VOLUME - 14, ISSUE - 04, APRIL - 2025 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Psychiatry

MEDICAL COMORBIDITIES IN AUTISM SPECTRUM DISORDER: A NARRATIVE REVIEW

Francesco Ferrara	National Health Service, Department of Mental Health, Termoli, Italy
Francesco Vaira	National Health Service, Department of Mental Health, Termoli, Italy
Lucia D'Agostino	National Health Service, Department of Mental Health, Termoli, Italy
Luca Fiorilli	Order of Psychologist of Molise, Italy
Marina Ottaviano	National Health Service, Department of Mental Health, Termoli, Italy
Stefano Marini*	MD, National Health Service, Department of Mental Health, Termoli, Italy *Corresponding Author

ABSTRACT Autism Spectrum Disorder is a group of neurodevelopmental disabilities characterized by persistent difficulties in social-communicative skills, language, behavior, personal skills, and executive functions. The diagnosis is usually made during childhood, although it can be difficult in mild forms. Psychiatric and medical comorbidities can worsen the clinical course of autism and determine resistance to pharmacological treatments. Medical conditions may remain undiagnosed in children with autism due to atypical presentation of symptoms. Recognizing the medical comorbidities is important because many of the medical conditions could stimulate or exacerbate the abnormal behavior occurring in children with autism. On the other hand, these medical disorders could be treated and consequently determine an improvement in the behavioral symptoms and quality of life of people with autism and their caregivers.

KEYWORDS : Autism spectrum disorder, neurological disorders, genetic comorbidities, metabolic comorbidities, immune disorders, medical comorbidities

INTRODUCTION

Autism Spectrum Disorder (ASD) includes a group of developmental disorders characterized by core symptoms that include social communication issues, the presence of restricted interests as well as repetitive behaviors that impact on quality of life of patients and their caregivers [1,2].

Some signs and symptoms may emerge between six and twelve months of age, but in many cases, a reliable diagnosis can be made by 24 months [3]. Recent guidelines suggest routine developmental screening visits at nine-, eighteen-, twenty-four- or thirty-months [4]. A structured interview and a diagnostic assessment should follow a positive screening test result at any age [5]. Clinical presentation depends on symptom severity, cognitive and language abilities, and co-occurrence of comorbid conditions [6,7]. Medical and psychiatric comorbidities in ASD might have atypical manifestations and symptomatology, often making their recognition more difficult [8,9].

The lack of sensitive diagnostic tools for differential diagnoses represents a major limitation. Indeed, many symptoms and behaviors often attributed to autism may be clinical manifestations of organic disorders such as pain, constipation, nutrient deficiencies, dental problems, food allergy, or intolerance [10]. For these reasons, evaluation for ASD should include a comprehensive assessment, preferably by an interdisciplinary team to exclude conditions that mimic ASD, identify comorbid conditions, and determine the level of functioning [11].

The annual prevalence of ASD is constantly growing and in 2023 in the USA was found to be around 1 in 36 children and 1 in 45 adults [12], with a male-to-female ratio of 4.5-to-1 [13].

Many different factors have been identified that may make a child more likely to have ASD, including environmental, biological, and genetic factors [14]. Furthermore, risk factors were classified into prenatal, perinatal, and postnatal [15]. Scientific literature supports a multifactorial etiopathogenesis of autism with numerous genetic, epigenetic, metabolic, neurotransmitter, and molecular data [16,17]. Recently, the hypothesis of intestinal dysbiosis has received great interest, especially for some symptoms of autism [18,19].

Although there are currently no approved medications for the treatment of ASD, psychiatric medications are commonly used in patients with ASD particularly for comorbid conditions [20,21]. Past literature has shown that psychiatric drugs are used in one-third of children and two-thirds of adolescents [22]. However, the effectiveness and tolerability of psychotropic medications are often questionable [23] and many times drugs are overdosed resulting in numerous side effects [24]. New instrumental therapies are demonstrating efficacy in the treatment of pathological conditions associated with ASD [25].

Given the questionable efficacy of pharmacological interventions, integration with psychosocial, educational, and rehabilitative interventions appears fundamental [26]. Furthermore, the association of pharmacological therapies with behavioral interventions is reported to be effective in improving functioning [27]. Since the publication of Lovaas' work [28], numerous enabling approaches have followed one another with differences in settings, environment, and procedures with multiple evidence in addressing the core impairments of ASD [29,30,31]. A recently published narrative review summarized the numerous rehabilitation interventions and treatment models for ASD that have been proposed over the years [32]. An often-forgotten aspect of habilitative approaches is the personal talents of people with autism, which are remarkably useful in the acquisition of new skills [33].

Cognitive-behavioral therapy appears to be fundamental for the psychotherapeutic aspects, characterized by numerous evidence in improving independence and in the acquisition of new daily living skills [34,35,36]. Finally, family members appear to have a key role in the enabling aspects [37].

Methods

A literature search was conducted on major databases to find useful studies for the aim of this paper.

DISCUSSION

Past literature highlighted numerous conditions and disorders more frequently associated with people with autism than in the general population. Still, in the present paper, the authors want to focus on genetic, neurological, gastrointestinal,

respiratory, cardiovascular, renal and urinary, hormonal and metabolic, inflammatory, immune, autoimmune, and allergic disorders (Figure 1).

Genetic Disorders

Registry studies in Denmark identified a highly significant increase in the frequency of congenital malformations in people with autism with 11.9% having one or more disorders [38]. Linkage studies have identified several candidate genes of promise related to ASD, but approximately only 15% of individuals with autism will be found to have an identifiable genetic diagnosis [39]. On the other hand, autistic symptoms can often be a behavioral manifestation of genetic pathologies (called syndromic autism). Moreover, some genetic disorders are more common in children with ASD than in the general population, such as Fragile X Syndrome (FSX), Rett-Syndrome, Tuberous sclerosis complex, Down Syndrome, Duchenne muscular dystrophy and neurofibromatosis type I (NF1) [40,41,42,43]. Among these, FSX is the most frequent genetic disorder comorbid with ASD and has been reported in approximately 3% of children with ASD. Furthermore, about 25-33% of FSX patients have a diagnosis of ASD [44].

Neurological Disorders

Past literature has shown that people with autism have a higher rate than the normal population of being affected by neurological pathologies such as epilepsy, macrocephaly, hydrocephalus, cerebral palsy, and congenital abnormalities of the nervous system. [45]. Epilepsy is the most common neurological comorbidity in autism. Data show that between 10 and 30% of children with autism also have a diagnosis of epilepsy. Moreover, up to 60% of children with autism have abnormal electroencephalogram (EEG), compared with 7% in controls [46]. These high percentages of comorbidity have led researchers to investigate a probable common etiopathogenetic mechanism between the two conditions [47]. Furthermore, the risk of developing epilepsy in children with ASD increases with the presence of intellectual disability and with female gender. Children with ASD and Intellectual Disability (ID) present a risk of epilepsy at about 50% compared to 21% of children with only ID [48,49]. Alterations of sympathetic/parasympathetic balance are commonly present in people with autism. They can present clinically with changes in heart rate, blood pressure, atypical pupillary light reflex, elevated plasma levels of nor-epinephrine, and respiratory arrhythmia [50]. Other neurological signs and symptoms that often characterize people with autism are motor disturbances such as toe-walking [51], repetitive behaviors, motor-coordination difficulties, deficit in performance in manual, posture, strength [52,53], and sensory processing alterations [54,55].

Gastrointestinal Disorders

Gastrointestinal (GI) disorders are very common in individuals with ASD, affecting between 46% and 84% of autistic children [56]. Precisely because of these high percentages, the new etiopathogenetic concept of the microbiota-gut-brain axis is emerging with ever greater weight, with related neuroinflammatory and immune implications [57]. The most common GI problems reported by past literature are represented by constipation, chronic diarrhea, gastroesophageal reflux, nausea and vomiting, chronic flatulence, abdominal pain, inflammatory bowel disease, and food intolerance [58]. Between 20% and 25% of children with ASD reported food allergies [59]. Abdominal pain, often unrecognized by doctors due to the poor verbal expressiveness of autistics, can lead to behavioral crises and self-injurious behaviors or a worsening of such behaviors [60,61]. The literature has also positively correlated the presence of severe GI symptoms with the symptomatic severity of autism [62].

Respiratory Disorders

The prevalence of respiratory disorders in people with ASD remains to date largely unstudied. Sleep-related breathing disorders, such as snoring or apnea are commonly reported more widely reported in autism than in typically developing children [63,64]. The electronic dataset reported more upper respiratory signs, ear infections, and otitis media with effusion [65,66]. The association of asthma and ASD has represented a particular field of interest. In the USA, the National Survey of Children's Health dataset demonstrated a higher prevalence of asthma and respiratory allergy among children with ASD [67,68].

Cardiovascular Disorders

Regarding cardiovascular (CDV) and cardiometabolic aspects, a recent meta-analysis has highlighted that people with autism have a higher risk than people without autism of developing diabetes mellitus, dyslipidemia, hypertension, and atherosclerotic heart disease [69]. Furthermore, a study showed that 87.3% of autistic adults self-reported a diagnosis of at least one CVD risk factor, such as diabetes, high cholesterol, high blood pressure, and overweight or obesity, and that 4.4% of autistic adults reported all four [70]. On the other hand, having congenital heart disease (CHD) is associated with almost double the odds of ASD compared with patients without CHD [71]. Some authors have hypothesized that autism and congenital heart disease could share common genetic and molecular aspects [72].

Renal and Urinary Disorders

There is emerging evidence that ASD and kidney disease have some overlaps with genetic copy number variants and environmental factors contributing to shared pathogenesis [73], but prevalence rates are currently not known. A recent paper identified 25,4% of adults with ASD affected by chronic kidney disease (CKD) [74]. Kidney disease and ASD can be seen to co-exist in many multisystem genetic disorders such as Tuberous Sclerosis also characterized by the presence of renal angiomyolipomata and cystic kidney disease. Moreover, the TSHZ3 heterozygous gene deletion at 19q12-13.11 is described in the literature to be associated with congenital kidney conditions with ASD [75]. Children with ASD have higher rates of bladder dysfunction with increased rates of nocturnal enuresis and daytime urinary incontinence compared with controls. They often take longer to achieve urinary continence and present with urinary symptoms of urgency [76]. For these reasons, the American Academy of Pediatrics recommended renal screening for ASD from infancy.

Hormonal and Metabolic Disorders

One aspect to take into consideration, especially in adolescents with autism is the hormonal changes typical of this period of life, which often determine behavioral changes. Hormonal changes may be reflected in early puberty, accelerated or reduced physical growth, and/or behavioral changes associated with menstrual pain. Congenital adrenal hyperplasia should also be considered [77,78]. Steroid and thyroid hormone alterations are often present with disruption of the hypothalamic pituitaryadrenalthyroid (HP AT) axis [79]. Moreover, obesity represents a growing concern in people with autism because of the use of food reinforcers as part of a behavioral program, the preference for carbohydrates shown by many ASD people, the use of pharmacological treatments, and the lack of physical exercise and activity [80].

The prevalence of metabolic and endocrinological disorders in ASD people is still largely unknown. The factors that contribute to metabolic alterations can be both genetic and non-genetic. In addition, epigenetic factors, such as deficiencies in zinc, calcium, and iron, are fundamental in modulating the metabolic profile [81]. Autistic features have been commonly observed in several metabolic disorders such as phenylketonuria, creatine deficiency syndromes, urea

cycle disorders, Wilson's disease, and Lesch-Nyhan syndrome [82,83,84]. Smith-Lemli-Opitz syndrome (SLOS) is another metabolic disorder that has been frequently associated with features of ASD [85]. It has been estimated that 50% to 75% of individuals with SLOS may meet the criteria for ASD. Furthermore, mitochondrial dysfunction may play a role in at least a subset of individuals with ASD [86] and can manifest with facial hypotonia, speech delay, epilepsy, etc. Mitochondrial dysfunctions could also result from various risk factors, including toxins, immune stimulation, drugs, metabolic abnormalities, increased production of reactive oxygen species, mast cell degranulation, etc. [87]. Some authors reported decreased oxytocin plasma levels in children with ASD [88,89]. Moreover, since oxytocin has been associated with bone mineral density score, Neumeyer et al. showed decreased bone mineralization in boys with ASD compared to controls [90,91].

Inflammatory, immune, autoimmune, and allergic disorders

Elevated levels of pro-inflammatory cytokines characterizing a chronic inflammation profile have been observed in individuals with ASD [92], which has led to the hypothesis of a role for the inflammasome in the etiopathogenesis of autism [93]. Higher pro-inflammatory cytokine levels have been associated with communication deficits and aberrant behavior [94]. Moreover, TNF-alpha concentrations have been positively correlated with the severity of ASD symptoms [95]. Post-mortem studies demonstrated increased microglial activation in the fronto-insular cortex, visual cortex, and cerebellum in ASD people [96,97]. These findings represent data of considerable importance since macrophages participate in synaptic pruning during normal neurodevelopment, mechanisms implicated in the etiopathogenesis of autism [98]. Alterations in natural killer (NK) cell activity have also been reported in ASD [99]. Data in the literature show that approximately 25% of children with autism have immune dysfunction [100]. Many studies demonstrated a high incidence of autoimmune disorders in ASD and direct associations between serum levels of autoantibodies and the severity of autistic symptoms [101,102 ,103]. Furthermore, a family history of autoimmune diseases is significantly higher in autistic children than in the general population [104]. Some studies have demonstrated the link between genes that predispose to immunological disorders and the risk of developing autism [105,106 ,107]. Food and inhalant allergies, including atopic diseases, and food intolerances are common findings in autism [108]. Children affected by mast cell activation syndrome appear to have a rate of autism ten times higher than the general population [109]. These data have given rise to the hypothesis that excessive mast cell activation could be a pathogenic mechanism in autism [110].

Finally, additional medical conditions that merit more attention by physicians include pain conditions such as headaches, migraine, dental, and abdominal pain.

Figure 1. Medical Comorbidities in Autism Spectrum Disorder

Acknowledgment

The authors entirely funded this paper, and no pharmaceutical companies were informed of or involved in it. The authors have no potential conflicts of interest directly relevant to the paper's contents.

CONCLUSIONS

Some characteristic symptoms of autism may be exacerbated by comorbid medical conditions that often go unrecognized and undiagnosed and may result in an atypical presentation of symptoms. Furthermore, there is little data in the literature on prevalence, clinical presentation, effective treatment modalities and prognostic data. Indeed, since many medical comorbidities are treatable, recognition of many of these conditions and subsequent appropriate treatment may result in improved quality of life for individuals with autism and possibly improved developmental trajectories in children. Finally, given the increased risk of mortality associated with autism, recognizing and treating associated medical conditions appears essential to lead a healthy and long-lived life. Based on what is stated in this article, it appears crucial that future research accounts for medical symptoms in people with autism.

REFERENCES

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th Edition. Arlington: APA Publishing, 2013.
[2] Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele J. Autism spectrum disorder. Lancet. 2018 11;392(10146):508-520. doi:10.1016/S0140-6736(18)31129-2.
[3] Guthrie W, Swineford LB, Nottke C, Wetherby AM. Early diagnosis of autism spectrum disorder: stability and change in clinical diagnosis and symptom presentation. J Child Psychol Psychiatry. 2013;54(5):582-590.
[4] Volkmar F, Siegel M, Woodbury-Smith M, King B, McCracken J, State M; American Academy of Child and Adolescent Psychiatry Committee on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder [published correction appears in J Am Acad Child Adolesc Psychiatry. 2014;53(8): 931]. J Am Acad Child Adolesc Psychiatry. 2014;53(2):237-257.
[5] Council on Children With Disabilities; Section on Developmental Behavioral Pediatrics; Bright Futures Steering Committee; Medical Home Initiatives for Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening [published correction appears in Pediatrics. 2006;118(4): 1808-1809]. Pediatrics. 2006;118(1):405-420.
[6] Waizbard-Bartov E, Fein D, Lord C, Amaral DG. Autism severity and its relationship to disability. Autism Res. 2023;16(4):685-696. doi:10.1002/aur.2898.
[7] Francesco Ferrara, Francesco Vaira, Lucia D'Agostino, Marina Ottaviano and Stefano Marini. Psychiatric symptoms and comorbidities in autism spectrum disorder: A narrative review. World Journal of Advanced Research and Reviews, 2025, 25(01), 1108-1116. doi.org/10.30574/wjarr.2025.25.1.0167.
[8] Belardinelli C, Raza M, Taneli T. Comorbid behavioral problems and psychiatric disorders in autism spectrum disorders. J Child Dev Disord. 2016;02. doi.org/10.4172/2472-1786.100019.
[9] D'Agostino L, De Lena R, Molinero M, Giacomodonato M, Sebasta S, Agense S, Ciamarra C, Marini S. Autism Spectrum Disorder and Hikikomori. Glob J Intellect Dev Disabil. 2024; 13(4): 555868. doi:10.19080/GJIDD.2024.13.555868.
[10] Summers J, Shahrami A, Cali S, D'Mello C, Kako M, Palikucin-Reljin A, Savage M, Shaw O, Lunsky Y. Self-Injury in Autism Spectrum Disorder and Intellectual Disability: Exploring the Role of Reactivity to Pain and Sensory Input. Brain Sci 2017; 7 doi:10.3390/brainsci7110140
[11] Zwaigenbaum L, Bauman ML, Fein D, et al. Early screening of autism spectrum disorder: recommendations for practice and research. Pediatrics. 2015;136(suppl 1):S41-S59.
[12] Maenner MJ, Warren Z, Williams AR, et al. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2020. MMWR Surveill Summ 2023;72(No. SS-2):1–14. doi:org/10.15585/mmwr.ss7202a1.
[13] Christensen, D. L., Baio, J., Van Naarden, B. K., Bilder, D., Charles, J., Constantino, J. N., et al. Centers for Disease Control and Prevention (2016). Prevalence and characteristics of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. MMWR Surveillance Summaries 65(3), 1–23.
[14] Matelski L, Van de Water J. Risk factors in autism: Thinking outside the brain. J Autoimmun. 2016;67:1-7. doi:10.1016/j.jaut.2015.11.003.
[15] Hisle-Gorman E, Susi A, Stokes T, Gorman G, Erdie-Lalena C, Nylund CM. Prenatal, perinatal, and neonatal risk factors of autism spectrum disorder. Pediatr Res. 2018; 84(2):190-198. doi:10.1038/pr.2018.23.
[16] Zhuang H, Liang Z, Ma G, Qureshi A, Ran X, Feng C, Liu X, Yan X, Shen L. Autism spectrum disorder: pathogenesis, biomarker, and intervention therapy. MedComm (2020). 2024 Mar 2;5(3):e497. doi:10.1002/mco2.497.
[17] Marini S, D'Agostino L, Mentana M, Ciamarra C, Gentile A. Modulation of Excitatory and Inhibitory Systems in Autism Spectrum Disorder: The Role of Cannabinoids. International Journal of Clinical Studies & Medical Case Reports (IJCMCR) 2023: 30(1): 005. doi:10.46998/IJCMCR.2023.30.000730.

[18] Mihailovich M, Tolinački M, Soković Bajić S, Lestarevic S, Pejovic-Milovancevic M, Golić N. The Microbiome-Genetics Axis in Autism Spectrum Disorders: A Probiotic Perspective. Int J Mol Sci. 2024 Nov 19;25(22):12407. doi:10.3390/ijms252212407.

[19] Zarimeidani F, Rahmati R, Mostafavi M, Darvishi M, Khodadadi S, Mohammadi M, Shamlou F, Bakhtiyari S, Alipourfard I. Gut Microbiota and Autism Spectrum Disorder: A Neuroinflammatory Mediated Mechanism of Pathogenesis? Inflammation. 2024 Aug 2. doi:10.1007/s10753-024-02061-y.

[20] Murray, M.L., Hsia, Y., Glaser, K., Simonoff, E., Murphy, D.G., Asherson, P.J., Eklund, H. and Wong, I.C. (2014), "Pharmacological treatments prescribed to people with autism spectrum disorder (ASD) in primary health care", Psychopharmacology (Berl), Vol. 231 No. 6, pp. 1011-1021.

[21] Marini S, D'Agostino L, Ciamarra C, De Berardis D, Gentile A. Gabapentin treatment for challenging behaviors in autism spectrum disorder and coexisting intellectual disability: a case report. Advances in mental health and intellectual disabilities, 05 Sep 2024, Vol. 18, Issue 3, pages 101 – 109.

[22] Coury DL, Anagnostou E, Manning-Courtney P, Reynolds A, Cole L, McCoy R, Whitaker A, Perrin JM (2012) Use of psychotropic medication in children and adolescents with autism spectrum disorders. Pediatrics 130(Suppl 2):S69–S76

[23] Sharma, A. and Shaw, S.R. (2012), "Efficacy of risperidone in managing maladaptive behaviors for children with autistic spectrum disorder: a meta-analysis", Journal of Pediatric Health Care, Vol. 26 No. 4, pp. 291-299.

[24] Branford, D., Gerrard, D., Saleem, N., Shaw, C. and Webster, A. (2019), "Stopping over-medication of people with intellectual disability, autism or both (STOMP) in England part 1 – history and background of STOMP", Advances in Mental Health and Intellectual Disabilities, Vol. 13 No. 1, pp. 31-40.

[25] Marini S, D'Agostino L, Ciamarra C, Gentile A. Deep brain stimulation for autism spectrum disorder. World J Psychiatry. 2023 May 19;13(5):174-181. doi:10.5498/wjp.v13.i5.174.

[26] Volkmar F, Siegel M, Woodbury-Smith M, King B, McCracken J, State M, American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI) (2014) Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 53:237–257

[27] Aman MG, McDougle CJ, Scahill L, Handen B, Arnold LE, Johnson C, Stigler KA, Karen Bearss K, Butter E, Swiezy NB, Sukhodolsky DD, Yaser Ramadan Y, Stacie L, Pozdol SL, Roumen Nikolov R, Lecavalier L, Arlene E. Kohn AE, Koenig K, Hollway JA, Korzekwa P, Gavaletz A, Mulick JA, Kristy L. Hall, Dziura J, Louise Ritz L, Trollinger S, Yu S, Vitiello B, Wagner A (2009) Medication and parent training in children with pervasive developmental disorders and serious behavior problems. J Am Acad Child Adolesc Psychiatry 48:1143–1154

[28] Lovaas OI. Behavioral treatment and normal educational and intellectual functioning in young autistic children. J Consult Clin Psychol. 1987;55(1):3.

[29] Slocum TA, Detrich R, Wilczynski SM, Spencer TD, Lewis T, Wolfe K. The evidence-based practice of applied behavior analysis. The Behavior Analyst. 2014;37(1):41–56.

[30] Leaf JB, Leaf R, McEachin J, Taubman M, Ala'i-Rosales S, Ross RK, et al. Applied behavior analysis is a science and, therefore, progressive. Journal of autism and developmental disorders. 2016;46(2):720–31.

[3] Marini S, D'Ambrogio T, Esposito M, Sergi MR, Sorge G. Rehabilitation in Autism. Pilot Project on the Health Centre-Based Primary Care Model within the National Health Plan Implementation Projects. 2018, 8 (2).

[32] D'Agostino L, Ferrara F, Ottaviano M, Vaira F, Marini S. Re-habilitative interventions and Different Treatment Models for autism spectrum disorder: A review. World Journal of Advanced Research and Reviews, 2024, 24(03), 1258–1263. doi.org/10.30574/wjarr.2024.24.3.3817

[33] Marini S, Ciamarra C, De Lena R, Giacomodonato M, Molinero M, Sebasta F, Agnese S, Mastrodonato F, D'Agostino L. Invisible Talents and Overcomeable Limits in Autism Spectrum Disorder. International Journal of Clinical Studies and Medical Case Reports (IJCSMCS), 2024, 39(1). doi:10.46998/IJCMCR.2024.39.000953

[34] Drahota A, Wood JJ, Sze KM, Van Dyke M. Effects of cognitive behavioral therapy on daily living skills in children with high-functioning autism and concurrent anxiety disorders. J Autism Dev Disord. 2011 Mar;41(3):257-65. doi:10.1007/s10803-010-1037-4.

[35] Marini S, D'Ambrogio T, Battista P, Sorge G. Cognitive-behavioral therapy in high-functioning autism spectrum disorder adults: A longitudinal observational study, European Neuropsychopharmacology, 2019, 29, Supplement 1. doi.org/10.1016/j.euroneuro.2018.11.258.

[36] Weston L, Hodgekins J, Langdon PE. Effectiveness of cognitive behavioural therapy with people who have autistic spectrum disorders: A systematic review and meta-analysis. Clin Psychol Rev. 2016 Nov;49:41-54. doi:10.1016/j.cpr.2016.08.001.

[37] Mussey, J., Dawkins, T., & AFIRM Team. (2017). Cognitive behavioral intervention. Chapel Hill, NC: National Professional Development Center on Autism Spectrum Disorders, FPG Child Development Center, University of North Carolina. Retrieved from http://afirm fpg unc edu/cogniltive behavioral intervention

[38] Lauritsen MB, Mors O, Mortensen PB, Ewald H (2002) Medical disorders among inpatients with autism in Denmark according to ICD-8: a nationwide register-based study. J Autism Dev Disord 32: 115–119

[39] Lauritsen MB, Pedersen CB, Mortensen PB. Effects of familial risk factors and place of birth on the risk of autism: a nationwide register-based study. J Child Psychol Psychiatry 2005;46:963–971.

[40] Specchio N, Pietrafusa N, Trivisano M, Moavero R, De Palma L, Ferretti A, Vigevano F, Curatolo P. Autism and Epilepsy in Patients With Tuberous Sclerosis Complex. Front Neurol 2020; 11: 639 doi:10.3389/fneur.2020.00639

[4] Oxelgren UW, Myrelid Å, Annerén G, Ekstam B, Göransson C, Holmbom A, Isaksson A, Åberg M, Gustafsson J, Fernell E. Prevalence of autism and attention-deficit-hyperactivity disorder in Down syndrome: a population-based study. Dev Med Child Neurol 2017; 59: 276-283 doi:10.1111/dmcn.13217

[42] Parisi L, Di Filippo T, Glorioso P, La Grutta S, Epifanio MS, Roccella M. Autism spectrum disorders in children affected by Duchenne muscular dystrophy. Minerva Pediatr 2018; 70: 233-239 doi:10.23736/S0026-4946.16.04380-2

[43] Walsh KS, Vélez JI, Kardel PG, Imas DM, Muenke M, Packer RJ, Castellanos FX, Acosta MT. Symptomatology of autism spectrum disorder in a population with neurofibromatosis type 1. Dev Med Child Neurol 2013; 55: 131-138 doi:10.1111/dmcn.12038

[44] Devitt NM, Gallagher L, Reilly RB. Autism Spectrum Disorder (ASD) and Fragile X Syndrome (FXS): Two Overlapping Disorders Reviewed through Electroencephalography-What Can be Interpreted from the Available Information? Brain Sci 2015; 5: 92-117 doi:10.3390/brainsci5020092

[45] Pan PY, Bölte S, Kaur P, Jamil S, Jonsson U. Neurological disorders in autism: A systematic review and meta-analysis. Autism 2020; 1362361320951370 doi:10.1177/1362361320951370

[46] Pacheva I, Ivanov I, Yordanova R, Gaberova K, Galabova F, Panova M, Petkova A, Timova E, Sotkova I. Epilepsy in Children with Autistic Spectrum Disorder. Children (Basel) 2019; 6 doi:10.3390/children6020015

[47] Lee BH, Smith T, Paciorkowski AR. Autism spectrum disorder and epilepsy: Disorders with a shared biology. Epilepsy Behav 2015; 47: 191-201 doi:10.1016/j.yebeh.2015.03.017

[48] Amiet C, Gourfinkel-An I, Bouzamondo A, Tordjman S, Baulac M, Lechat P, Mottron L, Cohen D. Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. Biol Psychiatry 2008; 64: 577-582 doi:10.1016/j.biopsych.2008.04.030

[49] Besag FM. Epilepsy in patients with autism: links, risks and treatment challenges. Neuropsychiatr Dis Treat. 2017 Dec 18;14:1-10. doi:10.2147/NDT.S120509.

[50] Ming X, Patel R, Kang V, Chokroverty S, Julu PO. Respiratory and autonomic dysfunction in children with autism spectrum disorders. Brain Dev 2016; 38: 225-232 doi:10.1016/j.braindev.2015.07.003

[51] Accardo PJ, Barrow W. Toe walking in autism: further observations. J Child Neurol 2015; 30: 606- 609 doi:10.1177/0883073814521298

[52] Samara Helena da Silva, Matheus Ribeiro Felippin, Letícia de Oliveira Medeiros, Cecília Hedin-Pereira, Anaelli Aparecida Nogueira-Campos, A scoping review of the motor impairments in autism spectrum disorder, Neuroscience & Biobehavioral Reviews, Volume 169, 2025, doi.org/10.1016/j.neubiorev.2025.106002.

[53] Miller HL, Licari MK, Bhat A, Aziz-Zadeh LS, Van Damme T, Fears NE, Cermak SA, Tamplain PM. Motor problems in autism: Co-occurrence or feature? Dev Med Child Neurol. 2024 Jan;66(1):16-22. doi: 10.1111/dmcn.15674.

[54] Phoebe Pui Pui Cheung, Benson Wui Man Lau, Chapter Six - Neurobiology of sensory processing in autism spectrum disorder, Editor(s): Mirolyuba Ilieva, Way Kwok-Wai Lau, Progress in Molecular Biology and Translational Science, Academic Press, Volume 173, 2020, Pages 161-181, doi.org/10.1016/bs.pmbts.2020.04.020.

[55] Robertson, C., Baron-Cohen, S. Sensory perception in autism. Nat Rev Neurosci 18, 671–684 (2017). doi.org/10.1038/nrn.2017.112

[56] Chandler S, Carcani-Rathwell I, Charman T, Pickles A, Loucas T, Meldrum D, Simonoff E, Sullivan P, Baird G (2013) Parent- reported gastro-intestinal symptoms in children with autism spectrum disorders. J Autism Dev Disord 43(12):2737–2747.

[57] De Sales-Millán A, Aguirre-Garrido JF, González-Cervantes RM, Velázquez-Aragón JA. Microbiome–Gut–Mucosal–Immune–Brain Axis and Autism Spectrum Disorder (ASD): A Novel Proposal of the Role of the Gut Microbiome in ASD Aetiology. Behavioral Sciences. 2023; 13(7):548. doi.org/10.3390/bs13070548

[58] Wasilewska J, Klukowski M. Gastrointestinal symptoms and autism spectrum disorder: links and risks - a possible new overlap syndrome. Pediatric Health Med Ther. 2015 Sep 28;6:153-166.

[59] Xu G, Snetselaar LG, Jing J, Liu B, Strathearn L, Bao W. Association of Food Allergy and Other Allergic Conditions With Autism Spectrum Disorder in Children. JAMA Netw Open 2018; 1: e180279.

[60] Prosperi M, Santocchi E, Muratori F, Narducci C, Calderoni S, Tancredi R, Morales MA, Guiducci L. Vocal and motor behaviors as a possible expression of gastrointestinal problems in preschoolers with Autism Spectrum Disorder. BMC Pediatr 2019; 19: 466 doi:10.1186/s12887-019-1841-8

[6] Fulceri F, Morelli M, Santocchi E, Cena H, Del Bianco T, Narzisi A, Calderoni S, Muratori F. Gastrointestinal symptoms and behavioral problems in preschoolers with Autism Spectrum Disorder. Dig Liver Dis 2016; 48: 248-254 doi:10.1016/j.dld.2015.11.026

[62] Adams, J.B., Johansen, L.J., Powell, L.D. et al. Gastrointestinal flora and gastrointestinal status in children with autism – comparisons to typical children and correlation with autism severity. BMC Gastroenterol 11, 22 (2011).

[63] Hodge D, Carollo TM, Lewin M, et al. Sleep patterns in children with and without autism spectrum disorders: developmental comparisons. Res Dev Disabil 2014;35:1631–8.

[64] Schreck KA, Richdale AL. Sleep problems, behavior, and psychopathology in autism: inter-relationships across the lifespan. Curr Opin Psychol 2020;34:105–11.

[65] Doshi-Velez F, Ge Y, Kohane I. Comorbidity clusters in autism spectrum disorders: an electronic health record time-series analysis. Pediatrics 2014;133:e54–63.

[66] Adams DJ, Susi A, Erdie-Lalena CR, et al. Otitis media and related complications among children with autism spectrum disorders. J Autism Dev Disord 2016;46:1636–42.

[67] Kotey S, Ertel K, Whitcomb B (2014) Co-occurrence of autism and asthma in a nationally-representative sample of children in the United States. J Autism Dev Disord 44:3083–3088. doi.org/10.1007/s10803-014-2174-y

[68] Xu G, Snetselaar LG, Jing J, Liu B, Strathearn L, Bao W (2018) Association of food allergy and other allergic conditions with autism spectrum disorder in children. JAMA Netw Open 1:e180279.

[69] Dhanasekara CS, Ancona D, Cortes L, et al. Association Between Autism Spectrum Disorders and Cardiometabolic Diseases: A Systematic Review and Meta-analysis. JAMA Pediatr. 2023;177(3):248–257.

[70] Bishop L, Charlton RA, McLean KJ, McQuaid GA, Lee NR, Wallace GL. Cardiovascular disease risk factors in autistic adults: The impact of sleep quality and antipsychotic medication use. Autism Res. 2023 Mar;16(3):569-579. doi: 10.1002/aur.2872.

[71] Gu S, Katyal A, Zhang Q, Chung W, Franciosi S, Sanatani S. The Association Between Congenital Heart Disease and Autism Spectrum Disorder: A

Systematic Review and Meta-Analysis. Pediatr Cardiol. 2023 Jun;44(5):1092-1107. doi: 10.1007/s00246-023-03146-5.

[72] Rosenthal, S. B., Wilsey, H. R., Xu, Y., Mei, Y., Dea, J., Wang, S., Curtis, C., Sempou, E., Khokha, Mu. K., Chi, N. C., Willsey, A., J., Fisch, K. M., & Ideker, T. (2021). A convergent molecular network underlying autism and congenital heart disease. Cell Systems, 12. 1094-1107. doi.org/10.1016/j.cels.2021.07.009

[73] Clothier J, Absoud M. Autism spectrum disorder and kidney disease. Pediatr Nephrol. 2021;36(10):2987-2995. doi:10.1007/s00467-020-04875-y.

[74] Miot S, Akbaraly T, Michelon C, Couderc S, Crepiat S, Loubersac J, Picot M-C, Pernon É, Gonnier V, Jeandel C, Blain H, Baghdadli A (2019) Comorbidity burden in adults with autism spectrum dis- orders and intellectual disabilities—a report from the EFAAR (Frailty Assessment in Ageing Adults With Autism Spectrum and Intellectual Disabilities) study. Front Psychiatry 10:617

[75] Caubit X, Gubellini P, Andrieux J, Roubertoux PL, Metwaly M, Jacq B, Fatmi A, Had-Aissouni L, Kwan KY, Salin P, Carlier M, Liedén A, Rudd E, Shinawi M, Vincent-Delorme C, Cuisset J-M, Lemaitre M-P, Abderrehamane F, Duban B, Lemaitre J-F, Woolf AS, Bockenhauer D, Severac D, Dubois E, Zhu Y, Sestan N, Garratt AN, Kerkerian-Le Goff L, Fasano L (2016) TSHZ3 deletion causes an autism syndrome and defects in cortical projection neu- rons. Nat Genet 48:1359–1369

[76] Van Herzeele C, Vande Walle J (2016) Incontinence and psychological problems in children: a common central nervous pathway? Pediatr Nephrol 31:689–692

[77] Herzog A. Hormonal abnormalities may be present in a subset of girls with ASD. Unpublished data, 2008.

[78] Carr EG, Smith CE, Glacin TA, Whelan BM, Pancari J. Menstrual discomfort as a biological setting event for severe problem behav- iors: assessment and intervention. Am J Mental Retard 2003;108: 117–133.

[79] Gao J, Zou J, Yang L, Zhao J, Wang L, Liu T, et al. Alteration of peripheral cortisol and autism spectrum disorder: a metaanalysis. Front Psychiatr. 2022; 13:928188. doi.org/10.3389/fpsyt.2022.928188

[80] Curtin C, Bandini LG, Perrin EC, Tyboi DJ, Must A. Prevalence of overweight in children and adolescents with attention deficit hy- peractivity disorder and autism spectrum disorders: a chart review. BMC Pediatr 2005; 5:48 –58.

[8] Indika NLR, Frye RE, Rossignol DA, Owens SC, Senarathne UD, Grabrucker AM, et al. The rationale for vitamin, mineral, and cofactor treatment in the precision medical care of autism spectrum disorder. J Personalized Med. 2023;13(2):252. doi.org/10.3390/jpm13020252

[82] Nasrallah F, Feki M Kaabachi N. Creatine and creatine deficiency syndromes: biochemical and clinical aspects. Ped Neurol 2010;42: 1–13.

[83] Gorker I, Tuzun O. Autistic-like findings associated with a urea cycle disorder I a 4-year old girl. J Psychiatry Neurosci 2005;30: 133–135.

[84] Trauner DA. Cognitive and behavioral manifestations of metabolic and chromosomal disorders. In: Frank Y, ed. Pediatric behavioral neurology. New York: CRC Press, 1996:251–268.

[85] Bukelis I, Porter FD, Zimmerman AW, Tierney E. Smith-Lemli- Opitz syndrome and autism spectrum disorder. Am J Psychiatry 2007; 164:1655–1661.

[86] Khaliulin, I., Hamoudi, W. & Amal, H. The multifaceted role of mitochondria in autism spectrum disorder. Mol Psychiatry 30, 629–650 (2025). doi.org/10.1038/s41380-024-02725-z

[87] Frye RE, Rossignol DA. Mitochondrial dysfunction can connect the diverse medical symptoms associated with autism spectrum disorders. Pediatr Res. 2011;69:41–47.

[88] Husarova VM, Lakatosova S, Pivovarciova A, Babinska K, Bakos J, Durdiakova J, Kubranska A, Ondrejka I, Ostatnikova D (2016) Plasma oxytocin in children with autism and its correlations with behavioral parameters in children and parents. Psychiatry Investig 13:174–183. doi.org/10.4306/pi.2016.13.2.174

[89] Zhang H-F, Dai Y-C, Wu J, Jia MX, Zhang JS, Shou XJ, Han SP, Zhang R, Han JS (2016) Plasma oxytocin and arginine-vasopressin levels in children with autism spectrum disorder in China: associations with symptoms. Neurosci Bull 32:423–432. doi.org/10. 1007/s12264-016-0046-5

[90] Neumeyer AM, Cano Sokoloff N, McDonnell E, Macklin EA, McDougle CJ, Misra M (2017a) Bone accrual in males with autism spectrum disorder. J Pediatr 181:195–201.e6. doi.org/10.1016/j.jpeds. 2016.10.080

[9] Neumeyer AM, Cano Sokoloff N, McDonnell E, Macklin EA, McDougle CJ, Misra M (2017b) Bone microarchitecture in adolescent boys with autism spectrum disorder. Bone 97:139–146.

[92] Thom RP, Keary CJ, Palumbo ML, Ravichandran CT, Mullett JE, Hazen EP, et al. Beyond the brain: a multisystem in- flammatory subtype of autism spectrum disorder. Psychopharmacology. 2019;236(10):3045–61.

[93] Saresella M, Piancone F, Marventano I, Zoppis M, Hernis A, Zanette M, Trabattoni D, Chiappedi M, Ghezzo A, Canevini MP, la Rosa F, Esposito S, Clerici M. Multiple inflammasome complexes are activated in autistic spectrum disorders. Brain Behav Immun. 2016 Oct;57:125-133. doi: 10.1016/j.bbi.2016.03.009.

[94] Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Pessah I, van de Water J (2011) Elevated plasma cytokines in autism spectrum dis- orders provide evidence of immune dysfunction and are associated with impaired behavioral outcome. Brain Behav Immun 25:40–45. doi.org/10.1016/j.bbi. 2010.08.003

[95] Xie J, Huang L, Li X, Li H, Zhou Y, Zhu H, Pan T, Kendrick KM, Xu W (2017) Immunological cytokine profiling identifies TNF- as a key molecule dysregulated in autistic children. Oncotarget 8:82390– 82398.

[96] Morgan JT, Chana G, Pardo CA, Achim C, Semendeferi K, Buckwalter J, Courchesne E, Everall IP (2010) Microglial activation and increased microglial density observed in the dorsolateral prefrontal cortex in autism. Biol Psychiatry 68:368–376. doi.org/10.1016/j. biopsych.2010.05.024

[97] Tetreault NA, Hakeem AY, Jiang S, Williams BA, Allman E, Wold BJ, Allman JM (2012) Microglia in the cerebral cortex in autism. J Autism Dev Disord 42:2569–2584. doi.org/10.1007/s10803-012-1513-0

[98] Hughes V (2012) Microglia: the constant gardeners. Nature 485:570– 572. doi.org/10.1038/485570a

[99] Enstrom AM, Lit L, Onore CE, Gregg JP, Hansen RL, Pessah IN, Hertz- Picciotto I, van de Water JA, Sharp FR, Ashwood P (2009) Altered gene expression and function of peripheral blood natural killer cells in children with autism. Brain Behav Immun 23:124–133. doi.org/10.1016/j.bbi.2008.08.001.

[100] Gładysz D, Krzywdziska A, Hozyasz KK. Immune Abnormalities in Autism Spectrum Disorder- Could They Hold Promise for Causative Treatment? Mol Neurobiol 2018; 55: 6387-6435.

[101] Mostafa, G.A. and Al-Ayadhi, L.Y. (2011) Increased serum levels of anti-ganglioside M1 auto-antibodies in autistic children: relation to the disease severity. J Neuroinflammation, 8: 39.

[102] Frye, R., Sequeira, J., Quadros, E., et al. (2012) Cerebral folate receptor autoantibodies in autism spectrum disorder. Molecular Psychiatry, 2012 Jan 10. doi: 10.1038/mp.2011.175.

[103] Chen, M.-H., Su, T.-P., Chen, Y.-S., et al. (2013) Comorbidity of allergic and autoimmune diseases in patients with autism spectrum disorder: A nationwide population-based study. Research in Autism Spectrum Disorders, 7: (2): 205-212.

[104] McDougle, C.J. and Carlezon, W.A. (2013) Neuroinflammation and Autism: Toward Mechanisms and Treatments. Neuropsychopharmacology, 38: (1): 241- 242.

[105] Abdallah, M., Mortensen, E., Greaves-Lord, K., et al. (2012) Neonatal levels of neurotrophic factors and risk of autism spectrum disorders. Acta Psychiatrica Scandinavica, 252: (1-2): 75-82.

[106] Brown, A., Sourander, A., Hinkka-Yli-Salomäki, S., et al. (2013) Elevated maternal C-reactive protein and autism in a national birth cohort. Molecular Psychiatry. 2013 doi:10.1038/mp.2012.197.

[107] Saxena, V., Ramdas, S., Ochoa, C.R., et al. (2012) Structural, Genetic, and Functional Signatures of Disordered Neuro-Immunological Development in Autism Spectrum Disorder. PloS one, 7: (12): e48835.

[108] Schieve, L.A., Gonzalez, V., Boulet, S.L., et al. (2012) Concurrent medical conditions and health care use and needs among children with learning and behavioral developmental disabilities, National Health Interview Survey, 2006– 2010. Research in developmental disabilities, 33: (2): 467-476.

[109] Angelidou, A., Alysandratos, K.-D., Asadi, S., et al. (2011) Brief Report: "Allergic Symptoms" in Children with Autism Spectrum Disorders. More than Meets the Eye? Journal of Autism and Developmental Disorders, 41: (11): 1579-1585.

[110] Theoharides, T.C., Angelidou, A., Alysandratos, K.-D., et al. (2012) Mast cell activation and autism. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1822: (1): 34-41.