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Integrating Treatment for Autism: Etiology and Life Cycle

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Autism Spectrum Disorder (ASD) is linked to a multitude of genes, epigenetics, and environmental factors, which contribute to the complexities of treating ASD. A large body of literature suggests benefits from perinatal, early, and later intervention. It is common for physicians to struggle with making a diagnosis of ASD, but once it is made, parents who have been taught effective strategies can be impactful in their child's positive development. Neuroimaging studies of children, adolescents and young adults with ASD suggest that their brain structures change over time and are also capable of being shaped through appropriate interventions. Interventions are also being adapted for adults with ASD to better address their needs, such as employment training programs. We review the wide array of risk factors and interventions to mitigate the challenges individuals with ASD face in their daily lives.

Keywords: autism, risk factors, endophenotypes, intervention, adaptive functioning, primary care.

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Интеграция помощи людям с РАС: этиология и жизненный цикл

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Расстройства аутистического спектра (РАС) связаны с большим количеством генетических, эпигенетических и средовых факторов, что усложняет организацию помощи людям с данным диагнозом. Во множестве опубликованных работ описываются преимущества перинатальных, ранних и более поздних вмешательств. Как правило, врачам бывает непросто диагностировать РАС, однако после постановки диагноза родители, ознакомленные с эффективными стратегиями помощи, могут оказать существенное положительное влияние на развитие своего ребенка. Исследования детей, подростков и молодых людей с РАС, выполненные с применением методов нейровизуализации, показывают, что структуры их мозга меняются с течением времени, и что они также могут меняться под воздействием подходящих вмешательств. Данные вмешательства также адаптируют для взрослых с РАС таким образом, чтобы они лучше соответствовали их потребностям; примером могут служить программы профессиональной подготовки. В статье представлен обзор многих факторов риска и типов вмешательств. Это позволит уменьшить проблемы, с которыми сталкиваются люди с РАС в своей повседневной жизни.

Ключевые слова: аутизм, факторы риска, эндофенотипы, вмешательство, адаптивное функционирование, первичная помощь.

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Integrating Treatment for Autism Spectrum Disorders Through the Life Cycle

According to the Center for Disease Control, Autism Spectrum Disorder (ASD) is currently increasing in prevalence, with 1 in 54 children in the United States receiving the diagnosis. Although reasons for this are inconclusive, factors could include changing diagnostic knowledge and criteria, increased research and monitoring, a change in epigenetic processes, and exposure to environmental toxins and infections. Due to the heterogeneous nature of ASD, individuals with ASD face unique difficulties that may call for flexibility and creativity in multi-level targeted treatments. As the number of people with ASD are being recognized, it is vital to consider the most efficacious implementation of prevention, intervention and treatment for ASD throughout the life cycle.

Genetic and Environmental Etiology

There is a strong link between specific genes and ASD. Multiple genes are associated with ASD, including: CHD8, DYRK1A, FMR1, TSC1, TSC2, CNTNAP2, SMARCC2, CDH8, SHANK3, NRXN1, 15q11.2q13, 15q13.3, 16p11.2, NLGN2, GRIN2B, CDH8, and PTEN [8]. For approximately 25% of people with ASD, there is a clear genetic etiology [32] Many studies have found that there is a 64–88% concordance rate in identical twins with ASD, and between a 9-40% concordance rate in dizygotic twins, where at least one is affected by ASD [32; 39]. De novo ("new") mutations in neurologically expressed genes are associated with ASD that may carry widespread effects. In sibling studies, gene-disrupting mutations (splice site, frame shifts, and copy-number variations) were significantly higher in children with ASD than their unaffected siblings [20]. Researchers in Sweden estimated the genetic heritability influence on ASD to be about 50% [45] So, what comprises the remaining 50%?

ASD does not appear to be solely genetic in origin. Susceptibility to ASD has a larger shared twin environment component than genetic heritability. Polygenic models in which spontaneous coding mutations in a wide number of genes increase risk for ASD by 5–20 times [34]. Recent studies on the genetics suggest that the cause of ASD is also related to gene-by-environment interactions manifested in epigenetic processes [15; 17; 44] Epigenetics is the reversible regulation of mechanisms independent of DNA sequence, mediated largely through DNA methylation, chromatin sequence, and RNA-mediated gene expression [1]. The related endophenotypes connect underlying biologic aspects of a disease to an observable factor [42]. Research hints that epigenetic processes could be reversible by factors such as nutrition, socialization, behavioral interventions, and drugs [43].

Environmental factors are also a related cause of ASD. Evidence has been documented for risk factors including prenatal or early postnatal exposure

to viral infections (such as rubella), valproic acid, and thalidomide [36]. There has also been limited evidence for factors such as maternal metabolic conditions, fever during pregnancy, paternal/maternal age, use selective serotonin reuptake inhibitors (SSRIs), maternal smoking, and environmental pollution [2; 18; 19; 46; 60]. More evidence is needed to determine whether the following environmental factors increase the risk of ASD: mercury, lead, environmental toxins, vaccines, and lack of vitamin D [4; 11; 30; 40; 52; 58].

Parenting from Before Conception

Recent studies reveal that parental experiences also exert effects through epigenetic information. One study found variations in sperm and oocyte cytosine methylation and chromatin patterning, noncoding RNAs, and mitochondria [23]. Transgenerational epigenetic effects often interact with conditions at the time of conception in order to code the trajectory of the developing embryo and fetus, which will affect the health of the child for the rest of their life. For example, Mazina and colleagues [28] linked the presence of copy number variations and maternal infection to social communicative impairments and repetitive/restricted behaviors in study participants. Further investigation of such effects could give insight on how epigenetic variations give rise to ASD itself.

Risks

Various maternal attributes during pregnancy may lead to autism. For example, women aged 35 years or older are less likely to take supplemental iron and five times more likely to give birth to a baby with ASD [48]. Furthermore, prenatal steroid perturbations by the mother may create hormonal changes in a fetus and increase the risk of the child having ASD [13]. During the birth, pre-term babies who are small for their gestational age or delivered via Cesarean section are at a modest increased risk [12; 54; 59]. According to a study by Lyall and colleagues [26], higher maternal intake of certain nutrients and supplements containing folic acid can reduce the risk of ASD. Rodent studies indicate a strong causal relationship between maternal immune activation during pregnancy and ASD symptoms in offspring [49].

Certain obstacles in healthcare prevent important information regarding environmental risk to be passed onto expecting parents. In Stotland's study [51], surveys were sent to fellows from the American Congress of Obstetricians and Gynecologists and three obstetrician focus groups. 78% of obstetricians agreed that environmental health hazards could be reduced through education by counseling patients about them, but 50% reported that they rarely discussed the environmental health history of patients. Furthermore, less than 20% reported routinely asking about environmental hazards in pregnant women in the United States. Only 1 in 15 reported receiving training on the topic. There were several barriers which kept physicians from warning expecting mothers, including lack of education on hazardous environmental evidence, potential lack of capacity in patients to reduce harmful exposures, and concern of causing anxiety in patients. More education on environmental hazards (outlined in the next section) for both providers and expecting parents needs to be disseminated.

Can Autism be Prevented?

As previously mentioned, various factors may impact ASD. These include avoiding environmental toxins, longer duration of breastfeeding, modifying gut flora composition through probiotics, improved nutrition, avoiding acetaminophen use, and limiting the use of antibiotics and/or avoiding infections [33]. Mumper et al.'s study followed 294 general pediatric patients with ASD from 2005 to 2013 and found no new cases of ASD in the families who followed these guidelines. This case series also added vitamin D3, folinic acid, omega-3's and spaced out vaccinations. Given the prevalence of ASD, it is worth researching whether a comprehensive primary care intervention could reduce the risk. Evidence from other studies supports efficacy of folic acid supplements during pregnancy and choline and iron intake during fetal development to reduce ASD rates in children [21; 24; 48]. There are also programs in place to help families understand the factors that impact ASD.

Early Intervention

The majority of research and clinical programs target younger children where neurodevelopment

is more plastic. One such study by Keen et al. [22] found preliminary evidence regarding the impact of family intervention. At or shortly after an ASD diagnosis, parents received training on how to effectively support the communication of their child with ASD. They either learned on a DVD or received support at a parent group workshop and 10 home visits with a facilitator. Those who received the training in person demonstrated a greater improvement over those who watched the training on a DVD about parenting stress and efficacy. There was significantly greater improvement of social communication for the professionally supported group than the self-directed group, and a significant increase in adaptive behavior for participants with a low score at baseline — a promising result.

Many pediatricians struggle with effectively working with patients who have ASD and may not even realize their shortcomings. For instance, practitioners rated themselves higher than parents on ability to address ASD-specific needs and related conditions [5]. In Zuckerman et al.'s study [62], children with ASD were younger when parents first had concerns and first discussed those concerns with a provider than those with ID/DD (intellectual disorder/developmental disorder). However, when compared with parents of children with ID/DD, parents of children with ASD were more likely to be met with passivity or reassurance than with proactive responses when expressing concern. Among children with ASD, those with more proactive provider responses to concerns had shorter delays in being diagnosed compared to those with passive or reassuring provider responses. Furthermore, boys are four times more likely to be diagnosed with ASD than girls, and it is unclear if this is because being male is a risk factor for ASD or because girls show different symptoms that are easily missed by physicians [14]. Despite early parental concern, delays in diagnosis are common, especially when provider's responses are reassuring or passive, demonstrating the need for targeted improvements in primary care.

Later Intervention

Many ask, is late adolescence and young adulthood too late to intervene? Neuroimaging studies suggest that it is not. Structural MRI images have shown an increased brain volume in very early childhood for children with ASD, which typically developing children catch up to between six and eight-years-old. Furthermore, accelerated increase in frontal and temporal lobe volumes is documented in those with ASD [9]. This leads to perturbations in the temporal and regional sequence of typical early brain development. Brain development after early adolescence seems to be dominated by an accelerated age-related decline in total brain volume as well as cortical thickness and surface area.

Associations have been reported between ASD risk genes and neural connectivity. For example, the CNTNAP2-gene, which confers risk for the language phenotype in ASD, is associated with atypical structural and functional connectivity [37]. The thalamus, a key sensorimotor relay area implicated with ASD, appears to develop differently from the non-ASD population. Children with ASD have a distinct thalamic microstructure, but these group differences narrow over the years, suggesting that the thalamus continues to change into adulthood [29]. Another study investigated the dynamic functional connectivity network differences between participants with ASD and without. Compared to controls, the ASD group showed an increase in transient connectivity between the hypothalamus/subthalamus and some sensory networks in specific functional states, and diminished global meta-state dynamics of the whole brain functional network. These unusual dynamic patterns are associated with autistic symptoms using the Autism Diagnostic Observation Schedule [10]. Further investigation of gene-mediated neural differences could allow for more targeted interventions across the lifespan.

Researchers have found promising improvements in socio-emotional functioning of young adults with ASD through the PEERS Social Skills Treatment. Following treatment, participants were noted to exhibit decreased aggression, anxiety, and withdrawal, and improvements in emotional responsiveness, adaptability, leadership, and participation in activities of daily living [25]. This supports that improving social, behavioral, and emotional functioning may help develop and maintain quality peer interactions and remediate social isolation in adolescents with ASD.

Adaptive Functioning in ASD

Adaptive functioning refers to the skills someone needs to succeed in their environment and get along

with others. Many individuals with ASD struggle with this, making transition periods extra difficult. Matthews et al. [27] examined the adaptive functioning of 75 participants with ASD between 16–58 years old using the Vineland Adaptive Behavior Scales. Subscales consist of daily living, communication, and socialization, each with their own subdomains. Daily living skills were relatively stronger than communication and socialization in adults but not adolescents. On average, participants scored highest in writing skills (a subdomain in communication) and lowest in interpersonal skills (a subdomain in socialization). Regardless of participants' cognitive capacity, all standard scores were significantly below average, indicating that lifelong intervention for adaptive functioning is necessary for those with ASD.

Wallace et al. [53] suggest that executive functioning deficits in ASD are associated with internalizing symptoms and adaptive functioning difficulties, regardless of age or IQ. Among children and adolescents with ASD, peak weaknesses were in planning/organization and flexibility, which were robustly associated with adaptive functioning deficits. Appropriate interventions in adaptive functioning for adolescents and adults with ASD can support them at a period of transition as they reach new milestones in their life.

Post-Secondary Employment Experiences Among Young Adults with ASD

Many individuals with ASD face barriers when seeking employment. For young adults with ASD in the workforce, Postsecondary education employment experiences were compared to those of young adults with different disabilities [41]. Approximately one-half (53.4%) of young adults with ASD had ever worked for pay outside the home, the lowest rate among disability groups. Young adults with ASD earned an average of 8.10 USD an hour, significantly lower than average wages in the comparison groups and held jobs that clustered within fewer occupational types. Odds of ever having had a paid job were higher for those who were older, from higher-income households, and with better conversational abilities or functional skills.

Wehman et al. [56] utilized a randomized controlled trial (RCT) design to assess employment outcomes for youth with ASD in their last year of high school. Participants placed in the treatment group moved through three different 10–12 weeklong medical internship rotations, while also receiving instructions on how to reach proficiency in professional skills and adaptive work behavior. They were placed in departments including neonatal and pediatric intensive care units, diabetic wellness units, the hospital pharmacy, the coronary care unit, environmental services, and ambulatory surgery. Historically, youth with ASD have been placed into entry-level service jobs in hospitality or cleaning, so placements of study participants were unusual to them. However, their internships were typically comprised of high-level repetitive tasks that require great attention to detail and focus on order and structure to be successful. Most students in the treatment condition were hired in competitive placements after their internship and received up to 24% higher than the minimum wage. This is one of the first RCTs to demonstrate that young people with ASD can demonstrate success in the workplace as long as they have the proper tools.

Older Adults with ASD

It is estimated that 1 in 75 people of all ages has ASD, however most outcome and prevention studies focus on the experiences of children with ASD [38]. Far less research is being conducted on the health of older adults with ASD. Adults with ASD are more likely than the general population to face a wide array of hardships including mental health difficulties, injurious behavior, chronic health conditions, and nutritional problems [3]

Starkstein et al. [50] discovered preliminary data associating higher rates of parkinsonism in adults with ASD older than 39 years old. A preliminary study included direct examination and diagnosis of 19 adults with ASD over 49 years of age. The method was replicated in an independent sample of 37 adults with ASD over the age of 39 years. Frequency of parkinsonism occurrence rose from 20% in the first study to 25% after the second. While the association between both disorders should be further studied, these findings could lead to further investigation of the neurological underpinnings of ASD and parkinsonism. These findings should also be taken into consideration when delivering care services to older adults with ASD.

Another study measured the quality of life of 52 adults with ASD whose mean age was 49 years. Using the WHO Quality of Life-Brief Questionnaire, informant ratings and self-reports were measured. On self-report ratings, quality of life was significantly negatively correlated with repetitive behaviors and was positively associated with better adult social outcomes (ratings of employment, relationships, and independent living). However, informant ratings indicated few correlations between quality of life and any childhood or adulthood factors. Not all of the participants were able or willing to partake in the self-report [31]. It is possible that the validity of this popular measurement is low, indicating a need for a new tool for assessment of wellness in adults with ASD.

Primary Care for Adults with ASD

Most research on the challenges of ASD focuses on young children and their family. Unfortunately, there is a shortage of research on adults with ASD and effective healthcare practices for this population [6]. Lack of appropriate healthcare for people with ASD can be linked to the biologically based difficulties mentioned in the previous section, as well as social support, employment, level of education, access and delivery of accurate health services, and age of diagnosis [3].

Strengths and weaknesses in adults with ASD can vary. They can develop great abilities in their focused area of interest or utilize their need for consistency to manage their chronic conditions, as well as maintain strong friendships or relationships. With that being said, people with ASD have a wide variety of individual challenges including spoken language, written communication, performance of daily living activities, need for consistency, sensory sensitivity, and emotional regulation [35].Youth aged 11–22 years with ASD and ID (intellectual disability) reported thriving less than peers with ID only. Group differences in socio-communicative ability and school participation mediated the relationship between ASD and less thriving students [57].

Waiting room and wait time are main obstacles adolescents and adults with ASD encounter in receiving care. This was especially pertinent to those who have ID, history of aggressive behavior, or seizures, who found a large benefit in doing the assessment over the phone [47]. Communication barriers with providers is another obstacles people with ASD also face in the primary care office. Potential resolutions are creating tailored communication channels between providers and patients and creating a clinical environment that is more calming (such as having rounded corners and white noise) and allowing for people with ASD to control their stress more easily (such as having distractions, a quiet room, or a clock count down to their appointment time). Future use of input from individuals with ASD in various healthcare settings can be beneficial to accessibility and equity.

Physician Perspectives on Providing Primary Medical Care to Adults with ASD

Physicians experience a vast number of challenges to providing care to adults with ASD. Challenges providing care on a system-level includes: a dearth of services and supports for patients with ASD, a general lack of health-care providers willing to work with individuals with ASD and financial disincentives for potential increased time for providers to include adults with ASD in their practice. On a practice/provision level, challenges include time constraints, the complexity of family involvement, physical inaccessibility, and difficulty communicating with patients during visits. Training and educational challenges include a lack of formal education or training provided from medical school/residency and lack of general knowledge about working with individuals with ASD [55]. In a survey of 922 physicians, 77% rated their knowledge/skills of ASD as fair or poor, and only 13% agreed or strongly agreed that they have the adequate tools/referral resources/practice models to accommodate patients with ASD in their practice [61].

There are solutions and interventions to ameliorate these difficulties. On a systems level, solutions include increasing incentives to enhance provider capacity or decrease financial disincentives related to reimbursement and insurance. On a practice/provision level, it is possible to create a list of local resources and communication techniques, prioritize patients with ASD to lessen their wait time, improve the physical and sensory accessibility of office space, and facilitate communication between pediatricians and general practitioners. On the training and education level, it could be help-

ful to connect physicians to existing programs and services, as well as provide meaningful education about ASD and exposure to practitioners early in their professions as well as training of their office staff [55].

Conclusion

Throughout the life cycle different challenges arise and persist for those with ASD. Early prevention and intervention are commonly touted; our review demonstrates that it is also important to continue treatment and support for adolescents and adults. To get a holistic understanding of this disorder, it is equally important to research the specific genes and mutations linked to ASD as to the environmental risk factors, including birth complications, toxin exposure, and vitamin deficiency.

The promising understanding and interventions covered in this review target ASD from multiple areas, such as: giving expecting mothers specific guidelines to mitigate risk of ASD in their newborn, parental training in juvenile ASD support, social skills and adaptive functioning training for youth with ASD, and employment coaching. Based on our findings, we also suggest adapting the primary care setting to be more accessible to adults with ASD by incentivizing providers to treat more of this population, providing stronger education on how to effectively work with patients who have ASD, and implementing novel practices in the office setting. Asking individuals with ASD for their suggestions on how to implement change in primary care can allow for novel solutions to be executed. It is also crucial to further investigate health and wellbeing in older adults with ASD. Taken together, targeting ASD throughout the lifespan and its associated societal obstacles can be greatly beneficial for individuals with ASD.

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