

# Autism Spectrum Disorder in Israel

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The notion that autism spectrum disorder (ASD) prevalence in children is rising causes great apprehension in both parents and clinicians, with potentially harmful implications for public health, such as avoiding vaccinations.

On one side there are skeptical clinicians who believe in the 'over diagnosis' theory, and on the other are those who feel that real epidemiological change is taking place. Both attitudes carry options for better diagnosis and treatment alongside possible harm.

The theory that over diagnosis is the cause for this rise is based on the fact that this rise had happened in parallel with the change in diagnostic criteria, the higher rates among higher socioeconomic populations, and in certain areas of the country, mainly around Tel Aviv and central Israel where most clinical centers are located and where there is more public awareness of the problem [1].

The estimated heritability of ASD is 0.7–0.8, which is similar to many other developmental-cognitive phenomena. In addition, non-inherited factors also play a role, including de novo mutations and epigenetic factors. Environmental influences, such as prematurity, perinatal injury, and infection, may also play a significant role [2].

When there are two children with ASD in the same family, the risk for any additional pregnancy is 25%–35% higher, similar to rates for recessively inherited disorders. Genetic influences are strong. In

identical twins, when one twin has autism, the risk to the second twin is 80%–90%. The ratio between boys and girls in ASD is 4:1 suggesting a correlation between changes on the X chromosome and ASD. Nevertheless, the condition is not inherited in the classic X-linked pattern. In view of this data, a rise in the prevalence of ASD can be related to either a genetic or an environmental change (e.g., a de novo mutation that occurs more frequently or some environmental-cultural process). In addition, changes in diagnostic practice, such as the move from an emphasis on autism to autistic spectrum disorders, have developed.

A study performed in Israel by Kerub and colleagues [1] found a correlation between ethnicity and sociodemographic clusters and ASD rates. The proportion of people with autism among those of European and American origin in Israel 2013 was higher than those of Asian and African descent. Higher rates were found in the Tel Aviv area compared to Haifa, Jerusalem, and Beer-Sheva. This data tends to support the idea that the rise in prevalence is related to higher awareness, better access to clinical care, and more medical support. The median age of a diagnosis of ASD in the United States is between 4 and 5 years, although the recommendations encourage a much earlier diagnosis, preferably in the second year of life. Later diagnosis probably leads to inclusion of milder forms of ASD which may have escaped diagnosis before the adoption of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and DSM-5 criteria [3,4].

There is no question that the definition of ASD has been widened. This change is in part due to the dropping of the terms Asperger and pervasive developmental disorders, which are no longer in use, and

many children with different forms of atypical development are now included under the umbrella term of autism spectrum. The advantage of this broad approach is that many of the treatment modalities available are effective for a wide range of developmental problems and make for effective advocacy. One of the benefits of the buzz around the diagnosis of Autism is the increased legislation for support for these children both in the social and educational spheres.

One of the dangers is that children with other treatable developmental disorders, such as schizophrenia or obsessive compulsive disorder, will not be diagnosed properly. Although diagnostic purity has obvious advantages, this success should not be at the expense of other children in need. Indeed, there is now increasing realization among clinicians that the descriptive approach endorsed by the DSM has many limitations and many of the classifications, including autism, do not have clear biological underpinnings.

One of the alternative approaches gaining support is that of a dimensional transdiagnostic approach, such as that of the Research Domain Criteria (RDoC) [5], which is partially endorsed by the U.S. National Institute of Mental Health.

There is still a long way ahead in sorting and defining developmental disorders. The great expectations from the advances in the genetic areas are only partially fulfilled, and many new questions arise.

## CONCLUSIONS

We still have to work with the official classifications, and the review by Kerub and co-authors in this issue of *Israel Medical Association Journal* [1] provides a rich and complete approach that should provide an invaluable reference for pediatricians, psy-

chologists, neurologists, child psychiatrists, and all others who work with children in Israel.

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**Capsule**

**Endogenous glucocorticoids control host resistance to viral infection through the tissue-specific regulation of PD-1 expression on NK cells**

Controlling the balance between immunity and immunopathology is crucial for host resistance to pathogens. After infection, activation of the hypothalamic-pituitary-adrenal (HPA) axis leads to the production of glucocorticoids. However, the pleiotropic effects of these steroid hormones make it difficult to delineate their precise role(s) in vivo. **Quatrini** and co-authors found that the regulation of natural killer (NK) cell function by the glucocorticoid receptor (GR) was required for host survival after infection with mouse cytomegalovirus. Mechanistically, endogenous glucocorticoids produced shortly after infection induced selective and tissue-

specific expression of the checkpoint receptor PD-1 on NK cells. This glucocorticoid-PD-1 pathway limited production of the cytokine IFN-γ by spleen NK cells, which prevented immunopathology. Notably, this regulation did not compromise viral clearance. Thus, the fine tuning of NK cell functions by the HPA axis preserved tissue integrity without impairing pathogen elimination, which reveals a novel aspect of neuro-immune regulation.

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**Capsule**

**Double-stranded DNA-positive, hypocomplementemic patients with systemic lupus erythematosus**

**Doria** and colleagues investigated the efficacy and safety of belimumab, a human immunoglobulin monoclonal antibody against B lymphocyte stimulator, in a subset of patients with systemic lupus erythematosus (SLE) who were hypocomplementemic (C3 < 90 mg/dl and/or C4 < 10 mg/dl) and anti-double-stranded DNA (anti-dsDNA) positive (≥ 30 IU/ml) at baseline. In this phase III, double-blind, placebo-controlled study (BEL112341; ClinicalTrials.gov identifier: NCT01484496), patients with moderate to severe SLE according to the Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) (score ≥ 8) were randomized (2:1) to receive weekly subcutaneous belimumab 200 mg or placebo, plus standard SLE therapy, for 52 weeks. The primary endpoint was SLE Responder Index 4 (SRI-4) response rate

at week 52. Secondary endpoints were time to severe flare and reduction in corticosteroid dose (weeks 40–52). Safety was assessed throughout. Of the 836 patients in the intent-to-treat (ITT) population, 356 were hypocomplementemic and anti-dsDNA positive at baseline (108 in the placebo group and 248 in the subcutaneous belimumab 200 mg group). Compared with placebo, the belimumab group contained more SRI-4 responders (47.2% versus 64.6%; *P* = 0.0014), had a lower incidence of severe flare according to the SELENA-SLEDAI flare index (31.5% vs. 14.1%), and had a greater percentage of patients who reduced corticosteroid dosage by ≥ 25% to ≤ 7.5 mg/day during weeks 40–52 (11.4% vs. 20.7%; *P* = 0.0844). Adverse events were similar in treatment groups.

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**“A goal is a dream with a deadline”**

Napoleon Hill, (1883–1970), American author

**“The joy of learning is as indispensable in study as breathing is in running”**

Simone Weil, (1909–1943), French philosopher, Christian mystic, and social activist