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Editor-in-Chief of *World Journal of Virology*, Hai-Hui Huang, MD, Chief Physician, Institute of Antibiotics, Huashan Hospital, Fudan University, Shanghai 200040, China. huanghaihui@fudan.edu.cn

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Mohammed Al-Beltagi, Nermin Kamal Saeed, Adel Salah Bediwy, Rawan Alhawamdeh, Samara Qaraghuli

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Mohammed Al-Beltagi, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31527, Alghrabia, Egypt

Mohammed Al-Beltagi, Department of Pediatrics, University Medical Center, Arabian Gulf University, King Abdulla Medical City, Arabian Gulf University, Manama 26671, Manama, Bahrain

Mohammed Al-Beltagi, Department of Pediatrics, University Medical Center, Dr. Sulaiman Al-Habib Medical Group, Manama 26671, Manama, Bahrain

Nermin Kamal Saeed, Department of Medical Microbiology Section, Pathology Department, Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain, Manama 12, Manama, Bahrain

Nermin Kamal Saeed, Department of Microbiology Section, Pathology Department, Irish Royal College of Surgeon, Busiateen 15503, Muharraq, Bahrain

Adel Salah Bediwy, Department of Chest Disease, Faculty of Medicine, Tanta University, Tanta 31527, Alghrabia, Egypt

Adel Salah Bediwy, Department of Pulmonology, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Manama 26671, Manama, Bahrain

Adel Salah Bediwy, Department of Pulmonology, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Dr. Sulaiman Al-Habib Medical Group, Manama 26671, Manama, Bahrain

Rawan Alhawamdeh, Research and Development Department, Pediatric Occupational Therapist and Neuropsychologist, Genomics Development and Play Center (Genomisc WLL), 0000, Manama, Bahrain

Rawan Alhawamdeh, Research and Development Department, Pediatric Occupational Therapist and Neuropsychologist, Sensory Middle East (SENSORYME DWC-LLC), 282228 Dubai, United Arab Emirates

Samara Qaraghuli, Department of Pharmacognosy and Medicinal Plants, Faculty of Pharmacy, Al-Mustansiriyah University, Baghdad 14022, Baghdad, Iraq

Corresponding author: Mohammed Al-Beltagi, MBChB, MD, MSc, PhD, Chairman, Professor, Department of Pediatrics, Faculty of Medicine, Tanta University, AlBahr street, Tanta 31527, Alghrabia, Egypt. mbelrem@hotmail.com

Abstract

The coronavirus disease 2019 (COVID-19) pandemic affects all countries and populations worldwide, significantly impacting people with autism with a high risk of morbidity and mortality due to COVID-19. Approximately 25% of children with autism have an asymptomatic or symptomatic immune deficiency or dysfunction. In addition, they frequently have various comorbid conditions that increase the severity of COVID-19. In addition, severe COVID-19 during pregnancy may increase the risk of autism in the offspring. Furthermore, severe acute respiratory syndrome coronavirus 2 could target human nervous system tissues due to its neurotrophic effects. The COVID-19 pandemic intensely impacts many patients and families in the autism community, especially the complex management of autism-associated disorders during the complete lockdown. During the complete lockdown, children with autism had difficulties coping with the change in their routine, lack of access to special education services, limited physical space available, and problems related to food and sleep. Additionally, children with autism or intellectual disabilities are more liable to be abused by others during the pandemic when the standard community supports are no longer functioning to protect them. Early detection and vaccination of children with autism against COVID-19 are highly indicated. They should be prioritized for testing, vaccination, and proper management of COVID-19 and other infectious diseases. In this review, we discuss the various effects of COVID-19 on children with autism, the difficulties they face, the increased risk of infection during pregnancy, how to alleviate the impact of COVID-19, and how to correct the inequalities in children with autism.

Key Words: Autism; ASD; Autism Spectrum Disorder; Children; COVID-19; Testing; Vaccination; Neurotropism; SARS-CoV-2

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Core Tip: The pandemic of coronavirus disease 2019 (COVID-19) has dramatically impacted children with special needs. Besides the COVID-19-related high morbidity and mortality, other changes associated with the pandemic negatively impacted the educational and health-related issues of children with autism. The lockdown adversely affected sensory-motor development, cognitive abilities, sleep, morale, behavior, and social interactions in a large proportion that may reach 50% of children with special needs. Children with autism should be prioritized for testing and proper management of COVID-19 and other infectious diseases.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic affected worldwide countries and populations. It is caused by a strain of coronaviruses called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)[1]. It has cast great shadows and impacts on children with special needs. It deprived them of many opportunities to improve their condition, especially with the massive interruption of medical follow-up and rehabilitation during the lockdown and the difficulty in physical communication that a child with special needs requires to develop and upgrade his mental and physical abilities, as we follow the policy of physical distancing[2]. The lockdown significantly impacted the sensory-motor development, cognitive skills, sleep, morale, behavior, and social interactions in about 50% of children with special needs. There is also plenty of evidence suggesting the adverse effects of SARS-CoV-2 and the measures we take to limit its spread to children with disabilities and their families[3]. In addition, some primary health conditions in children with disabilities and special needs may expose them to a higher risk of contracting the virus and suffering from complications to a higher degree. These children, particularly those who suffer from sensory processing and integration such as tactile, vestibular, proprioceptive, and difficulties in hearing, vision, and cognitive performance, also face problems taking necessary preventive measures during epidemic periods such as wearing masks, keeping a physical distance, washing hands, and using sanitizer[4]. Autism is a spectrum disorder (ASD) with a wide variation in clinical manifestations. In this manuscript, we will use the term autism rather than ASD.

Autism itself poses a significant burden on the family with a child affected by it. It puts a severe financial and psychological burden on the family. This effect has multiplied several times with the COVID-19 pandemic[5]. This review aims to highlight the various impacts of COVID-19 on children with autism, the difficulties they encounter, including vaccination and testing, the infection-induced risk during pregnancy, and the different suggestions to alleviate the effects of COVID-19 and correct the inequalities in children with autism.

IMMUNE STATUS OF CHILDREN WITH AUTISM

Approximately one-quarter of children with autism have an asymptomatic or symptomatic immune deficiency or dysfunction. Many of these children may have asymptomatic immune dysregulation, so it is imperative to rule it out, particularly in children with gastrointestinal disorders[6]. Rose *et al*[7] found that children with autism have more oxidative stress and less glutathione-mediated redox/antioxidant ability than typically developed children. This oxidative stress and impaired glutathione redox homeostasis have a significant role in immune dysregulation observed in children with autism. Gastrointestinal dysbiosis is frequently encountered in children with autism and causes impaired mucosal barrier, gastrointestinal dysfunction, and immune system and nervous system dysregulation. The gastrointestinal dysfunction and the increased oxidative stress induce mitochondrial dysfunction, affecting both the mental function and immune status of children with autism[8]. Thus, during long-term exposure of children with autism to toxic stress and environmental deprivation during the COVID-19 pandemic, they suffer regressions in sensory-motor, physical, and mental health development[9].

Despite children with autism having low serotonin concentrations in the brain, they have an elevated blood count of mast cells with high blood and urine serotonin levels. These elevated serotonin concentrations in tissues out of the blood-brain barrier are related to mast cell activation with increased mast cell cytokines/chemokines; another significant contributor to the immune and neuroinflammatory dysregulation observed in children with autism[10,11]. Natural killer cells may be crucial in developing neurodevelopmental disorders, including autism. Enstrom *et al*[12] found abnormal gene expression and altered natural killer cell function in children with autism with increased production of interferon-gamma (IFN γ), granzyme B, and perforin under resting conditions and decreased production under stressful conditions. In addition, Manzardo *et al*[13] found that three cytokines involved in hematopoiesis and five cytokines involved in the attraction of T-cells, monocytes, and natural killer cells are lower in children with autism than in typically developed siblings.

Heuer *et al*[14] found significantly decreased plasma IgG and IgM levels in children with autism than in children with developmental delay or typical development. They also found that the degree of IgG and IgM levels reduction was significantly correlated with the Aberrant Behavior Checklist score; the more the drop is, the more the aberrant behavior. In addition, IgA deficiency is associated with an increase in the autism rate. Wasilewska *et al*[15] found that insidious changes in serum immunoglobulins with low-normal IgA and increased B cell activation marked by the rise in CD19/CD23-positive cells occur in children aged 3-6 years with regressive autism. These immune and neuroinflammatory dysregulations are major pathogenic components in autism, as evidenced by the high pro-inflammatory cytokines in postmortem biopsies obtained from the brain of children with autism. These immunological changes can serve as a marker for the development of autism.

Furthermore, individuals with autism have an increased prevalence of a positive family history of autoimmune disorders (such as rheumatoid arthritis and autoimmune thyroiditis), specific major histocompatibility complex haplotypes, and abnormal immunological marker levels[16]. Consequently, autism is strongly linked to abnormal immune responses, which may be an area for targeted intervention to prevent or treat children with autism. Unfortunately, COVID-19 effects on the immune system make children with autism more vulnerable to other diseases and further regression[17].

NEUROTROPIC EFFECTS OF SARS-COV-2

Besides respiratory illness, COVID-19 causes unexpected neurological complications, possibly due to direct viral effects on the central nervous system (CNS) or the peripheral nervous system (PNS) or as a part of the virus's systemic effect. Recent studies using human brain organoids showed that SARS-CoV-2 could target human nervous system tissues[18]. Although neurological disorders are relatively uncommon with coronavirus infections, two strains can enter and persist in the brain cells, including SARS-CoV and SARS-CoV-2[19]. COVID-19 showed moderately severe neurological problems (Figure 1), ranging from mild symptoms such as headache, dizziness, and smell and taste impairment to severe manifestations including Guillain-Barre syndrome, encephalitis, neuropsychiatric disorders, neurocognitive impairment, psychosis, vision impairment, dementia, and cerebrovascular defects as ischemic strokes, or intracerebral hemorrhages[20-22].

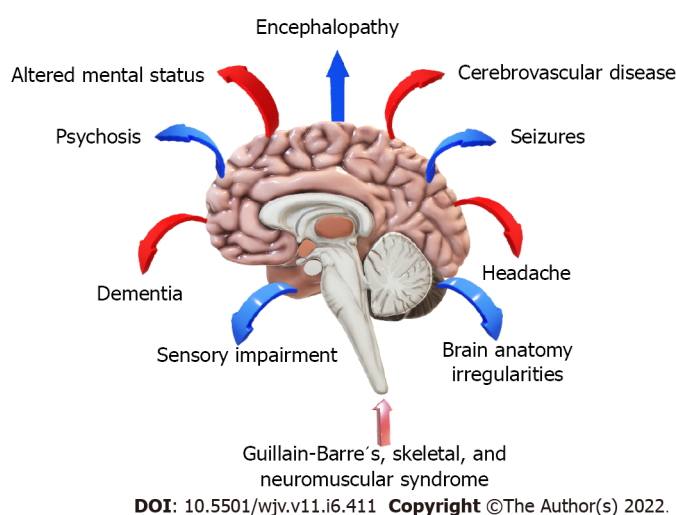


Figure 1 The various neurological symptoms observed in patients with coronavirus disease 2019.

The structural brain damage detected by magnetic resonance imaging and the presence of viral RNA in cerebrospinal fluid (CSF) and autopsy brain samples from patients with COVID-19 and neurological manifestations proves SARS-CoV-2-induced neurological effects. These neurological sequelae of SARS-CoV-2 are either due to the direct CNS toxic effect of the virus (as many brain cells express angiotensin-converting enzyme-2 (ACE2) receptors, the primary SARS-CoV-2 receptor, and other linked proteins and receptors such as Neuropilin-1 (NRP-1) and CD147) or as a result of a virus-mediated CNS inflammation and immune dysregulation due to the aggressive cytokine storm or the abnormal immune response[23-25].

COVID-19 AND MORTALITY RATES IN CHILDREN WITH AUTISM

COVID-19 is a systemic disease that could affect any organ or system. Many risk factors increase the rate and severity of infection with SARS-CoV-2, including male gender, older age, and medical comorbidities such as obesity, immune deficiency, autoimmune diseases, diabetes mellitus, or hypertension. Children with autism have many physical and behavioral risk factors that expose them to higher infection, morbidity, and mortality rates related to COVID-19[26]. Children with autism may require more exposure to outside caregivers and other children with a higher chance of encountering carriers of SARS-CoV-2. They frequently have persistent oral sensory-seeking behavior, which exposes them to an increased risk of contracting the virus[27]. Pica is approximately seven times more common in children with autism than in the general population, which exposes them to more infection risk. They also have challenges applying the pandemic's social distance and hygiene-related guidelines[28]. They are not able or scared to wear a mask and maintain physical distance, exposing themselves and others to a higher risk of spreading or catching COVID-19. They do not understand what COVID-19 is and cannot tolerate the sensory inputs related to preventive measures they require to protect themselves[29].

Children with autism frequently have various comorbid conditions that increase the severity of COVID-19 when encountered. Immune deficiency is commonly reported in children with autism, increasing the risk and severity of infections, including COVID-19[30]. IgA deficiency is a significant risk factor for both autism and infection with SARS-CoV-2. Serum IgA levels positively correlate with total lymphocyte counts and negatively correlate with C-reactive protein levels. Consequently, IgA deficiency, low lymphocyte count, and high C-reactive protein levels are significant risk factors for severe COVID-19[31]. Patients with autism have cytokine dysregulation with increased inflammatory cytokines production and impaired immune response at different levels[32]. Autism is four times more common in males than in females. Males are more prone to infection, particularly with SARS-CoV-2[33, 34]. Gut dysbiosis is frequently found in children with autism and is linked to many gastrointestinal and neurobehavioural symptoms[35]. There is a bidirectional relation between infection with SARS-CoV-2 and the gut microbiota. Infection with SARS-CoV-2 causes respiratory and gastrointestinal microbiota dysbiosis, which negatively impacts gastrointestinal and respiratory health. Dysbiosis of the gut microbiota produces an appropriate environment for replication of SARS-CoV-2 and subsequent pathogenic effects. Gut dysbiosis can induce pulmonary dysbiosis through the gut-lung axis, which determines the course and severity of COVID-19. On the other hand, gut microbiota diversity and the predominance of beneficial bacteria can improve the course of COVID-19 and alleviate the severity of the disease[36,37].

Schott *et al*[38] showed an increased risk of SARS-CoV-2 infection in patients with autism, especially in those who live in a residential facility, those who receive home services from outside caregivers, who need a lengthy hospitalization, and those with comorbidities. Krieger *et al*[39] showed an increased rate of infection and hospitalization in persons with autism, especially men between 40 to 60 years. Karpur *et al*[40] showed that persons with autism are nine times more likely to be hospitalized and six times more likely to have extended hospital stays than those without autism.

When hospitalized, children with autism have difficulties in social communication, the ability to express their symptoms, and understanding and following the safety guidelines. Many children with autism also have various challenging behaviors (*e.g.*, spreading and spitting saliva, pica and licking staff, and spreading stool that helps spread the virus. They strongly resist the change in the hospital environment and have aggravated stereotyped behavior patterns. Wearing protective equipment by the healthcare provider is another challenge and increases stress among children with autism[41]. In addition, people with autism may suffer some discrimination in the priority of receiving medical care depending on their counties' Intensive Care Unit (ICU) Triage Protocols and Policies. For example, the triage system in Spain used "severe baseline cognitive impairment" as an exclusion criterion for ICU admission in their triage guidance for COVID-19 ICU admission, according to the "Working Group of Bioethics of the Spanish Society of Intensive, Critical Medicine and Coronary Units." These features increase the risk of morbidity and mortality when hospitalized[41,42]. A systematic review and meta-analysis by Catalá-López *et al*[43] showed a higher mortality rate in persons with autism or attention-deficit/hyperactivity disorder than in the general population (relative risk of 2.37 and 1.97, respectively).

COULD COVID-19 DURING PREGNANCY INDUCE AUTISM?

Febrile maternal infection during pregnancy doubles the risk of autism in their offspring[44]. Currently, there is no evidence for the vertical transmission of SARS-CoV-2 from the mother to the fetus, which could be related to the preventive effect of lactoferrin at the placental interface. However, the virus could be transmitted postnatally through the mother's respiratory droplets or breastmilk[45]. In addition, severe COVID-19 during pregnancy induces the release of the inflammatory cytokine storm, which may cause fetal damage if not controlled. The brain is one of the target organs affected by inflammatory damage that could present later with autism manifestations[46]. The etiology of autism is multifactorial, with interacting genetic and environmental factors. Maternal immune activation is a significant risk factor for the offspring's neurodevelopmental diseases such as schizophrenia and autism[47]. Children with autism are more liable to many mental health disorders such as depression, sleep disorders, addiction, attention deficit, and hyperactivity behaviors since the COVID-19 pandemic started[48] (Panda).

Moreover, children with autism are among the most vulnerable populations affected by extended hours of online learning, flat-screen media, and mental health consequences during and after the COVID-19 pandemic[9,49]. Prenatal brain inflammation causes neurodegenerative changes and "short-circuiting the electrical system" in the amygdala, crucial for emotional feeling ability and fear regulation. Children with autism have exaggerated fear responses compared to their peers in neutral events. The Hypothalamic-Pituitary-Adrenal (HPA) axis system is hyper-responsive due to unpleasant sensory stimuli and/or benign social situations[50].

Insulin-like growth factor-1 (IGF-1) is a central component in perinatal oligodendrocytes-mediated neo-neuronal myelination, as it is essential for the survival of Purkinje cells in the cerebellum. IGF-1 deficiency is implicated in the pathogenesis of autism[51]. It is formed together with the growth hormone by the placenta. Maternal COVID-19 infection induces maternal immunologic activation with a marked increase in the production of pro-inflammatory cytokines, which inhibit placental IGF-1 synthesis. Reduced IGF-1 production downregulates perinatal myelination of the developing nervous system and brain dysconnectivity. If this downregulation is not corrected, a permanent neurologic deficit will occur or worsen[52,53].

In addition, SARS-CoV-2 can activate mast cells which in turn cause microglial activation. These changes release excess inflammatory molecules, stop synapses "pruning," impairing neuronal connectivity, and reduce the fear threshold, disrupting the emotional expression observed in children with autism[54]. The effects of impaired neuronal connectivity and reduction in the fear threshold worsen the problem as children with autism already have an overall sluggish HPA axis in responding to physiological or physical manipulation. These children have shown hypo-responsiveness to stressors that involve social evaluative threats[50].

The infection-induced inflammatory antenatal immune milieu is the chief trigger causing impaired fetal brain development, with long-term cognitive impairments. It is advisable to delay future pregnancy until the pandemic ends, immunization before preplanned pregnancies, follow safety guidelines with frequent hand washing, and regular testing in pregnant ladies to discover asymptomatic infection early[55]. A study in the New York metropolitan area showed that about 15% of pregnant women who presented for delivery were COVID-19 positive and mostly asymptomatic[56].

This percentage can indicate how many pregnant ladies carry the SARS-CoV-2 without symptoms worldwide, especially in areas without proper testing facilities. The effects of asymptomatic COVID-19 on the offspring are still unknown and need further research. To minimize the impact of COVID-19 infection during pregnancy, the mother is advised to have a high choline and luteolin supplement in addition to vitamin D, n-3 polyunsaturated fatty acids, and folic acid, which have beneficial effects on brain function development in infants of mothers who encountered viral infections in early pregnancy [57]. Luteolin is a potent natural flavonoid inhibitor of mast cells and microglia activation and blocks SARS-CoV-2 binding to its ACE2 receptor[54].

IMPACT OF COVID-19 ON AUTISM MANAGEMENT

To minimize the risk of COVID-19 spread, most governments imposed a near complete lockdown with extreme measures such as home confinement and shutting of special education systems. Most children with autism stopped receiving the required education and clinical therapies during the lockdown. In addition, children with autism usually resist changes in their routines. Consequently, most of them suffered during the lockdown with the closure of their kindergartens, schools, and other services they usually attend daily. At the same time, the family showed changes in its structure with the availability of a parent who is frequently absent from home, more time spent with a sibling, or separation from their grandparents who were usually present. The uncertainty about COVID-19 and the rapid and constant flow of information could devastate people with autism and increase their distress[58,59]. In addition, children with autism or intellectual disabilities are more liable to be abused by others during the pandemic when the standard community-protecting supports are no longer functioning[60]. In addition, the extended homestay increases inattentive-hyperactive behavior, screen and games addiction, and sleep disorders that lead to comorbid mental health disorders in children with autism. Depriving children with autism of their therapeutic intervention induces environmental deprivation of specific sensory tools, equipment, and inputs that help to accelerate developmental shifting and progress rates. This change is critical since online education and home training on their own cannot overcome clinical symptoms in children with autism[61].

These changes impose additional stress upon them and their families, with interrupted language development, exacerbated anxiety, more frustration, and short temper related to the fear of regression of the gained skills and sadness due to cessation of general care and support by dedicated clinical therapists and teachers. Children with autism had a significant increase in stimming, self-injury, nervousness, violence, impulsiveness, and binge eating behaviors during the pandemic[62]. Tokatly *et al* [63] showed a link between the absence of speech therapy and the increased rate of repetitive behaviors. In addition to the increased COVID-19-related infection, morbidity, and mortality rate observed in children with special needs, the pandemic deepens the gap in the healthcare inequalities provided for people with autism, adding excess risk for morbidity and mortality.

The COVID-19 pandemic poses various challenges to individuals with autism, their families, and caregivers. In recent Simons Powering Autism Research for Knowledge (SPARK) surveys, most adults with autism and caregivers of children with autism reported adverse effects in almost every field of their lives. While many are handling it well and even have encouraging experiences to share, 82% of families included in the survey reported mental health adverse effects on their children with autism. In comparison, 95% of parents and 93% of adults with autism reported adverse effects on their mental health[64]. In addition, several parents of children with autism committed suicide due to the severe psychological pressure and stress during the care of their children[65].

Mutluer *et al*[28] showed that individuals with autism had difficulties understanding what COVID-19 is and the actions it needs with challenges in applying hygiene-related and social distance regulations of the pandemic. Furthermore, the classic online learning programs do not have supportive accommodations that help children with autism learn while modulating the audio-visual sensory stimuli overload. Consequently, most of them are less likely to follow the proposed behavioral and hygienic habits such as routine hand washing that aim to prevent or reduce the risk of infection or the constant wearing of face masks due to their age, maturity, and limited developmental capacities and disabilities. The majority of the studied individuals stopped getting the required special education during the studied period of the pandemic. They also showed some features related to post-traumatic stress disorders, such as behavioral problems (including increased stereotypies and aggression), hypersensitivity, reduced and impaired sleep, and appetite alterations. They also had significant differences in all Aberrant Behavior Checklist subclasses (ABC) before and after the pandemic conditions. Their caregivers showed an increased anxiety level related to their behavior with a high ABC total score; specifically, the lethargy/social withdrawal subscale score predicted the parents' anxiety score.

Being parents of a child with autism is a real challenge, especially during the COVID-19 pandemic. During the lockdown, shutting down special education and rehabilitation facilities made the parents primarily the only full-time caregivers. Consequently, they depend on their skills to cope with their kids, with the loss of support and guidance from specialists and experts. In many cases, the caregivers of these children are not educated or trained enough to care for their children and manage them like their

typical peers. They may be unable to provide adequate care for their children's clinical symptoms such as seizures, tics, bulimic behavior, or sensory cravings and avoidances. Thus, the developmental rate drops dramatically without adequate clinical and professional special education services for children with autism[66].

Tokatly *et al*[63] showed that the most common problem encountered by the parents of children with autism is coping with the change in their routine, lack of access to special education services, limited physical space available, and food and sleep-related problems. Despite that, some children suffered worsening in their behavioral, developmental, or social domains; others succeeded in overcoming the challenges they encountered and even benefited from them. The researchers emphasized that the best way to help children with autism catch up with these severe modifications in their routine lifestyle is to provide a robust support system to their parents. Many parents lost their jobs or at least had a decrease in their income during the pandemic, with reduced affordability for the cost of special education and rehabilitation services for their children and increased anxiety levels[67]. The long-term effects of the pandemic and infection with SARS-CoV-2 on children with autism need more time to be evaluated.

In contrast, some individuals with autism and their families may manage autism more efficiently during COVID-19-related circumstances. For example, lockdown allowed the parents to spend more time with their children, allowing more sharing of activities, more co-watching, more adherence to rules and routine and limited socialization and physical contact in individuals with autism which could decrease the social-related stress and less physical contact with infected people. The lockdown also reduced the sensory overload for some children with autism and helped them enroll in online schooling that they could not attend in person due to their atypical behaviors in the classroom[68]. Asbury *et al*[68] found that a few children with autism and their families reported some positive effects of lockdown, such as decreased stress related to facing the daily routine challenges such as going to school and other public places or worrying about socializing with others. Some children could change their routines, accept new routines or make their routines. Some of them started to eat foods that they were not familiar with. Increased free time permitted for repetitive trials helped improve their abilities and skills. The availability of family time to spend together enhances the child's communication skills and allows the parent to identify these abilities[63]. The key factors that determine the successful coping of parents during the lockdown are their abilities to satisfy the child's needs, positive attitude in general, their creativity, and attending inventive problem-solving training by healthcare professionals and an occupational therapist specialized in Ayres Sensory Integration® (ASI) for sensory environmental adaptations, functional abilities, and independence in activities of daily living[69] (Dubois-Comtois).

In addition, Sergi *et al*[70] showed that children with autism involved in an Applied Behavior Analysis (ABA) based intervention during the lockdown period showed improvements in their communication, socialization, and personal autonomy. They also showed the significant effect of parents' training in avoiding delays in the generalization of socially significant behaviors following the radical treatment interruption in this group of children. Perhaps the best thing related to the COVID-19 pandemic is our awareness of how good our pre-COVID-19 lives were. Research has shown that consistent telehealth and home-based in-person occupational, physical, and speech therapies were beneficial in helping children with autism maintain their developmental rates and progress to the next level. However, parents and caregivers reported less satisfaction with telehealth services than with in-person therapy sessions. Furthermore, parents who reported higher emotional dysregulation in their children were less satisfied with ABA services[71].

INDIRECT IMPACT OF COVID-19

An indirect effect of COVID-19 was the significant reduction of the national income in most countries, which led to a lack of spending on health services related to the management of autism and giving priority to patients with COVID-19. At the same time, numerous community-based services provided by non-profit organizations and the private sector stopped due to acute financial instability. These financial crises caused a delay in the available diagnostic services and, consequently, a delay in the required therapy with a waiting list that could extend to more than a year[72]. Another significant indirect effect is the accuracy of the conducted studies during the pandemic. For example, there were difficulties in performing autism research due to social distancing and the need for the participants to wear masks. These behavioral and environmental changes increase stress conditions, making interpreting the behavior of individuals with autism difficult and affecting the research results. In addition, there is a high risk of missing scientific accuracy during moments of crisis[17].

With social distancing becoming an essential method of COVID-19 prevention, telemedicine and telehealth possibly become the ideal communication methods between caregivers and patients[73]. There has been a flood of videoconferences, "live presentations" in social networks, online training classes on online learning platforms, telepractice concerning different fields such as psychiatry, psychology, occupational therapy, speech therapy, and other remote activities that offer support, guidance, and treatment when applicable. Telemedicine requires an effective internet service, which may not be available in less developed countries or areas, which deepens the inequalities in the health

services provided to children with autism[74]. Even with strong internet, most children with autism may have difficulties following the screen during online teaching. One of the vital factors is the shortage of the sensory, motor, and cognitive accommodations needed to support the mind, brain, and body functions during the learning process. Furthermore, governments are not sufficiently drawing and applying the contributions of healthcare professionals to the academic learning process. Thus, children with autism are generally more prone to gaps in their developmental and learning processes that can be successfully implemented and reflected in the nations' economies[75].

On the other hand, there is a silver lining to the pandemic; scientists hurry to find alternative ways to continue their research and invent reasonable solutions to assist remote diagnosis, proper assessment, and manageable treatment accessible for all and increase participation in their clinical research[76]. Simultaneously, the COVID-19 pandemic represents a perfect opportunity to study the epidemiology of autism and the effects of the pandemic on environmental, genetic, and psychosocial factors on autism mechanisms over a long period worldwide[77]. We may have an unprecedented chance to study how the environment, stress, mental health comorbidities, and autism interact. The pandemic is also an excellent chance to test the efficacy of social robots for education and medical care for individuals with autism. Social robots work in a highly predictable and lawful system and provide children with autism with a highly organized learning environment that helps them focus on essential stimuli. Robots can provide these services during epidemics without the risk of transmitting infection. In addition, children with autism communicate more engagingly and have better social behaviors with robots than with human trainees[78,79].

TESTING CHILDREN WITH AUTISM FOR COVID-19

Individuals with autism should have a high priority for COVID-19 testing and other similar pandemic situations because they have an increased incidence of medical comorbidities (such as cardiovascular or respiratory diseases, hypertension, autoimmune conditions, obesity, and diabetes), high incidence of living in residential care, and difficulties in adherence to strict personal hygiene and physical distancing practices. However, most countries do not consider people with autism as a high-priority group[80]. Individuals with autism have high sensory sensitivities. Consequently, nasal and throat swabs or aspirations become a real challenge for the patient, the family, and the performing healthcare personnel. Children with autism may even need sedation to carry out testing, which may not be available in many situations. Hence, it is better to have more flexible testing procedures, such as saliva testing. People with autism may also encounter the challenge of waiting for a long time and presenting in unfamiliar places for testing. They also may have a problem using the necessary personal protective equipment[59]. Symptoms of COVID-19 may be atypical in people with autism who may indicate the need for a high index of suspicion and the need for equitable access to proactive testing and screening, especially for those with medical comorbidities or who live in high-risk settings such as those who live in supported accommodation or residential care[59].

To alleviate the testing-related anxiety, the parents can create a social narrative that tells the individual with autism what will go on and what they will do during testing. This preparation is better in enumerated steps so the parents can mark done with each completed step[81].

Figure 2 is an example of a visual demonstration of the nasopharyngeal swabbing steps. The narrative should match the person's abilities to understand with fewer words. It is better to put every step on a separate page, and to read the social narrative many times on the day before testing in order for the person to get used to the steps. The caregiver can distract the person's attention during nasal swabbing by using any distracting activities such as coloring a picture or watching a video or alleviate their anxiety by using a relaxing activity such as rubbing their hands or squeezing a squeeze ball if they are used to this[81]. The visual demonstration can also be available in the special care kits to be used by the healthcare provider when encountering persons with special needs to alleviate their tension. Light sedation or analgesia can be given before the test if the person is too anxious and cannot be calmed down[82,83]. An occupational therapist specializing in ASI in the testing and vaccination units helps children with autism have successful testing and vaccination by calibrating the sensory stimuli towards the child's brain and body using standardized and modified measurable evidence-based methods[84].

COVID-19 VACCINES IN AUTISM WHY? AND HOW?

As COVID-19 has a significant negative impact on people with autism, they need to be rapidly vaccinated. Many people with autism have a delay in COVID-19 vaccination as many families are concerned about the vaccine's effects on their children or the country's policy that shows hesitation against vaccinating children with mental and developmental disabilities[85]. A study by Choi *et al* [86] showed that only 35% of the parents of children with autism are willing to vaccinate their children with anti-COVID-19 vaccines. The vaccination rate increases with proper education and evidence-based recommendations. This delay in immunizing children with autism poses an increased risk of severe



Figure 2 Visual demonstration of nasopharyngeal swab testing steps.

COVID-19, especially with continuous viral mutations. With the high mortality rate of COVID-19, individuals with autism, especially with intellectual disabilities and other health problems, should be vaccinated as soon as possible, as the vaccines can prevent their death. Individuals with autism and their family members and caregivers should have the vaccine to decrease the risk of COVID-19. These individuals are less likely to adhere to the proper hygiene protocol, cannot wear masks for a long time, and cannot express their symptoms, such as sore throat. Thus, vaccination of their close contacts is also indicated. Vaccination of the parents and caregivers will decrease the chance of getting sick and reduce the possibility of leaving the child without proper care. Interestingly, Weinstein *et al*[87] found a higher rate of COVID-19 vaccination among individuals with autism aged 16-40 years across both sexes than in the controls, but not below the age of 16.

There are different types of COVID-19 vaccinations: COVID-19 Inactivated Vaccines (*e.g.*, Sinovac, Sinopharm), COVID-19 Viral Vector / Adenovirus Vaccines (*e.g.*, Oxford/AstraZeneca, the Johnson and Johnson, CanSino, and Sputnik V vaccines), genetic/mRNA vaccines (*e.g.*, Moderna and Pfizer/BioNTech COVID-19 vaccines), and live attenuated vaccines (Codagenix vaccine: under trials)[88]. Currently, the "Center for Disease Control and Prevention" (CDC) recommends two doses of Pfizer-BioNTech COVID-19 vaccine for five through 11 years of age separated by at least three weeks and an additional primary dose at least four weeks after the initial 2-dose primary series with a total of three doses. According to the CDC, Moderna, and Pfizer/BioNTech, COVID-19 vaccines are at least 90% effective in preventing symptomatic infection by SARS-CoV-2 after two weeks from the second dose [89]. The vaccines are equally effective and safe for individuals with autism as they are for others. People with various disabilities, including autism, were included in most vaccine clinical trials, which showed that the vaccines were safe and effective for everyone. To date, there is no link between COVID-19 vaccination and autism. In addition, maternal COVID-19 infection during pregnancy doubles the risk of autism, emphasizing the importance of immunization[90].

As mentioned earlier, similar to COVID-19 testing, vaccination is also a real challenge for the individual with autism, the family, and the health care provider responsible for the vaccination. Getting a vaccination poses an added challenge, especially since the shots are often not given in a typical doctor's office without a supportive occupational therapist ASI certified. This change in the routine disrupts their usual way of therapeutic care and education, which can be very upsetting. Every parent knows their child best. Therefore, they need to introduce the idea that they need to go driving somewhere, be exposed to somebody, wear protective equipment, and is going to give the vaccine. The parents should explain this many times for a week or day before the vaccination, using a narrative teaching story, video modeling, or visual social demonstration, giving the child enough time to process, understand and accept this new information and routine before the expected appointment. The parents should also help them feel better if they experience vaccine side effects. The CDC and The Autism Society of America prepared various tools, resources, and visual explainers that the parents and caregivers could use to explain the vaccine and the possible adverse effects after receiving the vaccine [91,92].

Table 1 Recommendations to minimize the effects of pandemics on people with autism

Intensive education:	<p>Mandatory education of people with autism, their families, and caregivers about the symptoms and signs of COVID-19 and similar infections and the behavioral procedures to decrease the infection spread[28].</p> <p>Emphasize the importance of good sleep hygiene and nutrition during the pandemic[63].</p> <p>Educating, supporting, and strengthening the parents' ability to adjust could be particularly valuable in times of extreme life difficulties and during ordinary times that may not be expected[93].</p> <p>Training children with autism about how to use personal protective equipment (PPE) by their caregivers will prepare them for the social adaptations during pandemics[94].</p> <p>Launching regular mandatory education and updating all the healthcare providers about the management guidelines created for people with autism, supported by specialist providers such as psychiatrists, psychologists, occupational therapists, speech therapists, behavioral therapists, and other specialties as indicated[95].</p>
Prioritization:	<p>For testing and vaccination for people with autism, their families, and caregivers[86].</p> <p>For hospitalization and ICU admission in triage protocols[41,42].</p> <p>Regular or on-demand access to psychological services regardless of the enrolment[96].</p>
During quarantine:	<p>Allow for one-on-one home visits[97].</p> <p>Allow meeting the healthcare provider (<i>e.g.</i>, physiotherapist, behavioral therapist) in a previously disinfected open area[97].</p> <p>Allow for small classes, and preadmission testing, allowing people with COVID-19 negative testing results to enter the class[98].</p> <p>Give permitted exceptions for people with autism, granting them to leave their homes more than once daily[98].</p> <p>Providing a sensory-friendly sanitized space for children with autism to release their extra energy, or at least providing tools to help them remove their excess energy, such as a physioball or bringing a swing or trampoline at home to prevent behavioral regression. Encourage physical activity to preserve general well-being[99].</p> <p>Provide formal and informal care with psychological and financial support for the well-being and proficiency of parents of children with autism[100].</p> <p>Provide weekly or "hotline" consultations for the parents of children with autism to help manage rising general and specific COVID-19-related issues[63].</p> <p>Allowing a caregiver or support person to attend to the individual with autism in the hospital, following all required infection control protocols[97].</p> <p>During and after the pandemic, preventive measures: to implement an intensive preventive intervention program for children with autism to reduce and prevent relapse and future physical and mental health regressions in future pandemics and/or similar situations [101].</p>

CONCLUSION

The COVID-19 pandemic affects all countries and populations worldwide, including people with autism. Besides respiratory illness, COVID-19 causes unexpected neurological complications, possibly due to direct viral effects on the nervous system. Children with autism frequently have various comorbid conditions that increase the severity of COVID-19 when encountered. There is an increased risk of SARS-CoV-2 infection in patients with autism with high morbidity and mortality rates. Children with autism should be prioritized for testing, vaccination, and proper management of COVID-19 and other infectious diseases. We must correct the inequalities children with autism face in receiving education and healthcare services by collaborating with governmental, non-profit organizations, and individuals to reach this goal.

With the hope that the COVID-19 pandemic will be in the gasping stage, we learned many lessons to be implemented to prevent its adverse effects on people with autism when similar situations occur in the future. We should regularly re-evaluate the mental and physical conditions and development of children with autism and find alternative treatment methods. The medical and rehabilitation teams are critically required to support children with autism and their families and ensure the continuity of physical and mental healthcare during and after the pandemic. Some suggested recommendations to minimize the impact of such pandemics on children with autism are shown in [Table 1](#).

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Country/Territory of origin: Bahrain

ORCID number: Mohammed Al-Beltagi 0000-0002-7761-9536; Nermin Kamal Saeed 0000-0001-7875-8207; Adel Salah Bediwy 0000-0002-0281-0010; Rawan Alhawamdeh 0000-0003-3501-6275; Samara Qaraghuli 0000-0002-6909-2668.

Corresponding Author's Membership in Professional Societies: UMC/KAMC/AGU, Tanta University.

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