj autizmot (3, 9). Vtoro, bidej}i autizmot i izlo`uvaweto na `iva mo`e da go opfatat i avtoimunitetot, `ivata delumno se smeta kako rizi~en faktor kaj autizmot. Taka, postavivme hipoteza deka ako autizmot opfa}a vrska me|u izlo`uvaweto na `iva i avtoimunitetot, toga{ decata so autizam bi trebalo da imaat

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).

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 arisk 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, antinukleolarnite antitela i antilamininski antitela. Neodamna izvedovme laboratoriska studija na ovie dva avtoimuni markera kaj decata so autizam i normalnite deca. Rezultatite 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~en faktor za avtoimunitetot kaj autizmot (30). Ponatamu, otkrivme deka ogromen broj deca so autizam poka`aa serolo{ka povrzanost me|u virusot na morbilite i MBP-antitela, t.e. kolku {to e povisoko nivoto na antitelata kaj virusot na morbili, tolku e pogolema i promenata na MBP-antitelata. No, ovaa povrzanost ne be{e otkriena kaj drugite virusi i/ili drugite mozo~ni avtoantitela {to gi prou~uvavme. Jasno e deka ova e eksperimenten dokaz za etiolo{kata povrzanost kaj virusot na morbili so avtoimunitetot kaj autizmot (3, 8, 9).

Izvorot na virusot na morbilite kaj decata so autizam ne e dobro poznat. Bidej}i tie nemaat istorija za isipuvawe na germanskite morbili, ottuka ne e verojatna infekcijata na morbili od buren tip. Sepak, ima mo`nost od pojava na "atipi~na ili asimptomati~na# infekcija na morbili vo otsustvo na tipi~noto isipuvawe na morbilite. Takvata infekcija bi mo`ela da se javi ili od varijatna infekcija na morbili ili bi mo`ele da se dobie od imunizacija so MPR-vakcina. Edna atipi~na infekcija na morbili vo otsustvo na isipuvawe i nevoobi~aeni nevrolo{ki simptomi neodamna bea opi{ani i sugeriraa prisustvo na varijanten virus na morbilite kaj ma`i (31). Vo na{ata laboratorija neodamna sobravme eksperimenten dokaz koj potvrduva deka mnogu deca so autizam imaat abnormalni ili nesoodvetni antitela na MPR-vakcinata, no ne i za drugite vakcini, kako {to e difterija-tetanus-pertusis (DTP) ili difterija-tetanus (DT). I ovie antitela bea osobeno protiv podgrupata na morbilite 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 diptheria-tetanus-pertussis (DPT) or diptheria-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-vakcinata so autizmot ili so autisti~nata regresija {to se javuva po MPR-imunizacijata kaj deca (21). Sepak, potrebni se pove}e istra`uvawa na ovaa tema. Zatoa razmisluvame 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 zgolemuvawe na avtoimunitetot, {to pobuduva citokini, kako {to se interleukinot-12 (IL-12) i interferon-gama (IFN-gama) vo polza na Th-1 imunolo{kiot 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~ajnata vrska me|u MPR i autizmot (9, 21). Jasno e deka ovie otkritija se va`ni za da se razbere osnovniot mehanizam na avtoimunietot kaj autizmot, no potrebni se pove}e istra`uvawa za da se razbere nivnata 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 ovaa tema. Zatoa, pak, realiziravme po~etni studii i napravivme nekoi klu~ni opservacii. Studiite 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 cerebrospinalniot fluid, {to pretstavuva endogeno (ili *in vivo)* proizvedeni cirkulira~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 citokinite mo`e da se prou~uva preku perifernite krvni mononuklearni kletki (PKMNK) po mitogenska stimulacija *in vitro*; i (3.) Citokinskoto specifi~no iRNA izrazuvawe mo`e da se meri so PKMNK po mitogenska stimulacija. Nie na po~etokot go zedovme prviot metod, bidej}i toj pretstavuva *in vivo* sostojba i gi izmerivme cirkulira~kite nivoa na citokinite kaj decata so autizam. Otkrivme deka nivoto na serumot na samo tri citokini (IL-2, IL-12 i IFN-gama) be{e zna~itelno krenato kaj decata so autizam, a nivoto na serumot na drugite {est citokini (IL-1, IL-4, IL-6, IL-10, IFN-alfa i TNF-alfa) zna~itelno ne se razlikuvaa me|u normalnite i decata so autizam (7, 26, 28). Poradi specifi~noto zgolemuvawe na IL-12 i IFN-gama sugeriravme deka autizmot ja opfa}a Th-1 imunolo{kiot odgovor (7, 28). Posledovatelno, izvedovme studija za proizvodstvoto na IL-2, IL-6 i TNF na PKMNK. Otkrivme deka proizvodstvoto na IL-2 be{e zna~itelno zgolemen kaj decata so autizam. Proizvodstvoto na IL-6 i TNF na PKMNK kaj decata so autizam be{e umereno povisoko 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 prethodniot izve{taj (33). Naodamna dve drugi grupi istra`uva~i upotrebija alternativni metodi i otkrija deka PKMNK kaj decata so autizam proizveduva poka~eno nivo na IL-12 i IFN-gama ili izrazuva povisoki od normalni nivoa na iRNA za IFN-gama (za citirawe videte vo literatura #7). Ovie otkritija go poka`uvaat postoeweto na Th-1 tipot na imunolo{ki odgovor kaj decata so autizam i toa, isto taka, }e bide ednakvo so avtoimunata patologogija kaj autizmot, bidej}i IL-2, IL-12 i IFN-gama citokinite se dobro poznati pottiknuva~i na avtoimunite bolesti (34).

Vo pogled na patogenezata na imunoposreduvanite bolesti, imunoaktivacijata e eden od primarnite nastani kaj avtoimunitetot, inflamacijata i virusnite

(2.) Cytokine production can be studied by peripheral blood mononuclear cells (PBMNC) after mitogen stimulation *in vitro*; and (3.) Cytokine-specific mRNA expression can be measured in PBMNC 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 PBMNC. We found that the IL-2 production was significantly increased in autistic children. The production of IL-6 and TNF by PBMNC 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 PBMNC 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 izraz na aktivaciskite markeri na perifernite krvni mononuklearni kletki i zgolemena akumulacija na rastvorlivite antigeni dobieni od krvnata mononuklearna kletka, glavno, citokinite, citokinskite receptori i adhezivnite molekuli. Vrz osnova na ovie razmisluvawa, imunoaktivacijata se javuva prirodno kaj decata so autizam, bidej}i tie imaat podignati nivoa na imunoaktivaciski antigeni, kako {to se: sCD8, IL-2, IL-12 i IFN-gama (26, 28) i nivnata krv sodr`i aktivirani T kletki (26, 27). Taka, razumno e da se zaklu~i deka zgolemuvaweto na IL-12 kaj decata so autizam uka`uva na antigenska stimulacija na Th-1 kletkite, koi via INF-gama mo`e da pottikne avtoimunitet (7). IL-12 citokinot selektivno go pomaga razvojot na Th-1 kletkite (35) i Th-1 kletkite iniciraat patogenoza na organsko specifi~nite avtoimuni bolesti (34).

Testirawe na avtoimunitetot kaj autizmot

Neodamne{nite otkritija jasno poka`uvaat deka avtoimunitetot ima mnogu va`na uloga vo patogenezata na nevrolo{kite naru{uvawa, vklu~uvaj}i go autizmot (2, 3). Bidej}i mozokot e zaboleniot organ, avtoimunata reakcija }e bide protiv mozokot. Avtoimunitetot obi~no se manifestira so izvesni avtoimuni faktori {to gi identifikuvavme kaj deca so autizam. Ovie faktori se va`ni za da ja identifikuvaat mozo~no specifi~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 imunomodulaciska 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 NAFP. Otkrivme deka MBP-antiteloto kaj autisti~nata populacija e zabele`itelno povisoko otkolku kaj normalnata populacija; ottuka, toa slu`i kako primaren marker na avtoimunata reakcija kaj autizmot. Sprotivno na toa, NAFP-antiteloto kaj autisti~nite pacienti e samo marginalno pivisoko otkolku normalnite kontroli, pravej}i go vtor marker za izbor. Sepak, se prepora~uva ovie dva avtoimuni markera da se testiraat 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, vklu~uvaj}i gi MPR i DTP. Poka`avme deka zna~itelen broj deca so autizam, no ne i normalnite deca, zadr`uvaat edinstven tip antitelo na morbili na 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 avtoimunite bolesti, odnosno tie iniciraat 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 kleto~en avtoimunitet kaj pacienti so autizam (7, 28).

1. **Brain autoantibody profile**: This test detects antibodies to two brain proteins, namely the MBP and NAFP. 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 NAFP 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 DPT. 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. **Serotoninski profil**: Ovoj test go meri nivoto na serumot ili plazmata na serotoninot. Otkrivme deka pacientite so autizam imaat abnormalno nivo na serotonin, {to bi trebalo da se testira pred da se dade tretmanot so terapija na selektiven serotoninski inhibitor na povtorno vruvawe (SSRI). Nivoto na zgolemeniot serotonin kaj autizmot mo`e, isto taka, da bide povrzano so avtoimunata reakcija na serotoninskite receptori vo mozokot (21).

6. **Avtoimuni markeri pottiknati od `iva**: Ovoj test ja analizira avtoimunata reakcija na izlo`uvawe na `iva (ili te{ki metali). Ovie markeri opfa}aat nuklearni antitela sproti nuklearnite antigeni i antilamininskite antitela sproti proteinite na bazalnata membrana. Otkrivme deka samo mal broj na deca so autizam se pozitivni na ovie antitela, no nivoto na ovie antitela zna~itelno ne se razlikuva{e od normalnite deca (30).

Subjekti (pacienti) i laboratoriski proceduri vo na{eto istra`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 edinstveno vklu~ivme deca so autizam so cvrsta dijagnoza na autizam, a gi isklu~ivme drugite dijagnozi, kako {to se: pervazivni razvojni naru{uvawa (PRN), pervazivni razvojni naru{uvawa-nespecificirani na drug na~in (PRN-NDN) i Aspergeroviot sindrom. Subjektite bea grupirani spored vozrast i pol kade {to be{e mo`no, a nikoj ne be{e isklu~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 statisti~ki prira~nik za mentalni naru{uvawa*, ~etvrto izdanie (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 antilaminin 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 onie {to imaat cvrsto fizi~ko zdravje bez nikakov znak na mozo~na bolest ili, pak, mentalna bolest ili nekoja druga poznata medicinska sostojba. Pred da se zemat primeroci krv od licata, obezbedivme soodvetna dozvola od Institucionalniot reviziski odbor (IRO) na Dr`avniot univerzitet vo Juta i pred toa od univerzitetot vo Mi~igen. Sé na sé, gi iskoristivme prethodno sobranite serumski primeroci skladirani vo zamrznata sostojba vo zamrznuva~ na -20$^0$ C, odr`uvaj}i go ciklusot na zamrznuvawe i rastopuvawe na minimum. Detalite od razli~ni laboratoriski proceduri i metodi na analiza se opi{ani vo na{ite publikacii (3, 5, 7-9, 21, 23-25, 28, 30).

Imunomodulaciska terapija (IMT) kaj autizmot

Laboratoriskite otkritija jasno ja poka`uvaat ulogata na avtoimunitetot vo patogenezata na autizmot. Idejata deka autizmot e avtoimuno naru{uvawe dopolnitelno e zacvrstena od faktot deka autisti~nite pacienti reagiraat dobro na rehabilitacijata so imunomodulaciskite lekovi (2, 3, 7, 19, 29). Imuno intervenciite mo`e da predizvikaat imunomodulacija - sostojba na spre~uvawe ili stimulacija. Bidej}i autisti~nite pacienti ne poka`uvaat klasi~na primarna imunodeficiencija, ne e dobra strategijata ednostavno da zajakne nivniot imunitet. Sepak, tie, imaat imunoabnormalnosti i zatoa, zavisno od prirodata na imunoabnormalnosta, celta na IMT treba da se normalizira ili povtorno da se vospostavi imunata funkcija. Ova }e dozvoli pobalansirana imunoreakcija, odbegnuvaj}i gi glavnite 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. Slednoit spisok na imunomodulaciskite 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**: Steroidite, kako {to se Prednizon i/ili ACTH voobi~aeno se upotrebuvaat kako prv lek pri tretmanot na pacienti so avtoimuni bolesti. Osven za izve{taite za slu~ai {to poka`uvaat pozitivni reakcii na steroidi (36), ne se izveduvale klini~ki obidi. A sepak, mnogu semejstva davaat sopstveni izve{tai za klini~ko podobruvawe na autisti~nite karakteristiki koga nivnite deca primaat steroidi za medicinski sostojbi poinakvi od autisti~noto naru{uvawe.

2. **Terapija so transfer faktor**: Transferskiot faktor (TF) e imuno modulator za kontrola na kleto~niot imunitet na T-limfocitite, osobeno vo tekot na patogenite infekcii. Za da bide efikasen, TF normalno se pravi od leukociti ili od strogo selektirani donatori na krv. So koristewe na ovoj tip na TF, edna otvorena studija poka`uva klini~ko podobruvawe na autisti~nite simptomi kaj nekoi deca (29). Isto taka, postoi komercijalen brend na TF koj po definicija ne e TF, tuku e produkt na govedski kolostrum; negovoto koristewe vo lekuvaweto na autisti~nite pacienti ne e nau~no dokumentirano.

3. **Imunoglobulinska terapija**: Ovaa metoda za rehabilitacija ve}e se praktikuva za rehabilitacija na autisti~ni pacienti so avtoimuni problemi. Otvoreni obidi na intravenozen imunoglobulin (IV-Ig) poka`aa deka pove}eto, no ne site deca so autizam reagiraat pozitivno na ovoj tretman (19). Klini~ki, taka tretiranite deca poka`aa podobruvawa vo jazikot, komunikacijata, socijalnata interakcija i raspon na vnimanie. Pred nekolku godini, go predlo`ivme koristeweto na "Oral-Ig" kako alternativna metoda na IV-Ig. Oral-Ig poznato e deka dava zna~itelno 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. **Avtoantigenska terapija**: Rehabilitacijata na pacientite so avtoimuni bolesti

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 rehabbing 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 realizira so oralna primena na avtoantigeni. Ova, isto taka, e primenlivo za autizmot. Ovoj modalitet se potpira vrz faktot deka autizmot opfa}a avtoimuna reakcija na mozokot MBP. Ova otkritie otvori tesen pogled kon mo`nosta za rehabilitacija na autisti~ni pacienti so dodatoci vo ishranata {to sodr`at mozo~en MBP ili mielin, na primer: sfingolin (3).

5. **Glutatinska terapija**: Glutationot, tripeptid {to sodr`i tri amino-kiselini, e priroden imunomodulator, antioksidant i detoksifikator. Zaradi ovie tri biolo{ki funkcii, glutationot e najpotencijalen za{titnik na teloto od infekcii, avtoimuni problemi i drugi abnormalnosti, vklu~uvaj}i go i oksidativniot stres (37). Taka, glutationot se koristi za rehabilitacija na imunoproblemi kaj deca so autizam so klini~ko podobruvawe.

6. **Plazmafereziska terapija**: Ovaa procedura se koristi za lekuvawe na pacienti so infekcii, avtoimuni bolesti i imunokompleksni bolesti. Dodeka procedurata uspe{no se koristi za lekuvawe na pacienti so nevrolo{ki naru{uvawa, kako {to se opsesivno-kompulzivno naru{uvawe (38). Taa dosega ne se koristela za rehabilitacija na pacienti so autizam.

Zaklu~oci

Na{eto istra`uvawe poka`a deka avtoimunitetot e srcevina na problemot kaj mnozina pacienti so autizam. Avtoimunite abnormalnosti i reakcijata na pacientite na tretaman so imunomodulaciska terapija, ja zacvrsti idejata deka autizmot e avtoimuno naru{uvawe. Avtoimunata reakcija, najverojatno, e naso~ena kon mielinskata obvivka na mozokot, a mo`e isto taka da bidat opfateni i drugi nevralni strukturi dlaboko vo mozokot. Neodamna otkrivme (8) deka nucleus caudatus e involviran vo nevropatologijata na autizmot - novo otkritie od potencijalno golema klini~ka i terapevtska va`nost.

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 rehabbing 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 procesuirawe, koi se abnormalni kaj decata so autizam. Bidej}i tri ~etvrtini od autisti~nata populacija ima avtoimuni problemi, mislime deka najgolem broj autisti~ni pacienti bi mo`ele direktno da imaat polza od avtoimunoto istra`uvawe denes. Ovaa podgrupa, verojatno, e "dobiena# forma inicirana od virus, verojatno od virusot na morbilite, ta treba da se ispitaat i drugi etiolo{ki faktori. Vo 2002 ja ozna~ivme ovaa 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 vnimanie na avtoimunoto istra`uvawe i imunomodulaciskata terapija kaj autizmot.

Priznanie

D-r Sing im iska`uva ogromna blagodarnost na semejstvata {to u~estvuvaa vo negovoto istra`uvawe. Toj bi sakal da im zablagodari na nekolkumina studenti i tehni~ari za nivnata pomo{ vo laboratoriskata rabota. Negovoto istra`uvawe be{e poddr`ano bez nikakov 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.

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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