Neuroimmune diseases are increasing. Is there a possible vaccine link?

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Abstract. Autoimmune and neuroimmune diseases prevalence rates are rising enormously. It would be difficult to explain with genetic and environmental factors. Noteworthy, this rising may be related with childhood vaccine programs. There is also a lack of information about this topic in pediatric and family medicine practice in some countries like Turkey. Prevention and treatment of these diseases is possible if pathogenesis could be well understood. We attempt to review this topic in immunological and neurological perspectives for this purpose. We searched PubMed from year 2000 to date with neuroimmune, autoimmune, measles and vaccine link keywords in some combinations and related topics. The obtained information from this search dealt with some important subheadings. There is a need for further investigations of neuroimmune disease and the possible vaccine link.

Keywords: Neuroimmune, autoimmune, measles, vaccine link

1. Introduction

The national institutes of health of USA estimated that up to 23.5 million Americans suffer from autoimmune diseases like autism, multiple sclerosis (MS), asthma, type 1 diabetes mellitus and that the prevalence rates of these diseases are significantly rising [1, 2]. Genetic forms would account only a small percentage of these diseases. The sporadic forms of these diseases might be acquired from exposure to environmental factors such as viruses, vaccines, or chemical toxins and other unknown factors [3]. Although, this rising may be related with childhood vaccine programs, there is a lack of information about this topic in pediatric and family medicine practice in some countries like Turkey. We will discuss this topic in a few important subtitles, first by basic immunologic concepts, and second by, autoimmune – neuroimmune diseases and possible relationships with vaccines.

2. Immune factors

2.1. Immune response

To understand pathogenesis of these diseases especially autoimmune disorders, the basic response of human immune system to the inner and outer stimuli (allergen, self/foreign antigen and microorganisms) should be known. Defense against microbes is firstly mediated by the early reactions of innate immunity.
and the late response is mediated by adaptive immunity. Innate immunity consists of cellular and biochemical defense mechanisms that are in place even before infection and respond rapidly to the invading infectious agents. The principal components of innate immunity are; 1) physical and chemical barriers (such as epithelia), 2) phagocytic cells and natural killer cells, and 3) blood proteins including complement system and other members of the inflammation 4) cytokines. The mechanisms of innate immunity are specific for structures that are common to groups of related microbes and may not distinguish fine differences between foreign substances.

Adaptive immunity is defined with exquisite specificity for distinct molecules and an ability to “remember” and respond vigorously to repeated exposures to the same microbe. The components of adaptive immunity are T and B-lymphocytes and their products. The link between innate and adaptive immunity is antigen-presenting cells [4]. Because of vaccines administered mostly parentally, fundamental innate part of the immune response is passed [5]. So, immune response may be deviated to autoimmunity, antigenic memory could be dramatically reduced. Related to this reason, some vaccines need to be conjugated to adjuvants and multiple shots are required, especially for infants who have immature immune system. Additionally, adjuvants in vaccines work by engendering co-stimulatory signals causing autoimmunization [6].

2.2. Immune repertoire

Immune repertoire is defined as, the number of different recognizing subtypes that immune system makes by somatic hypermutation. During fetal and neonatal life, there is a lack of antigenic stimulation; so, there are low numbers of memory cells. The development of mucosal immunity in the newborn is closely linked to the colonization of the gut by commensally bacteria where initially, infants are colonized with Escherichia coli and streptococcus species. During early colonization, microbial products (lyopolysaccharides from gram-negative bacteria) in the gut lumen bind to toll-like receptors (i.e., toll-like receptor 4) on epithelial cells and thereby dampen signaling via these receptors that otherwise would create a harmful inflammatory response in the gut [7]. The immune system has an enormous repertoire of antigen receptors that allows reactivity not only against pathogens, but also against auto-antigens. This potential disadvantage is balanced by potent regulatory mechanisms that reduce the risk of harm itself [6]. A failure to shift to post-natal immune regulation by, for example, vaccines results in increased susceptibility to disease, or adverse reactions especially autoimmunity [7]. Thus, immune responses to vaccination vary widely, depending on titers of maternal antibodies, characteristics of specific vaccines, the age at vaccination, the vaccine dose and interval. Because of maternal antibodies, reduced immune responses have been noted with both modified live and non-replicating vaccines [8]. The first 6 mo of life and especially the neonatal period is important for vaccinations. We think that, more natural the repertoire, more powerful the immunity.

2.3. Brain immunity

Immunology concept has generally been considered as systemic immunology. However, characteristics of brain immunity in neuroimmune disease should be considered distinctly, because; 1) Brain and nervous system continues to develop after birth. 2) There is no lymphatic drainage in brain. 3) The main immune cell in the brain is microglia that is also a macrophage. 4) In cerebrospinal fluid, that quenches brain parenchyma, complement system is also important like immunoglobulins. Recent genome wide association studies have showed relations between complement system and some neurodegenerative disorders [9]. During prenatal and early postnatal development the brain is extremely vulnerable to neurotoxic insults. Also, the blood-brain barrier is incomplete and thus more permeable to toxic substances during these periods [10].

2.4. Microglia

In brain histology, microglial cells are the second population after neurons. They are the resident macrophages of the brain that serve both glial and immune-related functions. These include the monitoring of synapses, the detection and phagocytosis of infectious agents, and the removal of apoptotic and necrotic cells with subsequent suppression or promotion of neuroinflammation. Axon degeneration, involves fragmentation into short segments that can be individually phagocytized by microglia. Microglia-mediated neuroinflammation has been implicated in many
neuronal disorders, with various inflammatory factors present in the central nervous system of patients suffering from neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's disease [11, 12]. Microglia can also monitor and directly influence synapses. The selective elimination of inappropriate nerve connections involves complement proteins C1q and C3. In addition, directly modulate the functional integration of neurons. Microglia activity can influence inhibitory synaptic drive and is also able to mediate the ability of synapses to change in strength: induction of long-term potentiation and long-term depression was shown to be influenced by microglia in a TNF-alpha dependent manner. This is particularly interesting as long-term potentiation is thought to be among the major cellular mechanisms underlying memory and learning and long-term depression is hypothesized to be involved in the fine-tuning of motor skills, thereby putatively connecting microglia with higher order brain functions. It has been known for a long time that mice lacking functional Hoxb8 (a gene expressed only by microglia in the brain) exhibit obsessive grooming behavior, and these animals have been used as a model for the human compulsive hair pulling disorder, trichotillomania. Hox gene family is prominently engaged in patterning of the anterior-posterior axis during early embryo development. Even more strikingly, the abnormal behavior was shown that it is not due to neuronal defects but to loss of a Hoxb8 microglial population in the brain, thereby it could be a link between immune cells and behavior [11]. Microglia monitors the brain environment by interpreting and processing stimuli (environmental toxins like vaccine ingredients and adjuvants, endogenous proteins) or reactive microgliosis trough pattern recognition receptors. Inflammation-mediated neurotoxicity in neurodegenerative disease can occur as a consequence of microglial dysregulation and over-activation [12].

2.5. Microbiome

The human body is colonized by a vast number of microbes, collectively referred to as the human microbiota. This link between these microbes and human health is the focus of wide research. The collective genome of microbiota is called as microbiome, which extensively interacts with the host's immune system. Studies of germ-free mice showed that these animals are susceptible to infection and immunological dysregulation associated with dysbiosis of microbiota caused by some medical practice (vaccination, antibiotics, etc.) [13].

2.6. Hygiene hypothesis

Hygiene hypothesis states that a lack of early childhood exposure to infectious agents increases susceptibility to allergic and autoimmune diseases is more and more important to explain the pathogenesis of these diseases. Microbial exposure has little relationship with “hygiene” in the usual meaning of the word and the term “hygiene hypothesis” is therefore misleading. A better term would be “microbial deprivation hypothesis” [14]. As a homeopath, Teixera [15] has sought scientific evidence to endorse the belief that inhibition of acute disease manifestation in childhood can predispose to future of chronic diseases. Thus, the results of a very recent long-term epidemiological study suggest that childhood infectious diseases protected against asthma persisting in later life but pertussis and measles were associated with new-onset asthma after childhood [16].

2.7. Preventive medicine

Preventive medicine is the specialty of medical practice that focuses on the health of individuals, communities, and defined populations. Its goal is to protect, promote, and maintain health and well-being and to prevent disease, disability, and death. Good hygiene practices and vaccines are essential parts of preventive medicine of personal and community health maintenance. The worldwide distribution of child deaths shows the importance of preventive medicine for some regions of the world. Noteworthy, distribution of global child deaths by cause is also covering old colonies of some western countries [17]. Neonatal and especially small for gestational age babies, diarrhea and pneumonia are the most prominent causes of child deaths. When we look at this distribution, we could easily see that water and food deprivation are the most prominent cause of death. Death rate due to measles is relatively unimportant compared to other causes. However, it is a great public health achievement in 20th century to decrease annual morbidity from vaccine preventable diseases, but this reducing could be also related with more hygiene practices [18].

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2.8. Vaccine immunology

Following injection, the pathogen associated patterns contained in vaccine antigens attract dendritic cells, monocytes and neutrophils that patrol throughout the body. If vaccine antigens/adjuvants elicit sufficient “danger signals” this activates monocytes and dendritic cells, which changes their surface receptors and induces their migration along lymphatic vessels, to the draining lymph nodes where the activation of T and B-lymphocytes will take place. In the lymph nodes, vaccines cause an extrafollicular response that produce low affinity and low antibody levels. Whereas, natural infection cause a germinal center response that produce high antibody levels and T and B memory lymphocytes [19].

2.9. Childhood vaccination schedule

In our country like USA, an intensive compulsory immunization schedule is administered after birth. Childhood immunization is not as compulsory in some developed countries like United Kingdom [20]. In Baltic countries and Japan, vaccine doses and also infant mortality rates are half of that of USA [21]. Doses and number of vaccines in childhood vaccination schedule of US has nearly tripled, but there is no reducing in morbidity and mortality rates in USA [18]. In a recent evaluation of Dutch national immunization program, Houweling et al. [22] proposed seven ethics inclusion criteria (not compulsory) (Table 1). According to these criteria, most of childhood vaccines should be reassessed to administer especially before 2 yr of life.

2.10. Herd immunity and vaccine coverage

Herd immunity means the resistance of a group to attack by a disease to which a large proportion of the members are immune, thus lessening the likelihood of a patient with a disease contact with a susceptible individual. So, the presence of immune individuals could provide indirect protect to others. There is natural and vaccine-induced herd immunity. To eradicate an infectious disease, there is a need to keep herd immunity threshold at more than 70–95%. This could be possible with more than 95% vaccine coverage. Measles is the most intensely studied infection in terms of herd immunity. Before vaccine schedule, outbreaks of measles were observed in 2 to 3 yr periods, and 95% of population developed life-long natural immunity by the age of 15. By vaccination, vaccine-induced measles immunity shifted to older ages. Therefore, it seems that vaccination creates more vulnerability to measles in adult population [23].

2.11. Autoimmune epidemic

Loss of self-tolerance is essential to autoimmunity. Epigenetic is defined as the study of all inheritable and
potentially reversible changes in genome function that do not alter the nucleotide sequence within the DNA. Epigenetic mechanisms such as DNA methylation, histone modification, nucleosome positioning, and micro RNAs are essential to carry out key functions in the regulation of gene expression. Recent reports indicate that the environment can contribute to autoimmunity by modifying gene expression through epigenetic mechanisms [24,25]. In our opinion, vaccine ingredients could be related with epigenetic mechanisms. Researchers have identified 80–100 different autoimmune diseases and suspected at least 40 additional diseases of having an autoimmune basis. These diseases are chronic and can be life threatening. Although, epidemiological studies are needed to assess whether immunizations may increase the risk in some susceptible individuals; there is a huge increase in the rates of autoimmune diseases such as type 1 diabetes, autism, MS, asthma etc. [2,26]. Autism is a dramatic example to this increase in the rates of autoimmune diseases.

3. Neuroimmune diseases

The term of neuroimmune disease refers to a group of illnesses that are the result of acquired dysregulation of both the immune system and the nervous system, often resulting in lifelong disease and disability. Guillaine-Barre syndrome, autism, MS, acute disseminated encephalomyelitis, attention-deficit hyperactivity syndrome, poliomyelitis, subacute sclerosing panencephalitis (SSPE), inflammatory bowel diseases, Gulf war syndrome, chronic fatigue syndrome are some of them [3].

3.1. Guillaine-Barre syndrome

In a recent meta-analysis, researchers found an association with H1N1 vaccine with this syndrome [27].

3.2. Autism

Autism was first described more than 60 yr ago. It is not a simple developmental disorder but rather a biological disorder of complex etiology and heterogeneity. Autism is characterized by “qualitative deficits” in four major categories: 1) deficits of developmental rates and/or profiles, 2) deficits of responses to sensory stimuli, 3) deficits of speech, language, and communication capabilities, and 4) deficits of social interactions and/or manners of relating to other people. According to Singh [3], there are many immune abnormalities in autistic children. What triggers immune dysfunction in autism is not known, but there is some studies suggesting that measles virus (MV) (vaccine strain included) might be a culprit for autism pathogenesis [3,28].

3.3. Chronic inflammation

Vargas et al. [29] observed increased microglial and astroglial activation in the postmortem brains of autistic patients especially in cerebellums. Mercury; thimerosal (ethyl mercury) was added into vaccines to prevent potentially life threatening contamination with harmful microbes. Since this molecule negatively affects many of the same biochemical processes and enzymes implicated in the pathogenesis of autism so, it is no longer used. Aluminum is used instead of mercury; but it has also the same adverse effects [11]. When first described, autism was regarded as a rare condition affecting no more than 4 per 10,000; however, it is now much more common, occurring in at least 1 out of every 100 children. It is much difficult to explain with other environmental factors.

Although, many pediatricians and family physicians are not seemed to be aware of debate on autism and vaccine link, there is a great concern about this topic. Therefore, DeStefano et al. [30] from the centers for disease control and Abt associates incorporate, analyzed data from 256 children with autism spectrum disorder and 752 children without autism spectrum disorder and looked at each child’s cumulative exposure to vaccine antigen numbers. They found that the total antigens from vaccines received by age 2 yr. or the maximum number received on a single day, was the same and no relationship was found with logistic regression [30]. This study is not a double-blinded fashion and has no unvaccinated control group. They also did not evaluate immune status of the groups.

3.4. MV

Measles is a common and mostly mild childhood infection characterized with a maculopapular rush. The virus has some effects on immune system and a possible link between neuroimmune disorders. Because of these, both wild type and vaccine strains are drawing attention. CD46 is a widely distributed hu-
man complement regulatory protein and acts as a cofactor for the proteolytic inactivation of C3b/C4b by factor I, also induces proliferation and differentiation of regulatory T cells. Wild type strains do not use CD46 efficiently. The CD150 molecule (signaling lymphocytic activation molecule), as its name considers that it send activator signal to lymphocyte cytoplasm, is generally used by wild type strains (B-H types) [31]. CD150 does not exist on brain cells [32]. This is important because of SSPE development. Therefore, wild-type infection should have some effects on immune repertoire. Vaccine strain (A type) could cause a complement-mediated autoimmunity is a question mark. Cell-to-cell spread of virus appears to be an important mechanism supporting persistent infection [33].

3.5. SSPE

SSPE is a progressive neurological disorder caused by persistent MV infection. The earliest descriptions of measles are found in Arab writings of Al Rhazes in the 10th century anno domini but SSPE was firstly described in 1933. It was not until 1967–69 that MVs were established as the cause. When live measles vaccine became available in the early 1960s, the etiology of SSPE was still unknown [34,35]. SSPE affects one in 10,000–25,000 children after acute measles infection. The persistent brain infection leads to a hyperimmune antibody response that is a pathognomonic feature of the disease [34]. Although, the association between MV and SSPE was established there were concerns that measles vaccine virus might also cause this condition. In a recent review, Campbell et al. [35] attempt to refute these concerns as four theories. Interestingly, they report that some vaccine strains in a summary of viral RNA sequencing of MV were isolated from SSPE patients. Also, they give a figure that shows measles notifications, SSPE onsets and measles vaccine coverage in England and Wales that there was no SSPE before measles vaccination and a clear decreasing with measles-mumps-rubella vaccine includes a modified strain [35]. The authors claim that SSPE registries started after measles vaccinations, some SSPE cases had vaccination but they were not related with vaccine. They say that natural MV has consistently been isolated in SSPE brain biopsy material. This might be meant as an immunodeficiency to MV in such people and measles vaccination is already contraindicated to these people.

3.6. MS

The most common neurologic disorder of young adults and prevalence rate is somewhere 1/200 in women [34]. It is an inflammatory disease, in which the fatty myelin sheaths around the axons affected. A recent study supports and emphasizes a complex infectious and immunologic background of MS [36]. Also, serum and cerebrospinal fluid measles antibody levels increase over time in patients with MS [37]. Furthermore, adults receiving hepatitis B vaccine had significantly increased odds ratio with some autoimmune diseases, especially for MS diseases. Because of this controversy vaccination rates was low in some countries [38]. In a recent meta-analysis that aimed to systematically review all randomized clinical trials and non-randomized studies reporting on risk of developing MS following any immunization; risk of developing MS remained unchanged after Bacillus Calmette-Guérin, hepatitis B, influenza, measles-mumps-rubella, polio and typhoid fever immunization. However, as they had written, in many cases, these studies are merely case reports, poorly designed observational studies, or well designed studies with a small number of participants from which valid conclusions cannot be drawn [39]. Another recent example reported by Menge et al. [40] on four patients who developed symptoms of neuromyelitis optica within months after quadrivalent human papillomavirus vaccine.

3.7. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) syndrome

In recent years, four conditions sharing a common denominator silicosis, the Gulf war syndrome, and the macrophagic myofasciitis syndrome and post vaccination phenomena were linked with previous exposure to an adjuvant and accumulating data suggest the possibility of accelerated autoimmunity/inflammation following vaccination [41]. Shoenfeld and Agmon-Levin [41] suggest including these conditions under the name of ASIA. After then, they reported a 93 cases of ASIA syndrome that 70% neuropsychiatric manifestations after the exposure to hepatitis B vaccine [42].

3.8. Primary immune deficiencies (PID)

Another important but overlooked topic related with childhood vaccination schedules is PID. There
are more than 200 PID include individually rare but collectively diverse genetic defects that influence the development, function, or both of immunity. They result in a wide range of clinical symptoms, including but not limited to susceptibility to infections, autoimmunity, inflammation, allergy, and malignancy [43]. Although, it is well known that live vaccines could be mortal in PID [44], it is not well defined the childhood vaccinations effects on other PID. This is important because childhood vaccinations are being performed regardless of the immune status of the child generally. In Turkey, prevalence of PID is too high about 1 in 4 of pediatric immunology outpatient-basis [45].

4. Discussion

Vaccines represent a potent tool to prevent or contain infectious diseases with high morbidity or mortality. However, despite their widespread use, we still have a limited understanding of the mechanisms underlying the effective elicitation of protective immune responses by vaccines [5]. Although past vaccine development efforts against most of our infectious diseases have been aimed at inducing neutralizing antibody responses and memory B-cell responses, measured by serological assays, a new generation of vaccine development is tackling more difficult targets requiring strong cell-mediated immune responses through T-helper and cytotoxic T cells in order to mediate protection [46]. For long-term protection against disease, vaccines must generate durable memory T cells capable of responding to antigen. So, assessment of vaccine-induced immune responses includes measuring the frequency and functions of antigen-specific lymphocytes are essential for vaccine researches [47]. The live attenuated vaccines are characterized by a limited viral replication in the host and replicate where dendritic cells or other antigen-presenting cells, which migrate to lymphoid organs for presenting these antigens to T and B-lymphocytes, take them up. However, such vaccines may cause mild-to-severe adverse effects in patients. On the contrary, the inactivated vaccines do not replicate and are safer than live attenuated vaccines; however, they are generally less effective, requiring multiple administrations to boost the immune response antibody titer over time [5]. Also, multiple doses of adjuvanted vaccines that are given to very young children have some potential toxic impacts [10]. Findings of Miller and Goldman [21] demonstrate a counter-intuitive relationship: nations that require more vaccine doses tend to have higher infant mortality rate. An important point to be noted is that only one controlled experimental animal study to year 2000 was performed to test the effect of vaccination on the immune system. However, vaccines have been used extensively on children multiple dose as well as single dose [41]. Hewitson et al. [48] longitudinal, case-control pilot study examined amygdala growth in rhesus macaque infants receiving the complete US childhood vaccine schedule. Their results suggest that maturation changes in amygdala volume and the binding capacity of opioid antagonist in the amygdala were significantly altered in infant macaques receiving the vaccine schedule according to the unvaccinated macaques [48]. Additionally, the introduction of new techniques of vaccine virus production on cell cultures has lead to safer vaccines, but it has not completely removed the risk of virus contamination [49].

When we searched Pubmed from year 2000 to date with neuroimmune, autoimmune, measles and vaccine link keywords in some combinations and related topics, we could find only limited publications. Although, one of alternative reasons is the advent and availability of magnetic resonance imaging that increase the sensitivity of diagnosing, it would be difficult to explain the prevalence rates of autoimmune and neuroimmune diseases with genetic and environmental factors. We think that childhood vaccine programs deserve more extensive interest about possible neuroimmune link.

In conclusion, vaccines can cause engendering co-stimulatory signals causing autoimmunization especially neuroimmune diseases. Since, the first 2 yr of life central nervous system is much vulnerable, there is still a need to compare vaccinated vs. unvaccinated animal studies for childhood vaccines.

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