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REVIEW ARTICLES

The Effects of Gender in Neurological Disorders: A Special Focus on Autism Spectrum Disorders and Thiomersal Toxicity

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SUMMARY

Estrogen and testosterone serve as the main sex hormones in humans. In addition, they have many different functions in terms of metabolic, and body defense. Gender differences lead to various social, economic, physiological, and pathological outcomes. Gender differences may also cause different toxicokinetics for metalslike mercury.Mercury exposure is suggested to cause neurological disorders. Thiomersal which is one of the most widely used preservatives particularly in vaccines, consists of approximately 50% mercury by weight. Autism spectrum disorders (ASD) have been associated with thiomersal exposure from vaccines in the last decades. Recent studies show that the incidence of ASD is higher in boys compared to girls. However, studies and discussions continue in this area. It is thought that this situation may be related to the difference in the toxicokinetics of mercury in different genders. There are concerns that ASD in girls may have a distinct phenotype than boys. The studies are now focused on whether there is an overlook due to the difficulty of diagnosing in females or it is more common in males due to physiological and hormonal reasons or not. In this review, we evaluated the frequency of ASD in different genders, the association between thiomersal and ASD and whether thiomersal exposure from vaccines could be an underlying factor of ASD in boys or not.

Key Words: *Autism, gender, neurodevelopmental disorders, mercury, thiomersal*

Nörolojik Bozukluklarda Cinsiyetin Etkileri: Otizm Spektrum Bozuklukları ve Tiyomersal Toksisitesine Özel Bir Bakış

ÖZ

Östrojen ve testosteron, insanlarda ana seks hormonlarıdır. Ayrıca metabolizmanın düzenlenmesi ve vücut savunması açısından da çok farklı işlevleri vardır. Cinsiyet farkı, farklı sosyal, ekonomik, fizyolojik ve patolojik sonuçlara yol açar. Metallerin farklı cinsiyetlerde farklı toksikokinetiğe sahip olabileceği, cinsiyet farkının özellikle cıva kaynaklı nörolojik bozukluklarda önemli olabileceği bilinmektedir. Tiyomersal, özellikle aşılarda koruyucu olarak kullanılan organik bir cıva bileşiğidir ve tiyomersalin ~%50'si cıvadan oluşur. Otizm spektrum bozuklukları (OSB), son yıllarda aşılardan tiyomersal maruziyeti ile ilişkilendirilmiştir. Son araştırmalar, OSB insidansının erkeklerde kızlara göre daha yüksek olduğunu göstermektedir. Ancak, bu alanda çalışmalar ve tartışmalar devam etmektedir. Bu durumun farklı cinsiyetlerde cıvanın toksikokinetiğinin farklı olmasıyla ilişkili olabileceği düşünülmektedir. Kızlarda OSB'nin erkeklerden farklı bir fenotipe sahip olabileceğine dair endişeler vardır. Araştırmalar OSB'nin kadınlarda tanı koymanın zorluğundan kaynaklanan bir gözden kaçma mı yoksa fizyolojik ve hormonal nedenlerle erkeklerde mi daha sık görüldüğü üzerine odaklanmıştır. Bu derlemede, farklı cinsiyetlerde OSB sıklığını, tiyomersal ile OSB arasındaki ilişkiyi ve aşılardan tiyomersal maruziyetin erkek çocuklarda OSB'nin altında yatan bir faktör olup olamayacağının değerlendirilmesi amaçlanmıştır.

Anahtar kelimeler: *Otizm, cinsiyet, nörogelişimsel bozukluklar, cıva, tiyomersal*

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INTRODUCTION

Estrogen and testosterone are the leading sex hormones that determine the differences in the female and male bodies. It is well known that they have led to their different-sex characteristics. The World Health Organization (WHO) has clearly expressed the difference between gender and sex. Gender describes the roles, behaviors, activities and opportunities that communities and societies deem appropriate for women and men. In contrast, sex refers to the characteristics that are biologically determined (WHO, 2019a). In neurological and behavioral studies, this term is of great importance when gender predisposition evaluations are made as evaluating individuals from all aspects, not only physiologically and biologically, will yield more accurate results.

Various studies are showing that there may be gender differences in the metabolism and toxicity of heavy metals such as mercury, nickel or cadmium. These differences are thought to be related to exposure dose, period and duration. The excretion and accumulation of these particular metals in female and male bodies are clearly different. This phenomenon is related to the difference in the activity and amounts of xenobiotic-metabolizing enzymes in different sexes (Vahter, 2007).

As the number of males in children diagnosed with Autism spectrum disorder (ASD) is strikingly high, other than biotransformation, the role of sex hormones should be discussed (Halladay, 2015; Van Wijngaarden-Cremers, 2014; Hiller, 2014; Hanen Center, 2017). Studies suggest that the predominance of estrogen and testosterone has both advantages and disadvantages for the brain. It is emphasized that estrogens play a protective role in the female brain due to their antioxidant effects. Estrogens have vasoprotective and neuroprotective effects (Kenchappa, 2004). In various *in vitro* studies, estradiol was shown to protect neurons against oxidative stress at pharmacological and physiological concentrations (Behl, 1995,1997,1999). However, high levels of testosterone in the male brain may lead to oxidative stress as testosterone can decrease antioxidant levels in the brain and neurons, and this effect leads to neurodegeneration (Branch, 2009; Holmes, 2016; Son, 2016). On the other, low testosterone levels have been associated with various diseases, such as premature aging, diabetes, obesity, sexual dysfunction and stroke (Shores, 2018). Although estrogen seems to be protective, due to physiological reasons, the phenotype of autism in girls may differ from boys. Moreover, the diagnosis of girls with ASD may be overlooked by the current diagnostic criteria (Halladay, 2015; Van Wijngaarden-Cremers, 2014; Hiller, 2014; Hanen Center, 2017).

Heavy metals can cause oxidative stress in the central nervous system (CNS). The presence of high levels of testosterone in the male brain may aggravate the deterioration of oxidant/antioxidant balance. Therefore, it is suggested that males may be more sensitive to neurotoxicity caused by heavy metals. Various epidemiological studies and animal studies support this suggestion (Vahter, 2007; Niedhammer, 2000). However, industrial studies, such as the studies on methyl mercury, are mainly conducted on male workers, and this may cause bias (Niedhammer, 2000). In recent years, exposure to thiomersal, a vaccine preservative that consists of ethyl mercury, has been increasingly associated with neurological diseases such as ASD, although there are contradictory reports as well (Hurley, 2010).

The high incidence of ASD in boys compared to girls (1: 4-8) has also suggested that gender difference may be an essential factor in thiomersal toxicity (Halladay, 2015; Moseley, 2018; Lai, 2015; NAS, 2019; Loomes, 2017; Stamova, 2011; Gallagher, 2010a; Gallagher, 2010b).

First, this relationship has not been fully proven, and more mechanistic studies are needed to clarify whether or not an association is present. However, there are many question marks on the association between ASD and thiomersal exposure. Concerning

all the available data, this review will focus on the frequency of ASD in different genders, the possible association between thiomersal and ASD, and whether thiomersal exposure from vaccines could be an underlying factor of ASD in boys or not. We will mainly explain gender differences in neurological disorders, the possible underlying mechanisms, gender differences in thiomersal toxicity and the different effects of thiomersal in males and females.

Testosterone and estrogens

Estrogen and testosterone, which serve as the main sex hormones in humans, perform their functions by binding to specific steroid hormone receptors in different cell compartments, such as the nucleus, cytosol, and cell membrane. The long or short-term effects of sex hormones are determined by the location to which they are attached and the downstream gene activation (Cohen-Bendahan, 2005; Knickmeyer, 2006; Arnold, 2009).

Sex hormone receptors are present in different cell types. However, these receptors show differential general brain expression in prenatal, postnatal, and adult brains. Therefore, the levels of sex hormones and their interactions may differ in specific periods of life, and their effects may differ between two genders (Mccarthy, 2008; Tobet, 2009; Reddy, 2014).

Testosterone, the primary male sex hormone that performs male reproductive functions, was discovered in the 1930s (Shores, 2018). Testosterone is produced by the testicles of men (by Leydig cells), the ovaries (by ovarian follicular cells) and adrenal glands of females. This androgen is carried by sex hormone-binding globulins (SHBG) and albumin. SHBG levels increase with age in men. Therefore, the free testosterone levels decrease and reach the lowest levels in men after 60 years (Iqbal, 1983). Testosterone has various effects on different tissues, organs and systems. The free testosterone can cross the blood-brain barrier and thereby can affect neurons (Białek, 2004).

Low testosterone levels are associated with various diseases such as premature aging, obesity, sexual dysfunction, diabetes and stroke (Shores, 2018). High testosterone levels can be harmful to the cardiovascular system (Xie, 2017). Testosterone may decrease antioxidant levels and therefore can increase oxidative stress within the brain. However, the type of oxidation (lipid peroxidation, protein oxidation or both) may vary depending on the parts and conditions (such as stress) in the brain (Son, 2016). Moreover, testosterone has been reported to increase neurotoxicity (induced by oxidative stress in rats), subsequently leading loss of dopaminergic neurons and finally neurodegeneration (Holmes, 2016).

Orchiectomy may increase oxidative stress in the brain. It has been established that castration in male mice may cause loss of dopaminergic neurons in the *striatum* and *substantia nigra* and subsequently may lead to stimulation of Parkinson's disease (PD)-related pathogenesis (Khasnavis, 2013). In addition, high testosterone levels have been shown to be associated with cognitive decline, possibly due to increased oxidative stress, in male patients (Holmes, 2016). All these data may explain the interaction between testosterone and neurodegenerative diseases.

In females, estrogens are produced primarily by the ovaries, and by the placenta during pregnancy, while estrogens are secreted by the adrenal glands and the testes in males. Estrogens are known for their vasoprotective and neuroprotective effects and the incidence of neurodegenerative disorders in females is generally lower than that of males. They exhibit a different mechanism of action in pharmacological and physiological concentrations (Kenchappa, 2004; Son, 2016). In various studies, estradiol has been reported to inhibit lipid peroxidation, protect the neurons against *in vitro* oxidative stress and glutamate-induced excitotoxicity at the pharmacological concentrations (Behl, 1995,1997,1999). At physiological concentrations, estrogens affect estrogen receptors (ERs) by stimulating or suppressing gene expression

(Kenchappa, 2004).

Gender differences in immune responses

Researchers have sought a link between gender and immune responses. The prevalence of certain infectious diseases, as well as the difference in the resistance in two genders, were evaluated by several studies. Females can exhibit more robust immune responses than males. It is suggested that males are more susceptible to a wide range of diseases and infections. Differences in this peripheral immune response may also play a role in the development of autoimmune diseases (McCombe, 2009; Kivity, 2010). It is known that events such as the overproduction of pro-inflammatory cytokines play a role in the onset and progression of various neurological diseases and neurodegenerative disorders. Inflammatory mediators are synthesized in neurodegeneration sites in stroke (De Simoni, 2002; Marquardt, 2005), multiple sclerosis (MS) (Silberberg, 2001), amyotrophic lateral sclerosis (ALS) (Barbeito, 2004), Alzheimer's disease (AD) (Grammas, 2001; Moore, 2002) and PD (Hirsch, 2005). Inhibition of neuroinflammation by steroids or non-steroidal drugs decreases neurodegeneration (Kurkowska-Jastrzebska, 2004; Fahrig, 2005). Immune function and inflammatory processes in the brain can be affected by sex steroids, especially 17β-estradiol (Lei, 2003; Ospina, 2003).

The main effects of estrogens on neuroinflammation are (Mor, 1999; Baker, 2004):

- ✓ Reducing the activation of the neuroinflammatory cascade at the cellular level
- ✓ Preventing the progression of the inflammatory response with these effects
- ✓ Inhibiting the release of molecular factors.

The neuroprotective effects of estrogens are directly related to their immunomodulatory effects. Therefore, the gender difference in immune responses against different biological and chemical agents outstands as a crucial topic to investigate (Olsen, 1996; Gaillard, 1998; Klein, 2000; Bouman, 2005).

Gender differences in the male and female brain

Studies on the morphology and functions of male and female brains show that some brain structures are sexually dimorphic. Brain and related regions show biochemical, functional and anatomical differences between genders (Ruigrok, 2014). Anatomical differences include changes in size and weight, gray matter/white matter ratio, and structural differences in various regions of the brain. For example, the male brain is heavier than the female brain, and the head circumference of men is larger than females. However, when this difference is proportioned to body weight, it is determined that there is no relative difference (Zaidi, 2010). When the gray and white matter ratios are analyzed, gray matter is higher in the male brain, and white matter is higher in the female brain (Allen, 2003). In addition, many neurochemical sexual dimorphisms include neurotransmitter systems and anatomical differences. All these changes cause different responses of the brain to neurological diseases. Moreover, treatment of certain neurological and physiological disorders can differ between two genders (Cahill, 2006).

Gender differences in neurological disorders

Progressive and gradual impairments in functions such as movement, motivation and memory because of structural changes in neurons or irreversible loss of neurons are defined as "neurodegeneration" (Kovacs, 2016). In the development of neurodegeneration, biological processes like oxidative stress, mitochondrial impairments, endoplasmic reticulum stress, neuroinflammation, production and accumulation of misfolded proteins, and excitotoxicity are observed (Dong, 2009; Doyle, 2011; Jellinger, 2010).

The brain is highly sensitive because of the irreplaceable and nonrenewable nature of the neurons and is more vulnerable than other tissues and organs to destructive processes such as oxidative stress, as it contains highly peroxidizable fatty acids, as a lip-

id-rich organ, and has limited antioxidant enzyme activity (Angelova, 2015; Son, 2016). In addition, non-coding RNAs, genetic mutations [in PD genes (PARK1, PARK4, PARK8), Presenilin-1 (PS1), Presenilin-2 (PS2), Apolipoprotein E (APOE); in genes related to frontotemporal dementia (FTD)] and environmental factors (such as pesticides, fungicides, addictive drugs, heavy metals, viruses) may play a role in the development of neurodegeneration (Salta, 2017). Neurological and neurodegenerative diseases may be caused by not only physiological disorders occurring in the brain but also by various conditions affecting the general health of patients. These disorders occur because of gradual damage caused by the rapid and irreversible loss of critical cognitive and motor functions in neurons. Recent reports of WHO emphasize that neurological disorders affect more than 1 billion people throughout the globe (WHO, 2007).

This high incidence attracted the interest of the investigators to focus on the effects of gender on the progression of these diseases (Yanguas-Casás, 2017). The development, structure, function, and biochemistry of the adult brain vary significantly by gender, due to the differences in gender-determining genes and fetal hormonal programming. Gender-specific differences in the anatomic structure of a healthy human brain are likely to lead to alterations in the pathology, progression, and severity of various diseases in two different genders. Moreover, these differences may also alter the susceptibility of different genders to specific neurological conditions (Cahill, 2006; Cosgrove, 2007; Gillies, 2010; McCarthy, 2012). The discovery of the sexual dimorphisms in the brain is crucial for understanding the significance of sex at different phases of neurological diseases and disorders (Yanguas-Casás, 2017).

Several neurological disorders have a striking gender bias in incidence, prevalence, and progression (Hanamsagar, 2016). AD has a higher prevalence (1.6-3: 1) in women over 65 years. AD also causes more and faster cognitive impairment in women (Seshadri, 1997; Plassman, 2011; Irvine, 2012). The specific pathogenic mechanism underlying the higher incidence of AD in women is that at a younger age (before menopause), the mitochondria are protected against amyloid β toxicity due to estrogen. Thus, mitochondria generate less reactive oxygen species (ROS), and apoptotic signals are less in females compared to males. However, at older ages (after menopause), as estrogen levels decrease, all this advantage is lost. On the other hand, the incidence of PD in men is higher (2 - 3.5: 1) than in women (Viña, 2010). However, the differences in symptoms and cognitive effects of PD between men and women have not been extensively studied (Miller, 2010). It is suggested that PD progresses more slowly in women than in men (Baldereschi, 2000; Elbaz, 2002). When autoimmune diseases are analyzed, women experience more MS than men (2-3: 1), but the disease progresses more slowly in men (Confavreux, 2003; Voskuhl, 2012). In the case of motor neuron diseases such as ALS, the incidence is higher in men (1.6: 1). Although the onset of the disease starts earlier in men, ALS is more fatal in women than men (del Aguila, 2003; McCombe, 2010). Mood-related disorders (such as depression or anxiety disorders) are more common in women (2: 1). In addition, symptoms are more severe, and women show a higher incidence of subclinical depression (Nolen-Hoeksema, 1994; Altemus, 2014). On the other hand, in attention deficit hyperactivity disorder (ADHD), males show a higher prevalence (3: 1). In addition, men experience more severe deficiencies in motor skills and more distraction than women (Cole, 2008; Bálint, 2009; Catalá-López, 2012; Willcutt, 2012). Furthermore, males have a higher incidence in schizophrenia (1.4: 1) compared to females, and the onset of the disease is earlier in males vs. females. Men also have a weak prognosis with severe symptoms and respond more negatively to antipsychotics than women (McGrath, 2008; Goldstein, 2013). Many neurodevelopmental disorders, including autism, dyslexia, ADHD, and early-onset persistent antisocial behavior, are more common in male individuals

compared to female individuals (Rutter, 2003).

Autism spectrum disorders, causes and their prevalence

Autism, Asperger's syndrome and pervasive developmental disorder not otherwise specified (PDD-NOS) are gathered under the name "ASD". Although it was first defined in the USA and Europe in the 1940s and entered the medical literature, it is thought that the ASD profile was known a few centuries ago with references to fictional and historical individuals (Wing, 2002). Its importance was neglected since it was very rare in the 1980s (5 out of 10000 people) (Gillberg, 1991). Today, it is ranked second after mental retardation among the most common developmental severe disabilities in the United States (Bhasin, 2006; Yeargin-Allsopp, 2003). In 2021, the Centers for Disease Control and Prevention (CDC) reported that approximately 1 in 44 children (1 in 27 boys identified with autism while 1 in 116 girls identified with autism) in the U.S. is diagnosed with an autism spectrum disorder (ASD), according to 2018 data (Autism Speaks, 2022).

ASDs are generally characterized by disorders in mutual social interaction and communication, absence of creative play ability, and recurrent stereotypical behavior and interests. These behavioral changes do not occur equally in all individuals with ASD. Individuals with Asperger's disorder do not experience a significant speech delay and have above-average cognitive skills. Individuals with PDD-NOS show anomalies, especially in core social behavior. The most accepted diagnostic methods for ASD diagnosis are standard face-to-face interviews and direct observation (Newschaffer, 2007). In the literature, it is stated that in children diagnosed with ASD, there are insufficiencies regarding eye-to-eye communication, understanding social stimuli, using body language, facial expressions, and these children display problematic behaviors due to these insufficiencies (Keller, 2014). In the first six months of life, they do not exhibit sounding behaviors such as smiling and gurgling like healthy newborns. Delay in speech is often the first symptom that attracts attention in the families of children with ASD (Keller, 2014; Volkmar, 2017). With these methods, clinicians reliably detect deficiencies in social interaction and communication. In recent years, as ASD has more incidence than previously thought, studies have increased in routine clinical practices to improve existing tools for diagnosis and develop new tools (Lord, 2000; Newschaffer, 2007).

Although ASDs are known to be a sum of powerful neurobiological and genetic impairments, the factors causing these conditions are still not well known, and there are many different hypotheses discussed in the literature (Stodgell, 2001; Scott, 2002). Genetic factors are significant in autism development. Because of studies conducted on twins, the average heritability of autism is estimated to be 90%. Today, autism is considered a heritable and multi-factor psychiatric disorder that does not follow the classic Mendelian pattern (Lichtenstein, 2010). It is also thought that different features in autism may result from various genes associated with separate brain regions (Happe, 2006). Despite the importance of genetic factors, environmental factors are also important in autism. Indeed, epidemiological studies have identified numerous correlations between nongenetic influences and ASD. Several drugs, toxic chemicals, and metabolic and nutritional factors are suggested to increase the risk of autism in epidemiological studies. The risk of autism is higher when the exposure happens during the prenatal period. Moreover, immunologic risk factors, including maternal infections during pregnancy, autoantibodies to fetal brain proteins, and familial autoimmune disease, have consistently been observed across multiple studies, as have immune abnormalities in individuals with ASD (Matelski, 2016). Studies are showing the association of many environmental factors such as heavy metals, pesticides, endocrine-disrupting chemicals (EDCs) and some drugs with various neurological diseases, including autism. Antidepressant exposure in the prenatal period, especially exposure to selective serotonin reuptake inhib-

itors (SSRIs), has been shown to increase the risk of autism in children (Andrade, 2017; Croen, 2011; He, 2022; Ijomone, 2020, Kobayashi, 2016; Moosa, 2018). Exposure to various toxicants, including pesticides and EDCs such as polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs), can have detrimental consequences on neurodevelopmental processes (Newschaffer, 2007). In a recent meta-analysis, old parental age, maternal gestational bleeding and gestational diabetes are suggested to be the most important factors in the development of autism (Gardener, 2009). Causes of ASD are summarized in Figure 1.

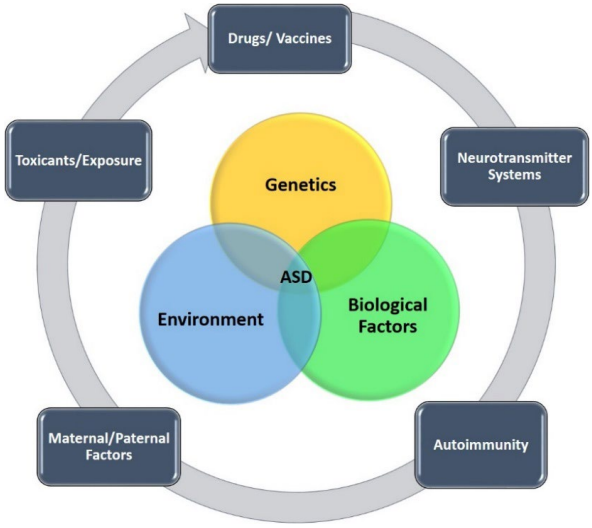

Figure 1. Causes of ASD.

According to the estimation of WHO, one in 160 children has ASD. This estimate represents the average reported prevalence obtained from several studies. However, some well-controlled studies reported substantially higher numbers. In addition, WHO stated that the prevalence of ASD in many low- and middle-income countries was so far not known (WHO, 2019b). In the USA, about one in 54 children has been identified with ASD, according to estimates from the Center for Disease Control and Prevention (CDC)'s Autism and Developmental Disabilities Monitoring (ADDM) Network (CDC, 2020). Over the past 50 years, the data obtained from different epidemiological studies show that the prevalence of ASD is increasing globally. This increase can be partly due to the improved awareness, expansion of diagnostic criteria, better diagnostic tools and improved reporting. However, there may still be unknown or uninvestigated factors that lead to this high prevalence (WHO, 2019b). In a large sample of children in the UK, the ASD prevalence was reported to be 61.9 per 10,000. In this group, the estimated prevalence of autism is 21.6, and the estimated prevalence of Asperger syndrome is 16.6 (Williams, 2008). Data obtained by screening more than 55,000 children aged 9 to 10 showed that the ASD prevalence was 77.2 per 10,000, and the autism prevalence was 38.9 per 10,000 in UK (Baird, 2006). In a report from the Danish Psychiatric Center Records, data from children under the age of 10 showed that the prevalence of autism was 11.8 per 10,000 children, and the estimated Asperger syndrome prevalence was 4.7 per 10,000 children under 10 (Lauritsen, 2004). In France, it is stated that approximately five out of every 10,000 children have autism (Fombonne, 1997).

Worldwide studies published after 2000 estimated that the prevalence of autism was between 16.8 and 40.5 per 10,000 people (CDC, 2018). In different studies that analyzed data from 11 years from 1997 to 2008, the prevalence of autism in children aged 3 to 17 was reported to be 47 per 10,000 (Baird, 2000; Bertrand, 2001; Chakrabarti, 2005; Boyle, 2011). There is no detailed research on the prevalence of ASD in Turkey. According to Autism Platform data, due to lack of healthy statistics, the estimated number of individuals with autism and the number of children (age:0-14) with autism has been reported to be approximately 550,000 and 150,000, respectively (Tohum, 2013).

Diagnostic criteria and effects of gender for autism spectrum disorders

Although autism symptoms can be detected in the first 12-18 months of life, a precise diagnosis is usually made between 24 to 36 months. Even in some cases, diagnosis can be made just before adulthood (Filipek, 1999). The most important disorders accompanying the differential diagnosis are childhood

schizophrenia, mental retardation, language skill disorders, psychosocial deprivation, and disintegrative psychosis (Sadock, 2000). American Psychiatric Association created a guide called "Diagnostic and Statistical Manual of Mental Disorders (DSM-5)" to diagnose mental disorders. According to DSM-5, the criteria for diagnosis are (NIH, 2018):

- ✓ Difficulties in communicating and interacting with people
- ✓ Having limited interests and showing repetitive behaviors
- ✓ Symptoms that interfere with the proper functioning of education, work, and survival skills

Autism has been described as a manifestation of the "extreme male brain". The extreme male brain hypothesis was initially based on certain factors that determine the brain "as a male brain type" or "a female brain type" during fetal life. Later, it was redefined that the male brain is more advanced in 'systematizing' and the female brain is more advanced in 'empathizing' (Baron-Cohen, 2002). Some researchers suggest that this theory not only helps to identify the causes of autism but also is very important in recognizing and correctly guiding the abilities and behaviors of children and adults with autism (Bartley, 2006). When a person's ability to systematize is unspoiled or excellent compared to normal, but his ability to empathize is impaired, it is the point where autism occurs (Lawson, 2004). It has been reported that individuals with ASDs perform badly in tests such as "Reading the Mind in the Eyes" where female subjects are generally superior to male subjects. However, male subjects are generally superior to female subjects in tests such as Embedded Figures Task (Jolliffe, 1997; Baron-Cohen, 2001). Two consistent findings from gender-related ASD studies have been reported in the literature. The first finding is that ASDs have a higher incidence and prevalence (4: 1) in men than in women, and this rate is increased in higher functional individuals (8-9: 1) (Mandy, 2012). The second is that women with ASD have lower intelligence than men with ASD (Lord, 1985; Volkmar, 1993). In addition, some researchers have stated that women with ASD show less serious repetitive/restricted behaviors and interests (RRBIs) (Fombonne, 2003; Hattier, 2011; Hiller, 2016). Frazier et al. (2014) investigated the effects of gender on ASD symptoms by analyzing the data from 304 females and 2114 males (age: 4-18 years) obtained from Simons Simplex Collection. They evaluated the relationship between gender and autism symptoms, cognitive and motor functions, and adaptive behavior problems. The researchers observed that women had fewer RRBIs without a consistent difference in social communication symptoms (Frazier et al., 2014). In a study conducted in North Carolina, a large sample group (384 boys and 91 girls, age: 3-8 years) of children with learning disabilities and ASD were recruited. It was reported that girls showed similar difficulties in social connections and communicational abilities, but less repetitive and stereotypical behavior (RSB) compared to boys (Lord, 1982). On the other hand, contradictory results were obtained from a study conducted by Hartley (2009). Between 2003 and 2007, 499 young children aged 18–47 months (157 males and 42 females) were transferred to the interdisciplinary autism clinic in a medical hospital in the northwestern USA. 199 (58.9%) of these children were diagnosed with ASD. They investigated gender differences by analyzing autistic symptoms, behavioral problems and learning scales. The researchers found that girls with ASD have fewer RSBs and worse communication disorders compared to boys (Hartley, 2009). In another study, Carter (2007) evaluated 90 children (22 girls and 68 boys) between 18 and 33 months. Researchers reported that the development profile of ASD showed gender-specific differences. Although they did not find any difference in RSBs between genders, they observed that social communication skills in females with ASD were lower than males. The researchers recruited 30 right-handed pre-menopausal women and 30 men with autism (18-49 years). The clinical diagnosis was officially made by a psychiatrist or clinical psychologist in the UK. Women were found to have more se-

vere symptomatology in social interaction, communication and RSBs, and they show less behavioral autistic features during interpersonal interaction (Lai, 2013). McLennan (1993) studied autistic behavior in 21 males and 21 females (between ages of 6-36 years) with ASD and reported that females had milder difficulties in social interests and communication abilities than males. In early childhood, females were reported to behave more successfully than males in mutual social interaction and communication. Studies were also conducted to examine the gender effect on ASD-related features; however, consistent findings have not been obtained. In studies on emotional difficulties accompanying ASD, it has been reported that women with ASD have higher (Hartley, 2009), lower (Mclennan, 1993) or similar (Lai, 2013) internalization problems. Studies investigating gender differences in brain structure regardless of the severity of RRBIs reported alterations between males and females. It was stated that there was a gender-specific white matter connection and the functional connection of the frontal lobe changes in males unlike females (Mclennan, 1993; Lai, 2013; Irimia, 2017). In a study, the researchers recruited 25 females and 25 males (7-13 years) with ASD and 19 females and 19 males as control. Subjects were identified from the National Database for Autism Research, a publicly available research repository in the USA. Researchers analyzed symptom severity and structural imaging data from Autism Brain Imaging Data Exchange using multivariate pattern analysis. Gender differences in the anatomy of the brain associated with RRBIs in the Autism Brain Imaging Data Exchange dataset were evaluated. Investigators reported that gray matter in motor areas could vary between boys and girls with ASD. In addition, RRBIs in girls were associated with the increased gray matter of the motor cortex, additional motor area and Crus 1 subsection of the *cerebellum*, while in boys, RRBIs only correlated with the right putamen. Brain anatomy and RRBIs can develop differently in different genders, suggesting that the behaviors that develop in ASD may occur *via* different pathways (Supekar, 2015). Researchers used a group of twins to study the relationship in the brain anatomy and RRBIs between two genders. In 75 twins (n = 150, 62 females, 88 males) with ASD (n = 32 twins, 20 males and 12 females) and other neurodevelopmental disorders (n = 25 twins, 16 males and 9 females), they investigated the relationship of RRBIs with the cortical volume, surface area and thickness of different networks in the brain (neocortical, subcortical and cerebellar regions). The investigation revealed a within-pair relationship between the increased thickness of the right intraparietal sulcus and decreased volume of the right orbital gyrus only in females and RRBI symptoms. Researchers have shown that structural changes related to RRBIs in frontoparietal networks occur in females, while striatal networks are more affected in males. It was suggested that the autism symptoms are affected by gender differences, which may be due to alterations in brain structure (van't Westeinde, 2019). Researchers examined the relationship between ASD and gender differences in high-functioning children with ASD between the ages of 3 and 18 (n = 325, 52 females). It was stated that there was no effect of gender on IQ scores. Through the parental report and observation of researchers, females were reported to exhibit fewer RRBIs compared to their male equivalents. Teachers reported that males with ASD have more externalization and social problems than females (Mandy, 2012). In a study, mutation burden analysis on corresponding candidate genes using the Transmission and *de novo* association test (TADA) model was performed. Researchers collected DNMs from 5748 ASD trios (4783 male probands and 965 female probands, 4-18 years) and 1911 control trios (900 unaffected brothers and 1011 unaffected sisters) from published studies. Researchers found that the prevalence of functional delayed-non-match to sample (DNMs) was significantly higher in women compared to men. This finding suggests that a higher genetic burden should occur in women to reach a diagnosis. One hundred seventy-four candidate genes (60 shared, 91 male-spe-

cific and 23 female-specific genes) were primarily examined in the study. Sodium voltage-gated channel alpha subunit 2 (SCN2A), an important autism-related gene due to voltage-gated sodium channel activity and ion channel activity, chromodomain helicase DNA binding protein 2 (CHD2) and phosphatase and tensin homolog (PTEN) (associated with dysfunction of estrogen dihydrotestosterone), the most important unique male-specific gene lysine demethylase 5B (KDM5B, associated with chromatin organization and associated with recessive developmental disorders), forkhead box protein P1 (FOXP1, another male-specific gene associated with androgen receptor signaling), transcription factor 4 (TCF4, the female-specific gene associated with autism and nuclear regulation of androgen receptor activity) were among the genes that were studied. It has been reported that all these genes were co-expressed significantly less in males compared to females. Analyses of different genetic components revealed evidence to support the protective effect of the female gender in ASD, and the researchers stated that more studies were needed to understand the effects of gender in ASD (Zhang, 2020).

Thiomersal

Thiomersal is an organic mercury compound containing approximately 50% ethyl mercury by weight. The chemical structure of thiomersal is shown in Figure 2. It has been used in some vaccines since the 1930s. The aim of the use of thiomersal in vaccines, cosmetic products and drugs is to prevent bacterial and fungal contamination. It is more likely to confront contamination, particularly in multi-dose vials of vaccines where repeated doses are withdrawn from the same vial (Geier, 2015).

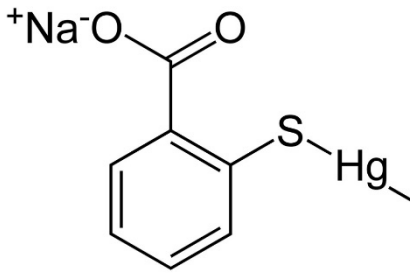

Figure 2. The chemical structure of thiomersal

In addition to vaccines, some cosmetic products and drugs (creams, eye drops, etc.) also contain thiomersal (Fonacier & Boguniewicz, 2016). In recent years, the presence of thiomersal in some vaccines recommended in routine immunization, such as hepatitis B and some influenza vaccines, has raised some health concerns. In systematic reviews and meta-analyses, mercury exposure has been associated with neurodevelopmental diseases (Jafari, 2017; Sulaiman, 2020; Yoshimasu, 2014). Several meta-analysis reports suggest that thiomersal exposure in infancy increases the risk of neurodevelopmental disorders such as ASD, ADHD and tic disorders (Dorea, 2018; Taylor, 2014; Yoshimasu, 2014). In addition, it was suggested that exposure to mercury during the developmental period could cause learning disorders and behavioral abnormalities like in autism. Some researchers indicate that early-life thiomersal exposure may be an essential factor for the development of ASD (Yassa, 2014; Pletz, 2016). There is evidence that the effects of toxic metals on health can occur differently in men and women due to their toxicokinetics, modes of action, and sensitivity. Generally, only male animals are used for experimental toxicological studies. Therefore, in many studies, the effects of gender-specific differences (such as specific hormone interactions and mechanism of action in two different genders) are usually neglected. Moreover, gender differences were not seriously considered in most of the environmental health risk assessment and toxicity studies until the last decades. Today, data for men and women are reported separately in epidemiologi-

cal studies though they are still very few (Niedhammer, 2000; Vahter, 2007).

Due to the epigenetic effects of sex hormones, differences can occur in brain function in different genders. In recent years, human and animal studies have revealed that gender differences in neurotoxicity are more common than expected. Recognition of gender-specific symptoms, observance of risk factors, and knowing that gender can make the person more vulnerable to the toxicity of certain metals and chemicals are extremely important for effective prevention and treatment strategies (Patočka, 2014). Mercury enters the environment because of the processing of fossil fuels, compounds used in industry and agriculture, and waste. The primary source for this metal is volcanic activity. The transition from soil to plant is limited, and trace amounts of mercury can be found in some edible mushrooms. However, in aquatic environments, there are very high concentrations of mercury in fish, marine mollusks and shellfish. Exposure to methyl mercury often occurs by consuming seafood, especially fish and marine mammals caught in their natural habitats (NRC, 2000; Patočka, 2014). There are studies showing differences in methyl mercury metabolism in different genders in both humans and experimental animals. However, the results are contradictory. For instance, mercury analysis was performed on human kidney cortex biopsy samples, and three times higher concentrations were detected in women than in men (Barregård, 1999). In animal studies, it has been found that after mercury exposure, male rats have significantly higher levels of mercury in their kidneys and brains compared to female rats. Moreover, females have been reported to eliminate mercury from their bodies more quickly than males. Although urinary excretion was specified as a more minor pathway for mercury clearance, sexual differences were also reported for this elimination route. While males excrete about 3.2% of the dose with urine, this rate has been reported as 7.5% in females. Urinary cumulative excretion of organic Hg accounted for 1.8% of the amount in males and 5.3% of the amount in females (Thomas, 1986; 1987). On the other hand, after mercury exposure, mercury levels in both blood, brain and muscles were significantly lower in male mice than in female mice. In contrast mercury kidney accumulation was significantly higher in male mice than in female mice. Moreover, the toxicokinetics of methyl mercury in male and female mice was found to be markedly different (Nielsen, 1991).

In vitro and *in vivo* studies have shown that interactions with sulfhydryl groups, microtubule destabilization, changes in intracellular calcium levels, and formation of ROS are critical mechanisms at the onset of methyl mercury neurotoxicity (Sarafian, 1991; Fredriksson, 1993; Atchison, 1994; Daré, 2000; Usuki, 2001; Carrillo, 1992; Borrás, 2003). It has also been reported that estrogen can provide additional protection against oxidative stress by inducing the synthesis of protective molecules through the activation of estrogen receptors (Behl, 1995; Singer, 1998; Olivieri, 2002). Therefore, the role of gender differences in chronic methyl mercury toxicity can also be explained in part by oxidative stress.

Researchers investigated the levels of mercury in newborns and mothers and the association between prenatal exposure to mercury and the neurobehavioral development of newborns in Zhoushan City of Zhejiang Province, China. Four hundred and eight surveys were conducted; 405 hair samples from mothers and 406 umbilical cord samples were collected, and behavioral neurological evaluations were performed on 384 newborns. In cord samples and maternal hair samples, mercury levels were determined as 5.58 mg/L (range: 3.96-7.82 mg/L) and 1246.56 mg/kg (range: 927.34-1684.67 mg/L), respectively. In 70% of newborns, mercury levels exceeded the reference dose (RfD = 5.8 mg/L) reported by Environmental Protection Agency (EPA). While the increase in prenatal mercury exposure was associated with a decrease in behavioral ability in men, this relationship was not observed in women (Gao, 2007).

A comparative study was designed to evaluate the toxicities induced by methylmercury and ethyl mercury, as well as by their complexes with cysteine in the C6 rat glioma cell line. Both of the organic mercury compounds markedly induced cytotoxicity. Significant cytotoxicity was also observed when cells were treated under the same conditions with methyl mercury-S-Cys and ethyl mercury-S-Cys, but the respective EC50 values were markedly higher. L-methionine significantly protected against the toxicities induced by both complexes. However, no protective effects of L-methionine were observed against toxicities of organic mercury compounds. Although it has not been fully elucidated how methyl and ethyl mercury enter the brain and generate its toxicity, its high affinity for thiols and selenols is suggested to be important in this regard (Zimmermann, 2013). It is assumed that the transition of the methyl mercury from the blood to the brain usually occurs by simple diffusion (Simmons-Willis, 2002). However, some studies have shown that this transport is in the form of a methyl mercury-cysteine (MeHg-S-Cys) complex with the L-type neutral amino acid carrier (LAT) system (Clarkson, 2007; Yin, 2008). When MeHg-S-Cys is applied in different cell lines, over-expression of LAT-1 (an important LAT subtype) has been reported to increase the uptake of mercury, the breakdown of LAT-1 reduces MeHg-S-Cys uptake and weakens its cytotoxicity (Simmons-Willis, 2002; Yin, 2008). In addition, *in vivo* studies have shown that administration of the MeHg-S-Cys complex results in a significant increase in mercury accumulation in the brain (cortex and cerebellum) and liver in mice compared to methyl mercury administration (Roos, 2010). Although methyl mercury and ethyl mercury are closely related chemically, and they both can cause similar damage to the brain at toxic doses and thiomersal has been shown to cause significant neurotoxicity *in vitro* and *in vivo*, it is anticipated that ethyl mercury has a shorter half-life compared to methyl mercury and is metabolized to inorganic mercury faster (Barregard, 2011). Although it was suggested that ethyl mercury compounds did not cross the blood-brain barrier, a systematic study on different articles in the literature indicated that ethyl mercury compounds, including thiomersal, can cross the blood-brain barrier and exposure to ethyl mercury-containing compounds (intravenously, intraperitoneally, topically, subcutaneously, intramuscularly, or intranasally administered) results in accumulation of mercury in the brain (Kern, 2020). Moreover, it was suggested that thiomersal crossed the barrier in both directions, with a slight accumulation in the basolateral, brain-facing compartment, after simultaneous incubation in both compartments (Lohren, 2016).

Gender differences in thiomersal toxicity

There is evidence that the harmful effects of toxic metals on health occur differently in men and women due to toxicokinetics, mode of action and sensitivity differences, but data are limited.

Researchers tested the assumption that exposure to thiomersal during the perinatal period disrupts CNS development and especially the cerebellum due to oxidative stress. Spontaneous hypertensive (SH) or normal Sprague-Dawley (SD) rats were given thiomersal (200 **µg**/kg) during pregnancy (between gestational days G10-G15) and lactation (P5-P10), evaluation was made by researchers to determine auditory and motor functions in male and female newborn rats. In SH rats exposed to thiomersal, the rollover time on P4 decreased by 59% in male offspring and only 13% in females. Testing of auditory functions was performed with a startle response. In SH rat pups exposed to thiomersal, the startle response measured on P14 decreased by 12.2% in males, not in females. In SD rats, male offspring showing startle response decreased by 27.8% and female offspring by 19.2%. It has been reported that perinatal exposure to thiomersal caused a significant decrease in cerebellar type-2 iodothyronine deiodinase (DIO2) activity by 60.9% in male SH rats but not in females. The data obtained in

the study showed that perinatal thiomersal exposure had adverse neurodevelopmental effects that seemed to be both strain and gender-dependent (Sulkowski, 2012). As the exposure to thiomersal was 200 **µg**/kg, these levels seem to be comparable to the amount of thiomersal received from one dose of a vaccine. However, chronic exposure to thiomersal cannot be observed after vaccine application, although humans are chronically exposed to thiomersal from other sources.

Researchers applied thiomersal *via* postnatal injections at different doses (12, 240, 1440, 3000 µg/kg) to young adult Wistar rats (n=4 in each group) on postnatal days 7, 9, 11 and 15 in four equal doses. An open field test was performed to evaluate general locomotor activity and anxiety in rats on the 30th day after birth. It has been reported that a significant reduction in overall locomotor activity was observed in all doses in thiomersal-treated male rats. A similar effect was recorded only at the highest dose in female rats. This finding indicated that male rats are more prone to the neurotoxic impacts than females (Olczak, 2011).

CONCLUSION

It is clearly known that females and males are quite different in both biological and social aspects and can react differently to the pathological and psychological conditions they encounter. The metabolism and toxicity of the metals and chemicals may have different effects on females and males depending on the enzymes, hormones and immune system. It can be stated that this situation is even more evident in terms of neurotoxicity and neurodevelopment. Neurological diseases such as ASD, which including behavioral changes, are seen in men at a much higher frequency. However, it is unclear whether this bias is due to physiological differences or problems in planning studies and determining diagnostic criteria. Concerns have increased over the last years that the criteria used in the diagnosis of ASD do not openly include the ASD phenotype in girls. In addition, studies on metal exposure examine occupational exposure and have been performed on men. This makes it difficult to make a clear comment about females. Considering all these data, new studies should be planned, and perhaps new criteria suitable for the phenotype in girls should be considered for the diagnosis of ASD. Physiatrists should provide new evaluation scales to accurately recognize the cases that are avoided attention in girls and make the correct diagnosis. New *in vitro* and *in vivo* test methods should be developed in order to show how male and female brains respond differently to different environmental chemicals or vaccine ingredients. Recently, we have created an *in vitro* test system to test how male and female neurons respond differently to thiomersal. This system can also be used for future research to investigate the toxic effects of mercury compounds in different genders (Erdemli-Köse, 2021).

The concern that thiomersal exposure may lead to ASD has caused hazardous consequences such as vaccine hesitancy and rejection. We have observed that vaccine rejection has caused an unending COVID-19 pandemic, and the world has experienced extraordinary economic and spiritual collapses. Although childhood vaccines used in USA and Turkey do not contain thiomersal as a preservative, parents may still be hesitant, and they may prevent their children from getting the necessary childhood vaccination. If vaccine hesitancy or rejection spreads in a wave, the immunization processes of the population will be significantly disrupted. There are not any studies in the literature that suggest ASD is entirely associated with thiomersal exposure. Therefore, more studies that are mechanistic are needed to clarify the association between thiomersal exposure and neurological conditions like ASD.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION STATEMENT

Selinay Basak ERDEMLI-KOSE, Aylin BALCI-OZYURT and Anil YIRUN searched the Scopus, Web of Science, PubMed and Google Scholar databas-

es for the relevant articles that are cited in this review. Selinay Basak ERDEMLI-KOSE was responsible for the thiomersal section. Aylin BALCI-OZYURT was responsible for the autism section. Anil YIRUN was responsible for drawing the figures and referencing. Pinar ERKEKOGLU reviewed the manuscript and wrote the "Conclusion" section.

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