Is autism curable?

SVEN BÖLTE[1,2]

1 Pediatric Neuropsychiatry Unit, Department of Women's and Children's Health, Center of Neurodevelopmental Disorders (KIND), Karolinska Institutet, Stockholm; **2** Division of Child and Adolescent Psychiatry, Stockholm County Council, Stockholm, Sweden.

Correspondence to Sven Bölte at Pediatric Neuropsychiatry Unit, Department of Women's and Children's Health, Center of Neurodevelopmental Disorders (KIND), CAP Research Center, Karolinska Institutet, Gävlegatan 22, S-11330 Stockholm, Sweden. E-mail: sven.bolte@ki.se

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ABBREVIATIONS

ASD	Autism spectrum disorder
ABA	Applied behavior analysis

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder of multifactorial origin. Today, ASD is generally not curable, although it is treatable to a varying degree to prevent worse outcomes. Some reports indicate the possibility of major improvements or even recovery in ASD. However, these studies are based on scientific shortcomings, and the lack of a clear definition of 'cure' in ASD further compromises interpretation of research findings. The development of animal models and decreasing costs of genome sequencing provide new options for treatment research and individualized medicine in ASD. This article briefly reviews several issues related to the question whether there is recovery from ASD, starting with a short overview of the presumed aetiologies.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder defined in DSM-5[1] by persisting deficits in social communication and social interaction across multiple contexts, alongside restricted, repetitive patterns, interests, or activities as manifested by at least two prototypically inflexible behaviors. An internationally increasingly accepted prevalence estimate for ASD in school-aged children is approximately 1% to 2%. Males are affected two to four times more often than females. There is a high degree of psychiatric and somatic comorbidity in patients with ASD; for example, the overlap of ASD and intellectual disabilities is in the range of 50%, the co-occurrence with attention-deficit–hyperactivity disorder is around 30%, approximately 20% with epilepsy, and about 10% with an identifiable single gene disorder, such as fragile X syndrome, tuberous sclerosis, or neurofibromatosis. In addition, an excess of a multitude of other conditions in ASD are noted (e.g. gastrointestinal problems and immunological dysfunctions).

ASD is phenotypically heterogonous, and several attempts have been made to conceptualize more homogenous forms of the disorder by subtyping. The most prominent are those related to level of IQ (low functioning [IQ<70] vs high functioning [IQ>70]), the presence of genetic/neurological syndromes (syndromic ASD vs idiopathic ASD), or abnormality of early morphogenesis in ASD (complex vs essential ASD). It has also been argued that ASD should be defined as an extreme end of a dimensional trait, a notion with significant implications for research and the definition of therapeutic targets. ASD is associated with substantial functional impairments in everyday life, lower lifetime outcome, and increased mortality.[2] Health economic calculations from industrialized countries indicate that societal costs for care, teaching, housing, and loss of productivity are considerable for ASD.[3]

The objective of this article is to briefly review whether autism is curable. For this purpose, a short overview on ASD aetiologies is provided, and possible definitions of cure as well as currently supported treatments for ASD according to systematic reviews are presented. Thereafter, the review discusses occasional claims of recovery and of cure after intervention, whether cure should always be an aim in ASD, as well as future options for treatment research.

AUTISM AETIOLOGIES

ASD has multiple causes, but most evidence suggests a high degree of heritability and modest environmental influences.[4] The genetics of ASD are complex. In addition to the comorbidity with known genetic syndromes, which may account for the phenotype, between 5% and 10% have known chromosomal rearrangements that include maternally inherited duplications of 15q11–q13, or inherited or non-inherited (de novo) copy number variations, predominantly in genes with synaptic functions (e.g. *NLGN3*, *NLGN4*, *NEUREXIN1*, *SHANK3*, *CNTNAP2*). These findings, coupled with genome sequencing data, suggest the existence of hundreds of ASD risk genes.[5] Furthermore, evidence suggests that dysregulation of epigenetic markers or mechanisms, such as DNA methylation, play an important role in ASD and integrate genetic and environmental influences to dysregulate neurodevelopmental processes.[6] Shared and non-shared environment factors are consistently reported in twin studies of ASD and related traits.[7] Specific environmental exposures that confer an increased risk for autism include maternal viral infections (e.g. rubella), and valproic acid and thalidomide use during pregnancy.[8] Moreover, the systemic and central nervous system pathophysiology in ASD, including

oxidative stress, neuroinflammation, and mitochondrial dysfunction, can be consistent with environmental influence (e.g. air pollution, pesticides, organophosphates, or heavy metals). Besides such specific exposures, studies implicate suboptimal prenatal, perinatal, and postnatal conditions to be a risk factor for autism. Several studies observed associations with low APGAR scores, and others report breech presentation or fetal distress more commonly in ASD. No rigorous study has found a link with the measles, mumps, and rubella (MMR) vaccine or with vaccines containing the preservative thimerosal (thiomersal).

Genetic and environmental aetiologies affect brain development at different stages of maturation. In ASD, macrocephaly is noted by age 12 to 24 months in a substantial proportion of children. Structural neuroimaging studies demonstrate alterations in both cortical and white matter regions, together with abnormal patterns of growth mainly localized in the frontal lobe, temporal lobes, and limbic structures, such as the amygdala. Diffusion tensor imaging has demonstrated the disruption of the white matter fiber bundle connecting brain regions associated with various high-level cognitive functions (e.g. social cognition, language). Functional neuroimaging studies have found alterations in activation and synchrony across cortical networks, with reduced functional connectivity relating to a variety of cognitive functions, including language, working memory, social cognition or perception, and problem-solving.[9] Neurochemical investigations with animal models and empirical drug studies remain inconclusive. Genetic differences in serotonin transport seem to have the most empirical evidence for a role in ASD, whereas data lending support to a role of the dopaminergic and glutaminergic systems are presently less robust but evolving.[10] These results indicate that ASD is characterized by a neuronal–cortical organization impacting on the developmental trajectory of social cognition, executive function and problem-solving mindset, and top-down versus bottom-up information processing with the integration of information into meaningful gestalt.

DEFINITIONS OF 'CURE'

Although ASD is viewed as a brain-based disorder of complex origin, it is an exclusively behaviorally defined disorder in the tradition of operationalized diagnostics in psychiatry. ASD is a psychiatric construct (latent) indicated by a range and combination of observable symptoms (manifest) in two domains: (1) social communication and interaction; and (2) repetitive, restricted behaviors and interests. These must have an onset during the neurodevelopmental period and be associated with qualitative functional disabilities and social exclusion. The ASD diagnosis is non-aetiological, although the designation 'neurodevelopmental' roughly indicates causal neurobiological pathways. As described previously, research on the aetiology of ASD and brain development offers promising genetic, environmental, neurobiological, and neuropsychological findings at a group comparison level (ASD vs typical development).

What this paper adds

- The question of recovery from autism spectrum disorder (ASD) is discussed from multiple perspectives.
- Priorities for future intervention research in ASD are highlighted.

However, these results are still too limited in terms of diagnostic accuracy to be transferred to single individuals with ASD and to be usable as biomarkers for diagnosing or treating the disorder in clinical practice. In the absence of clear etiologically or diagnostically informative biomarkers, defining change and cure in ASD is restricted to behavioral phenotypes. No agreement exists as to how clinically significant change or cure should be defined in ASD, and which measures might be appropriate. Therefore, different operationalization definitions are possible, and a serious discussion of cure and change in ASD must always explicitly involve a reference to which form of definition it refers. Briefly, possible definitions of substantial change and cure are the following: (1) absence of any psychopathology; (2) absence of functional impairment in everyday life; (3) absence of psychopathology and functional impairment; (4) sufficient quantitative change (partial remission) in psychopathology or functional impairment; (5) absence of the need for treatment; (6) psychopathology/impairment no longer mainly caused by ASD; (7) not/no longer fulfilling diagnostic criteria for ASD; and (8) normal/typical phenotype with qualitative change (full remission).

In addition, these general definitions of cure and change need concrete operationalization using psychometrically sound measures or expert consensus. In general, any statistically (not necessarily clinically) significant change on any scale for ASD symptoms, adaptive behavior, language skills, or developmental level/IQ is used to indicate change in ASD intervention or follow-up studies.[11]

AUTISM SPECTRUM DISORDER TREATMENTS

Cure or significant change in ASD is unlikely to appear spontaneously. Thus, the scientific evidence of available treatments is important when reviewing claims of cure and change. Countless forms of treatments have been postulated to bring improvements in ASD. Research Autism (www.researchautism.net), an initiative in cooperation with the National Autistic Society in the UK, is a reliable source of information about treatment. A multitude of interventions are reviewed regarding their evidence and side effects by independent ASD experts. Research Autism covers a broad range of diverse therapies (developmental, educational, psychological, pharmacological, as well 'alternative' or 'complementary'). Overall, the evidence base for most ASD treatments is weak. Only a few approaches are sufficiently scientifically endorsed. There are no evidence-based effective pharmacological options available for treating the core deficits of ASD.[12] Behavioral interventions show some evidence for improvements in ASD symptoms and cognitive or adaptive functioning.

Systematic reviews are deemed the gold standard for evaluating evidence in clinical science. Cochrane Systematic

Reviews of autism treatments report low to moderate efficacy of early intensive behavioral intervention, parent-mediated early intervention, and social skills training with regards to improvements of autism symptoms, cognitive abilities, or adaptive behaviors in randomized controlled trials.[13–15] Nevertheless, as even ASD intervention studies included in systematic reviews show some risk for bias and limited scope, conclusions from systematic reviews are debatable. For instance, while eclectic approaches are frequent in clinical reality, systematic reviews rarely examine combined treatments, they often focus on a limited repertoire of outcomes, and only weakly take into account the quality of the delivered treatment or the quality of the outcome measures that were used. Moreover, internal validity is the main focus of many systematic reviews, and the conclusions that can be drawn from systematic reviews in terms of external validity, that is generalizability to naturalistic settings, are often of unknown or limited.

CLAIMS OF RECOVERY

The concepts of cure and recovery have rarely been used in ASD research. A search of the scientific literature for ASD studies (PubMed, search term 'autism') yields approximately 25 900 hits (January 19, 2014), but only 85 hits for 'autism & cure', and 122 hits for 'autism & recovery'. It seems evident that ASD is a lifelong disability and currently generally not curable, but only treatable to a limited extent in certain individuals to avoid worse-case outcomes. Nevertheless, spontaneous recovery, significant remissions over time or idiosyncratic positive responses to certain treatments are impossible to categorically exclude for rare cases, even if excluded for the ASD population as a whole. Particularly, as ASD is not a neurodegenerative disorder, gradual improvements are conceivable.[16] Indeed, there have been claims of recovery in single cases or smaller groups of individuals with ASD. For instance, Fein et al.[17] reported optimal outcomes in 34 individuals with ASD, defined by losing all symptoms of ASD in addition to the diagnosis and functioning within the non-autistic range of social interaction and communication.

Another claim for cure that has received major attention in the ASD community is recovery after early intensive behavioral intervention using the Lovaas model and applied behavior analysis (ABA). The landmark case-control intervention study by Lovaas[18] reported that of 19 children who were treated, nine 'achieved normal educational and intellectual functioning' after long-term intensive intervention and were indistinguishable from other typically developing children. Subsequent studies using ABA also reported cases of recovery. Granpeesheh et al.[19] reviewed the clinical files of 38 children with autism who had participated in ABA trials for whom such optimal outcomes had been reported. Interestingly, the authors confirmed optimal outcomes in those individuals after intensive ABA services. However, methodological shortcomings in the ABA study designs and risk of bias, such as the unclear validity of the initial ASD diagnosis and the IQ assessment in the young low-functioning children, statistical regression, lack of comparability of experimental and control groups, and lack of active control groups make it difficult to judge the significance of these findings in terms of recovery from ASD after treatment.

FUTURE OPTIONS FOR CURE AND PREVENTION

By applying biological means, is a real cure for a broad population of individuals with ASD on the horizon? Currently, several large international consortia such as the European Autism Interventions – A Multicentre Study for Developing New Medications (www.eu-aims.eu) target the development and assessment of novel treatments for ASD. While, until more recently, most experts were pessimistic that biological treatments leading to recovery from autism would be in reach, advances in research techniques such as the development of more adequate and informative animal models give reason for conservative optimism.[20] Translational studies from the last decade indicate that phenotypic reversals of ASD might be possible at least for some aetiologies of the disorder.[21] A variety of drugs that are currently being tested in clinical trials to treat syndromes that have phenotypic overlaps with ASD may have promise even for ASD. Examples include mGluR5, a candidate for the treatment of fragile X syndrome,[22] and rapamycin, a candidate for the treatment of tuberous sclerosis.[23] Both agents have shown effects on the core pathology of their respective syndromes, as well as ease from autistic symptoms in mouse models.

While the identification of effective treatments is a relatively uncontroversial objective particularly in low-functioning ASD, the question of prevention is both ethically and scientifically more challenging. Primary prevention, which is reducing the risk of ASD in the first place, is not debated. An example of primary prevention in ASD is the avoidance of valproate use during pregnancy, because it has been associated with an increased risk for autism in children.[24] On the other hand, secondary prevention (i.e. to intervene as early as possible when a serious risk factor is diagnosed in order to avoid the syndrome) is controversial. Genetic testing (e.g. copy number variation[25] or other genetic markers) is an example of secondary prevention. Nevertheless, the accuracy of genetic testing is still very limited, and it is largely unknown how well genetic markers predict functional adaptation and outcome in ASD. Moreover, it is a fundamental ethical question as to whether decisions to conduct testing are really in the genuine interest of the child.

SHOULD ASD (ALWAYS) BE CURED?

ASD, on whatever level, is associated with functional impairments and low or underachieving outcome.[26] ASD almost exclusively demands at least some form of intervention and support to increase quality of life, adaptive skills, and to prevent worse-case outcomes. Nevertheless, a substantial minority of cases still have the potential to live an independent life. In addition, studies have shown the

occurrence specific talents in ASD, such as savant skills, scientific giftedness, and visual disembedding.[27] It is, therefore, legitimate to raise the question, whether cure should always be a goal in ASD, or if alternatives to cure are equally important. Such an alternative strategy is the Treatment and Education of Autistic and related Communication handicapped Children (TEACCH) programme, an intervention that designs a person's environment around their skills, interests, and needs. This enables the individual to be as independent as possible.[28] Interestingly, there is some indication that autistic talents might be susceptible to treatment. For instance, 'Nadia',[29] an autistic girl with extraordinary drawing skills, while benefiting from early intense intervention in terms of a decrease in autistic symptomatology, lost her artistic skills during the course of the treatment.

Other decisive points in the treatment of ASD are the treatment compliance in individuals diagnosed with ASD and the question of who wants people with ASD to be treated. An increasing number of individuals, particularly with high-functioning ASD, identify themselves with the notion of autism being a phenomenon of neurodiversity.[30] The latter states that ASD should not be viewed a disease per se, but rather an expression of natural neural variation and, therefore, should not be a primary target of treatment. Indeed, people with ASD often report that they experience autism to be an egosyntonic entity, not conflicting with their preferred self-image or state of being. Therefore, individuals with ASD do not necessarily experience themselves that they suffer from autism, but rather that they are autistic, which is an integral part of their self. They might reject causal treatment for autism, but would accept intervention to foster the skills that would allow them to better cope with the demands of everyday life and treatment for egodystonic comorbidities.

CONCLUSIONS

This article briefly and selectively reviewed whether ASD is curable. I hope it became clear that this is a multifaceted and controversial topic. ASD phenotypes and aetiologies are heterogeneous; there is no agreement as to the definition of recovery; interventions are many but the empirical support is limited; there are debatable claims of cure; and there are several questions as to whether prevention of ASD and its cure really should always be primary clinical targets. Compared to only a decade ago, there are now new possibilities for pharmacological treatment research in ASD. Owing to the nature of ASD, which presents with a spectrum of severities, compositions of symptoms, comorbidities, and functional disabilities as a consequence multiple causes, treatment towards cure using one and the same method in all cases is an unrealistic scenario. Moreover, it is unlikely that a certain treatment will have a comparable effect in all individuals with ASD. On the other hand is it probable that individual characteristics of individuals with ASD mediate treatment effects. Merely collecting information whether a single treatment shows an average effect on a common set of symptoms in a mixed group of participants with ASD is not an adequate target for future treatment research. In line with developments in other clinical disciplines, the target in ASD will need to be the identification of techniques or combination of methods that are likely to have a high effect on prioritized difficulties in individual patients with ASD. Responder and non-responder analyses are essential for this purpose, yielding differential insights into how sex, age, intellectual skills, language level, medical history, ASD severity, ongoing concurrent treatments, and comorbidity impact on the efficacy of a treatment. As costs are continuously declining, whole-genome sequencing will eventually also become ever more important in the predictive personalized treatment of ASD.[31]

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