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ENVIRONMENTAL FACTORS ASSOCIATED WITH EXPRESSION OF SYMPTOMS IN CHILDREN WITH AUTISM

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Abstract. The incidence rate of autism spectrum disorders (ASDs) has increased steadily over the last decades, and environmental factors are suspected to influence the onset of ASD on the basis of genetic factors. Therefore, we first reviewed the literature on the effects of environmental pollution on the development of ASD, and second, we examined the impact of social environmental factors on two patients with ASD who were followed-up for 13 years by one of the authors. There was serious concern that both air pollution and mercury exposure would affect ASD. During the clinical course of the two patients in this study, ASD symptoms and/or adaptation levels fluctuated several times, and involvement of social environmental factors were noted. Required support should include offering an optimal environment for a long period of time and comprehensive medical, educational, and local community support.

Keywords: symptoms of autism, air pollution, mercury exposure, ASD, social environment.

1. Introduction

The incidence rate of autism spectrum disorders (ASDs) has been steadily increasing over the last decades. Lotter (1966) reported a survey of children in 1966, with an autism prevalence of 4.5 per 10,000 [1]. Gillberg et al. (1991) reported that the frequency of autism was 4.0/10,000 in 1980, 7.5/10,000 in 1984, and 11.6/10,000 in 1988 [2]. According to a recent survey by Christensen et al. (2019), the overall prevalence of ASD was 13.4 per 1,000 in 2010, 15.3 in 2012, and 17.0 in 2014 and they also reported that the prevalence of ASD under the DSM-IV-TR case definition was 20% higher than the prevalence under DSM-5 [3]. The impact of different diagnostic tools on ASD prevalence needs to be considered, and it is important to determine the cause of the steady increase over the last decades. ASD is a heterogeneous disorder that is subjectively diagnosed on the basis of multiple criteria that have complex causes, and the underlying pathological mechanism remains unclear. Recent studies have investigated genetics [4], intrauterine environment [5], brain dysfunction [6], neurochemical [7], and immunological [8] factors. For genetic factors, Miles (2011) showed that the genomic hybridization technique has increased the identification of presumable autism genes and increased the percentage of children for whom an autism-related genetic change can be identified [4]. These results emphasize the involvement of genetic factors. However, because the concordance rate for autism in identical twins is 50%–77% [9], further studies are required

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to elucidate environmental factors as extrinsic factors.

In this paper, we reviewed the literature including our previously reported papers [10] [11], which focus on air pollution and heavy metal pollution. The social environment will also be discussed based on our own cases.

2. Content

2.1. Literature review

2.1.1. Air pollution

The environment surrounding us includes various factors such as environmental pollutants, food, climate, and social factors. For environmental pollutants, we examined associations between prenatal exposure to traffic-related air pollution and child behavioral development milestone delays, using data from a nationwide population-based longitudinal survey in Japan, and the results were reported elsewhere [10]. We analyzed data from singleton births with linked suspended particulate matter (SPM) exposure such as nitrogen dioxide and sulfur dioxide, and we showed that air pollution exposure during gestation was positively associated with a risk for behavioral problems related to attention and delinquent or aggressive behavior. Although this study did not directly examine the symptoms that are associated with autism, inattention is a characteristic symptom of attention-deficit/hyperactivity disorder (ADHD). Aggressive behavior is a characteristic symptom of oppositional defiant disorder, and this condition often develops as a secondary disorder during the course of developmental disorders. Thus, there is a concern that SPM is a risk factor for certain types of developmental disorders, including ASD. Additionally, Windham et al. (2006) surveyed 284 children with ASD who were born in the San Francisco Bay Area in 1994 for exposure to 19 air pollutants, including potential neurotoxins and endocrine disruptors [12]. In this research, they revealed that exposure to three heavy metals (mercury, cadmium, and nickel) and two chlorinated solvents (trichlorethylene and vinyl chloride) significantly increase the risk of ASD.

2.1.2. Mercury exposure

Thimerosal is a preservative that is frequently added to childhood vaccines, and it has been a concern as a major source of mercury in human infants. Bernard et al. (2000) described excessive mercury exposure from thimerosal in vaccine injections is an etiological mechanism for causing the traits of autism [13]. Similarly, Geier et al. (2004) reported a close correlation between mercury doses from thimerosal-containing childhood vaccines and the prevalence of autism from the late 1980s through the mid-1990s, and they proposed that thimerosal be removed from all vaccines [14]. However, several subsequent epidemiological studies have not found an association between MMR vaccination and autism, and despite strong evidence of its safety, some parents are still hesitant to accept MMR vaccination of their children [15].

Tang et al. (2008) showed that exposure to pollutants from coal-fired power plants in China had a negative impact on the development of children living in the area [16]. Blanchard et al. (2011) [17] found that higher levels of ambient mercury were geographically associated with point sources of mercury emissions, such as coal-fired power plants and cement plants with coal kilns, and in a 2009 article, Palmer et al. (2009) used geographic proximity to pollution sources as a predictor and found a significant positive association between environmental mercury emissions and autism rates across Texas [18]. Palmer et al. (2006) further reported that there was a significant increase in the rate of special education students and autism rates associated with increases in environmentally released mercury [19]. On average, for each 1,000 pounds of environmentally released mercury, there was a 43% increase in the rate of special education services and a 61% increase in the rate of ASD. Adams et al. (2007) measured the level of

mercury in baby teeth of children with ASD and typically developing children, and they found that children with ASD had significantly higher levels of mercury [20]. Because baby teeth are a good measure of cumulative exposure to toxic metals during fetal development and early infancy, they speculated that children with ASD had a higher body burden of mercury during fetal/infant development. Majewska et al. (2010) examined autistic children who were 3–4 and 7–9 years old and compared them to 75 age-matched healthy children including demographic information, perinatal, clinical and developmental measures, parental age, birth order, morphometric measures, vaccination history, and hair mercury content [21]. They reported that in children with ASD, the concentrations of mercury in their hair was significantly different from that of their healthy peers as follows: younger autistic children had lower levels while older autistic children had higher levels than their respective controls. These researchers speculated that children with ASD had different mercury metabolism compared with healthy children, which changed with age.

We examined neurological and neurocognitive functions of people with Minamata disease who were exposed by low-to-moderate methylmercury *in utero*, focusing on fine motor, visuospatial construction, and executive functions [11]. More than half of the participants had some fine motor and coordination difficulties. In addition, certain participants had lower performance on neurocognitive function tests. These deficits suggest diffuse brain dysfunction including prefrontal executive function. Several studies have suggested that higher brain dysfunction is the central cognitive impairment in ASD, and thus, exposure to mercury, even in small amounts during the fetal period, may be a potential risk factor for ASD [22], [23], [24]. Because Minamata disease is an epidemiological example of mercury neurotoxicity that dates back to the 1950s and is caused by consumption of methylmercury-contaminated fish [25], attention should be paid to air pollution and to marine pollution to determine the cause of the increase in ASD.

2.1.3. Age of parents

Recently, late marriage has increased in many countries, and the age of parents when their first child is born has been increasing. Thus, the effect of parental age on the development of various disorders should be investigated. For ASD, Treffert (1970) indicated a link between parents' older age and their children's risk of developing ASD [26], and several researchers have since made similar reports [27], [28]. Sasanfer et al (2010), however, revealed a significant association between an older paternal age, but not maternal age, and an increasing risk of autism [29]. There are also some reports [30], [31] that older fathers are a risk factor, and attention is focused on the mechanism by which a father's age leads to the onset of ASD. Possible biological mechanisms include *de novo* mutations that are associated with advancing age or alterations in genetic imprinting and genetic alterations in combination with other factors in long-term exposure to environmental and occupational risks [31], [32].

2.2. Cases with intense involvement of social environmental factors

The International Classification of Functioning, Disability and Health (ICF), which was adopted by the World Health Organization (WHO) in 2001, has introduced environmental factors and personal factors as contextual factors that affect human life functions. Environmental factors include the physical environment and the human environment. The environmental factors interact with living functions and becomes both a facilitator and a barrier [33]. For neurodevelopmental disorders, it is important to understand the developmental characteristics of children, clarify the environmental factors that prevent them from attending school, and provide an environment that encourages them to attend school [34]. To form a symbiotic society based on the diversity of development, it is necessary to compensate for the challenges faced by people with disabilities and to adjust the environment accordingly. In this

section, we examine the impact of social environmental factors on symptoms and/or the level of adaptation in two patients with ASD who were assessed based on the detailed ICF classification and who were followed-up for 13 years.

2.2.1. Method

Two male patients visited Oono Hagukumi Clinic due to ASD symptoms, and their long-term follow-up was investigated using their medical records. The patients' profiles are described below. Informed consent was obtained from the parents of both patients. Both cases have already been reported elsewhere [35], [36].

2.2.2. Subjects

Case 1

The patient's first clinic visit was at 2 years 7 months of age, and his age at the most recent clinic visit was 15 years 8 months. His most recent full-scale IQ (FIQ) was 117. The child showed normal developmental milestones until 1 year of age. Babbling appeared at the usual time; pointing, hand gestures, and eye contact developed by 1 year and 3 months, but they disappeared at around 1 year and 6 months shortly after a change in residence. Babbling reappeared at the age of 2 years and 3 months, and pointing reappeared at around 2 years and 8 months. He was reluctant to go to elementary school, and his mother went to school with him to support him. When he felt interpersonal stress, compulsive behaviors such as opening and closing doors and hand washing were prominent between 9 and 12 years of age, and remission and exacerbation have been repeated to date. Facilitators and barriers are shown in Table 1. The tendency to refuse to go to school became worse during exacerbation, and there were three school refusal periods in 6 years, but the patient's symptoms improved with a change in his education. Medication was also effective for symptomatic improvement.

Case 2

The patient's age at his first clinic visit was 13 years and the most recent clinic visit was at age 26 years. FIQ at 13 years was 97. His social relationships had been awkward since childhood, and since elementary school, he experienced bullying by his classmates, and consequently, he complained of fatigue and was often absent from school. However, when he was in the fifth grade of elementary school, his homeroom teacher tried to improve the environment, and he rarely missed school that year. From the sixth grade until high school graduation, although supportive teachers worked to improve the environment, and he was reluctant to go to school on many days. He got a job after graduating from high school. His supervisor and colleagues did not understand the characteristics of ASD and developed mental disorders such as anxiety and depression. After working in an inappropriate environment for 6 years, he changed jobs. The environment at his new workplace was ideal. He stopped taking his medicine without any mental health problems, and he is currently living a stable life.

2.2.3. Results

Table 1 summarizes the social environmental factors that are thought to have affected the expression of symptoms for the two patients.

For Patient 1, stressors that were postulated to lead to the exacerbation of symptoms included a change of residence, entering elementary school, and negative interpersonal relationships at elementary school, while factors that improved symptoms include medication, transfer from a regular class into a class for special needs education (SNE) , although this was a limited effect, entering a junior high school for SNE, and advancement to a high school that was supportive of children with school refusal.

Table 1 Environmental factors, facilitators and barriers influenced on the expression of symptoms

	Case1			Case 2	
Estimated stressor	Change of residence	Entering school	Negative interpersonal relationships at school	Negative interpersonal relationships at school	Negative interpersonal relationships at workplace
Symptoms	Loss of pointing/ handjesture/ eye contact	Anxiety	School refusal Compulsive behavior：Handwashing/ Rituals	School refusal	Anxiety・depression・inattention
Category of environmental factors	e310 e315		e330 e425 e585	e330 e425 e430	e330 e425 e430
Facilitator		Mother's escort	Positive attitude of family Positive attitude of a friend Transferred to SNE class Enter SNE junior high school Enter supportive school	Positive attitude of family Positive attitude of teacher Positive attitude of club advicor Positive attitude of peers Positive attitude of club members	Positive attitude of family Doctor's advice Job change Positive attitude by superior Positive attituden by colleagues
Barrier			Harsh remarks from peers	Negative attitude of homeroom Teased by peers	Negative attitude of superior Negative attitude of colleagues

e310: immediate family, e315: extended family, e330: people in positions of authority, e425: individual attitudes of acquaintances, peers, colleagues, neighbours and community members, e430: individual attitudes of people in positions of authority, e585: education and training services, systems and policies according to the reference 32

For Patient 2, stressors that were postulated to lead to the exacerbation of symptoms included negative interpersonal relationships at elementary school, junior high school, senior high school, and at his first job. Factors that improved symptoms included positive attitudes of his homeroom teachers, club advisor, supervisor, and colleagues at his second workplace.

2.3. Discussion

Both patients in this study were investigated using 13 years of their medical records, and fluctuation in autistic symptoms and/or the level of adaptation was repeatedly observed during the clinical course. It is speculated that such fluctuations in symptoms may be triggered by a stress factor. All of these stressors are considered to be social environmental risk factors, and we used the coded categorizations of environmental factors that were listed in the ICF to clarify these factors. This system has helped us to understand environmental factors from both a facilitator and barrier perspective, providing a comprehensive and analytical viewpoint. Therefore, it is expected to be further used as an important tool when first considering a support plan for children or adults with ASD.

Patient 1 showed developmental regression in early childhood. Previously, such autism cases were called knick-type autism in Japan [37]. However, the term autistic regression (AR) [38] has been used more recently. For AR, we have previously reported [35] that domestic events such as moving or the birth of siblings are speculated to be factors that trigger regression, and even if the patient’s IQ is high, many social environmental factors emerge, making school life difficult afterwards, and there is often a history of multiple school refusals. In patients with AS, it is thought that biological factors in addition to environmental factors play a role because abnormalities are already seen before the regression phenomenon is manifested [39]. Thus, regression is considered to develop when family environmental factors are combined with preexisting biological factors, and afterwards, people with AR are thought to be more affected by social environmental factors than people without AR due to the burden of biological factors. In these cases, it is desirable to provide an optimal environment for a long period of time.

During the clinical course of patient 2, symptoms such as school refusal, anxiety, and depression were repeatedly exacerbated and improved, and the negative attitudes of people at school and work were involved as facilitators. Suzuki et al. (2017) found that 87% of children with neurodevelopmental disorders and school non-attendance were not diagnosed until they refused to attend school due to interpersonal problems [40]. Patient 2 showed similar results to those of Suzuki et al. (2017) [40] and he was not diagnosed with ASD before developing school refusal due to a series of interpersonal problems. Yasuda et al. (2019) conducted a survey on children who had difficulties in their school life, and they found that the dominant grade at onset of school difficulties at school was the first grade followed by the third and fourth grades [41]. As an intervention, they suggested that establishing a cooperative framework among doctors, schools, home, and the community can help to solve problems at school. Ishizaki (2017) also described the importance of cooperation between schoolteachers and doctors to prevent psychosomatic and behavioral problems that can cause school refusal among children and adolescents with developmental disorders [34]. Thus, early diagnosis and early intervention are important for supporting children with ASD, and when problems occur, it is recommended to establish a cooperative framework among doctors, schools, home, and the community to solve problems.

3. Conclusion

In this study, we reviewed the literature on the effects of environmental pollution on the development of ASD. As a result, there was concern that traffic air pollution, heavy metal air pollution, and marine pollution would be factors in the development of developmental disorders. Additionally, this study also investigated the effects of social environmental factors to the clinical course based on the medical records of two cases of ASD. Receptive interpersonal relationships at school and workplace, and comprehensive medical, educational support are suggested to be crucial for the stable development of individuals with ASD.

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