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REVIEW ARTICLE

Evolution in the Understanding of Autism Spectrum Disorder: Historical Perspective

Mark Mintz[1]

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Abstract The study of the evolution in the diagnosis and treatment of autism is a lesson in the dangers of medical beliefs or doctrines that are not grounded in medical science. The early descriptions of autism suggested that it was the result of childhood psychoses or psychodynamic disturbances of parent-child relationships. This flawed conceptualization of autism spectrum disorders (ASD) gave way to advances in medical science, which have established ASD as a neurobiological disorder of early brain development. There are many genetic, epigenetic, metabolic, hormonal, immunological, neuroanatomical and neurophysiological etiologies of ASD, as well as an array of gastrointestinal and other systemic comorbid disorders. Thus, ASD are a biologically heterogeneous population with extensive neurodiversity. Early identification and understanding of ASD is crucial; interventions at younger ages are associated with improved outcomes. The advent of understanding the biological sub-phenotypes of ASD, along with targeted medical therapies, coupled with a multimodal therapeutic approach that encompasses behavioral, educational, social, speech, occupational, creative arts, and other forms of therapies has created a new and exciting era for individuals with ASD and their families: "personalized" and "precision" medical care based upon underlying biological sub-phenotypes and clinical profiles. For many individuals and their families dealing with the scourge of autism, their long and frustrating diagnostic journey is beginning to come to an end, with a hope for improved outcomes and quality of life.

✉ Mark Mintz
r[redacted]h.org

[1] The Center for Neurological and Neurodevelopmental Health, Voorhees, NJ, USA

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Introduction

Although medicine is in part an art, science is the fundamental foundation of good clinical practice. Science relies upon the systematic accumulation and interpretation of knowledge and facts that are obtained through objective observations and experiment. Although there are many historical examples where medical assumptions, premises, or dogma were later proven to be unfounded or incorrect, the beauty of medicine is its ability to change and alter doctrines as new evidence comes to light. Autism is a classic example of such an evolutionary process. In the absence of solid scientific proof of organicity for autism, the early conceptualization of autism was based on ingrained but misguided belief systems. With time, autism was conceptualized as a behaviorally, categorically, and dimensionally-defined developmental disorder [1]. However, later and ongoing advances in science and medicine have provided a solid foundation for the progression in understanding the biological/neurological nature of autism spectrum disorders (ASD), which has led to improved diagnostic accuracy, pragmatic therapeutic interventions, and enhanced patient outcomes and quality of life.

ASD are complex neurobiological disorders of early brain development, presently defined and characterized by qualitative impairment in social interaction and communication, as well as restricted, repetitive and stereotypic patterns of behavior, interests and activities [2, 3]. Since the features constituting the diagnosis of ASD are ubiquitous and non-specific, ASD populations are biologically and neurologically diverse, with an array of underlying biological sub-phenotypes. Yet, the early historical attempts at describing autism belied an

ignorance of its biological etiology. Even today there is a persistent adherence to classifying ASD within the framework of a "mental health" disorder, as the diagnosis of ASD remains within the Diagnostic and Statistical Manual of Mental Disorders (DSM), beginning with the DSM-III and continuing to the latest reiteration, DSM-5 [4–6]. Thus, the diagnosis of ASD can be assigned without regard to the inciting biological mechanisms, causes, and contributions. The classification of ASD as a mental health disorder has had many practical issues, ranging from stigmatization, service provisions, definition of research cohorts, insurance coverage, to specific personal and governmental rights [7, 8].

Leo Kanner, a psychiatrist administering a clinic at Johns Hopkins hospital in the 1930s and 1940s, is usually cited as the first clinician to describe autism [9, 10]. Kanner made prescient observations of 11 children with "autistic disturbances of affective contact", which he characterized in his research over the subsequent 15 y as social isolation, obsessive desire for sameness and routine, delayed echolalia, and many with "splinter" memory skills. Hans Asperger, a Viennese pediatrician, contemporaneously but independently described an "autistic psychopathy" that would eventually bear his name, Asperger syndrome [11–14]. He described patients with normal early language development but marked social difficulties with peers, marked circumscribed interests, but often highly intelligent [7]. Although Asperger disorder was eventually included as a subtype of Pervasive Developmental disorders in the DSM-IV, this inclusion was controversial; it has been eliminated from the DSM-5, with some researchers likening Asperger disorder to a form of non-verbal learning disorders [7, 15–17].

During the 1940s, psychiatrists and psychoanalysts maintained that autistic behavior patterns were a presentation of childhood schizophrenia [8]. However, both Kanner and Asperger were careful to differentiate and distinguish their disorders from childhood schizophrenia and intellectual disabilities [18]. During the 1950s through the 1960s, conceptualization of autism as a form of childhood schizophrenia led to etiological hypotheses that autism was due to an emotional disturbance deeply rooted in abnormal parent-child psychodynamics, such as an infant's response to an emotionally cold and distant mother (so called "refrigerator mothers") [18]. Still, there continued to be no consistent definition of autism. Misdiagnosis was prevalent, and, although the conditions can be co-morbid in some individuals, many patients with intellectual disabilities were misdiagnosed with autism, and *vice versa*. This promulgated an unfortunate era where many of these misdiagnosed children were left to flounder in crowded, underfunded psychiatric institutions, never receiving necessary behavioral, educational, or therapeutic interventions that could have improved their function and outcomes.

In the 1960s and 1970s, the psychogenic theories of autism began to fade as scientific evidence began to mount that autism is a neurobiological disorder. This included observations of high concordance rates of autism in identical twins, increased incidence and prevalence of seizures and epilepsy in autism, and true distinctions of autism from schizophrenia [19–22]. Subsequent and concomitant neuropathological and neuroradiological investigations have corroborated brain abnormalities in autism [23, 24]. However, it was not until 1980, with the publication of DSM-III, that autism was considered in a separate category. The DSM-III provided that for a diagnosis of autism, termed a "pervasive developmental disorder", presentation was necessary prior to 30-mo-old, with symptoms and signs of a lack of interest in people, gross impairment in communication, and "bizarre responses" to environmental stimulation and interactions [25]. In 1987, the revised edition, DSM-III-R, eliminated an age of onset requirement, and created a category for children not fully meeting criteria for autistic disorder, "pervasive developmental disorder-not otherwise specified". DSM-IV, and the "text revision" DSM-IV-TR, introduced an "umbrella" approach to the pervasive developmental disorders, with five subcategories, including autistic disorder, Pervasive Developmental Disorder - Not Otherwise Specified (PDD-NOS), Asperger disorder, Rett disorder, and Disintegrative disorder [4, 5]. In DSM-IV-TR, there remained three criteria for the diagnosis of Autistic disorder: communication impairment, social deficits, and repetitive behaviors with restricted interests. The latest DSM-5 reiteration of the diagnosis of autism purports to be more rigorous and specific [2, 6]. The DSM-5 has created a hybrid two-factor (dyad) dimensional diagnostic paradigm for autism, collapsing the three domains contained in the DSM-IV-TR to two domains: social communication and restricted interest/repetitive behaviors (Table 1). The terminology of pervasive

Table 1 DSM-5 criteria for autism spectrum disorders. Currently, or by history, must meet criteria A, B, C, and D [6]

A. Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifested by all 3 of the following:
1) Deficits in social-emotional reciprocity
2) Deficits in nonverbal communicative behaviors used for social interaction
3) Deficits in developing and maintaining relationships
B. Restricted, repetitive patterns of behavior, interests, or activities as manifested by at least two of the following:
1) Stereotyped or repetitive speech, motor movements, or use of objects
2) Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change
3) Highly restricted, fixated interests that are abnormal in intensity or focus
4) Hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment;
C. Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities)
D. Symptoms together limit and impair everyday functioning.

developmental disorders (PDD) and its five subcategories have been eliminated in favor of folding Autistic disorder and PDD-NOS into a single ASD diagnosis that must be present in early childhood. Controversially, Asperger syndrome/disorder has been removed from the ASD umbrella, instead folding it as well into the larger "spectrum" diagnosis, which has created a situation where some individuals with Asperger disorder under DSM-IV-TR will qualify for ASD under DSM-5, but others will not [26]. Additionally, disintegrative disorder and Rett disorder have been removed as subtypes of autism. Rett disorder, now known to be a result of genetic variations within the *MECP2* gene, is an example of how advances in medical science have changed the approach to the categorization and diagnosis of autism, and recognition of the neurobiological substrate of autism. Although ASD is now a single spectrum, there is allowance for individual variability, and the DSM-5 allows for concomitant diagnostic specifiers that include the pattern of onset and clinical course, etiological factors, intellectual/cognitive abilities, associated/co-morbid conditions, and the severity of ASD symptoms. Since the diagnosis of an ASD is based upon behavioral criteria, there is considerable phenotypic and genotypic heterogeneity within this class of disorders as well as ongoing debates over their clinical boundaries. Additionally, as with all DSM diagnoses, there are significant limitations in its clinical utility, as there has only been reliability of DSM diagnostic assignment when used by researchers or those with specific training, but not when disseminated to general practicing clinicians [27].

Nevertheless, despite better specificity with DSM-5, the diagnosis of ASD is still considered a "mental health" disorder, and thus, assigning an ASD diagnosis is not dependent on the array of known and potential biological causes and contributions to the disorder, and thus, does not recognize that ASD populations are biologically heterogeneous with extensive neurodiversity (Table 2). Yet, even the DSM-5 task force has recognized that ASD diagnostic paradigms for autism will need to evolve into biologically meaningful subphenotypes [2]. Clinically, children and adults with ASD demonstrate an array of neurological symptoms and signs signifying central, autonomic and/or peripheral nervous system dysfunction, as well as systemic disease (Table 3). In fact, the symptoms and signs of ASDs are similar to many types of neurological disorders. Thus, a comprehensive clinical evaluation can provide important information concerning the biological subphenotype of a child with ASD. Neurophysiological, laboratory, genetic, neuropsychological, neuroimaging (in select cases), and other neurodiagnostic data can enrich and enhance the biological phenotype and clinical profile of individuals with ASD.

The approach of biological sub-phenotyping for a neurobehavioral disorder may be new and novel to many. Yet, it should not be surprising. For example, clinicians would not be satisfied with diagnosing someone with "cancer" without more extensive evaluations to understand the type of cancer, the involved organ systems, and the extent and virility of the disease. No physician would provide therapeutic interventions for "cancer" without knowing the biological sub-phenotypes based on organ system, histology, radiology, and more. Without understanding the biological sub-phenotypes of cancer, treatments would only be targeting externalizing symptoms, such as pain or fatigue, and not alter the course of the disease. Then why have we departed from the medical model

Table 2 DSM-5 criteria for autism spectrum disorders: pitfalls and dilemmas

A. Ubiquitous and General Criteria
1) Nonspecific
2) Qualitative
3) Subjective
B. Ignores Neurobiological Etiologies
1) Diagnosis not dependent upon biological cause
C. Leads to Heterogenous Groups/Cohorts
1) Neurobiologically Diverse
2) Poor Phenotypic Differentiation
• Leads to:
[1] Flawed Research
[2] Poorly Targeted Therapies
[3] Missed Opportunities for Disease Modification, Prevention, Cure
D. Need to move to "biological sub-phenotyping" and "clinical profiling": "…*neurobiological studies will be useful for determining… whether the DSM-5 ASD diagnosis can be empirically parsed into biologically meaningful subphenotypes*…" [2]

Table 3 Autism spectrum disorders: neurological findings

A. Central Nervous System
1) Motor system: coordination, planning, tone
2) Cerebellar functioning
3) Motor stereotypies
4) Aberrations of head growth velocities
5) Neurodevelopmental delays
6) Neuropsychological deficits
7) Neuropathological changes
8) Neuroradiological findings
B. Autonomic Nervous System
1) Autonomic Over-Responsivity
2) Dysautonomia
C. Cognitive Disorders
D. Learning Disorders
E. Neurological Co-Morbidities: Epilepsy, Sleep
F. Medical Co-Morbidities: Gastrointestinal, Immunological, Hormonal, Metabolic
G. Neuropsychiatric Syndromes
H. Genotype-Phenotype Correlations

for the diagnosis and treatment of neurobehavioral/neurodevelopmental disorders? For too long the treatment of autism has been stuck at the stage of suppressing symptoms without understanding the biological nature of the disease. It is no longer sufficient to talk about broad, heterogeneous, dimensional, and subjective ASD diagnoses. Rather, it is important to define and characterize biological sub-phenotypes of ASDs so that outcomes and quality of life for affected individuals and their families can be improved by providing targeted and multimodal therapies based upon an understanding of various clinical profiles and presentations, underlying biological mechanisms, and associated co-morbidities of ASDs [28]. Eapen et al. have shown that understanding genotype-phenotype relationships can even help to predict response to behavioral interventions [29]. Additionally, a pragmatic, decision point, personalized medical approach to neurodiagnostic and medical investigations of ASDs can be cost-effective and have a major impact on public health by reducing or eliminating unnecessary diagnostic testing and ineffective therapies [28, 30].

Thus, assigning a DSM-5 diagnosis should only be a preliminary signal that leads to a comprehensive clinical and biological profile. By exploring for biological causes and contributions to ASD, such information can inform potential additional diagnostic pathways, and assist in developing targeted therapies, consistent with aspects of "personalized" and "precision" medicine. The assessment of a child or an adult with ASD should no longer cease with the DSM classification, but should trigger ongoing and vigilant biological sub-phenotyping and clinical profiling. Additionally, with ever changing knowledge in genetics, neurology, and other medical fields, previous non-diagnostic assessments should be revisited with consideration of re-evaluation and re-investigation for biological causes and contributions to the patient's condition.

Biological Phenotyping and Clinical Profiling

Clinical Evaluation

As in many areas of medicine, an insightful and detailed medical history coupled with a comprehensive physical, neurological, neuropsychological, and neurodevelopmental examination and evaluation can provide clues to the biological underpinnings of ASD (Table 3). Additionally, systemic organ system examination is essential to assess for co-morbid or associated medical complications.

Behavioral Evaluation

Repetitive and restricted behavior patterns are part of the definition of ASD. However, ASD can often be accompanied by severe maladaptive behavior patterns, including self-injury, aggressions and explosive outbursts. Many maladaptive behaviors are triggered by anxiety, other mood disorders and/or communication impairments, or may be triggered by systemic medical problems. Many children with ASDs and maladaptive behaviors are overmedicated; yet, there are many non-pharmacological approaches that can be as effective if there is an understanding of the behavioral, medical and neurological profile of the individual [31]. Thus, it is necessary to understand the functional *vs*. biological nature of maladaptive behaviors to determine their topography and function and provide effective treatment interventions.

There are important differences between learned behaviors that are maintained by socially mediated consequences ("functional" behaviors) and those that are unlearned or automatically reinforced and biologically driven [32, 33]. This differentiation is essential in determining maladaptive behaviors that can be targeted with behavioral management *vs*. those requiring a medical, pharmacological approach [31]. The lack of attention to the function, or environmental consequences, of behaviors and the reliance on indirect and subjective measures of behavior may explain why distinct behavioral phenotypes have been difficult to identify in ASDs [29]. Functional behavior assessments (FBA), including functional analysis (FA) can assess the environmental variables that evoke and maintain target behaviors (*e.g.*, behaviors that are socially mediated by parental attention or escape from work) and to differentiate these learned or operant behaviors from those that are automatically reinforced, or potentially biologically driven behaviors. FBAs involve direct observation and data collection for target behaviors and the environmental antecedents and consequences of those behaviors in the natural environment. In a FBA, specific antecedent conditions are arranged in a controlled setting and relevant consequences are provided following the occurrence of target behaviors (*i.e.*, access to attention, access to preferred items, escape from aversive stimuli or demands) to empirically determine if those consequences are functional reinforcers for the target behavior.

For individuals with self-injurious or aggressive behaviors for whom a behavioral function is not predominant, and thus, the behaviors are determined to be biologically driven, a systematic systemic survey for a medical cause, particularly painful precipitants, should be undertaken [31] (Table 4).

Neuropsychological Evaluation

Neuropsychological evaluation and testing can determine the degree of intellectual disability or cognitive impairment, characterize social deficits, and quantitate communication (language and social), even in minimally verbal children [34]. The differentiation between intellectual disability and cognitive shifting may impact externalizing problem behaviors [35]. Additionally, neuropsychological deficits can relate to

Table 4 Potential medical/systemic sources of pain and dysfunction triggering maladaptive behaviors

A. Dental
1) Infection
2) Trauma
B. Otolaryngological
1) Otitis Media infection
2) Impacted cerumen
C. Ophthalmological
1) Corneal abrasion
2) Glaucoma/increased intraocular pressure
D. Gastrointestinal
1) Constipation/bowel obstruction
2) Ulcer/*H. pylori infection*
3) Hepatitis/Pancreatitis
4) Celiac disease or gluten sensitivity
E. Pulmonary inflammation
F. Cardiovascular disease
G. Endocrine dysfunction
1) Thyroid disorders
2) Addison's disease
H. Hematological
1) Anemia
I. Genitourinary
1) Infection
2) Stones/Renal calculi
3) Dysuria
J. Orthopedic
1) Osteomyelitis
2) Fracture
K. Dermatological
1) Skin ulcers
2) Candidiasis
3) Pruritis
L. Rheumatological/Immunological
M. Medication side effects
N. Other infection/inflammation in any of the above organ systems

neurophysiological changes and abnormal metabolomics (see below).

Neurophysiological Testing

Epilepsy is a major co-morbid disorder in ASD, and ASD is a risk factor for the development of refractory epilepsy [36, 37]. The burden of epileptiform and spike activity in ASDs has been reported to be as high as 85 % in ASDs associated with intellectual disabilities [38]. Cortical electrical aberrations and abnormalities are frequent in children with ASD and forms of language impairment, in many cases manifesting as epilepsy, and in other cases presenting "sub-clinically" with neuropsychological disruption but no observable seizures [37, 39, 40]. Certain electroencephalography (EEG) patterns have been associated with autistic regression, and may be treatable in some cases [37, 41, 42]. Additionally, "subclinical spikes" or interictal epileptiform discharges associated with cognitive impairment or behavioral aberrations may improve with antiepileptic drug or other types of therapies [39, 43, 44]. With utilization of behavioral desensitization techniques and sensor nets, EEG information can be obtained in behaviorally challenged individuals without sedation or restraint [45].

Gastrointestinal Assessment

Gastrointestinal (GI) disorders are often associated with ASDs, exacerbating underlying maladaptive behaviors and hindering therapeutic progress [46–50]. Microbiome imbalance can contribute to maladaptive behaviors in autism, and possibly contribute to the development of autism itself [48]. Thus, homeostasis of the microbiome is an important treatment intervention for certain individuals with ASD.

Inflammatory/Immunologic/Infectious Complications

Systemic immunologic disorders can complicate the symptoms of ASDs, and studies have demonstrated that neuroinflammation stems from innate rather than adaptive activation of the immune system [51–54]. Awareness of the influence of potentially treatable immunological dysfunction and the deleterious effects of infection/inflammation should trigger vigilance in identification of these factors in developing a clinical profile for children with ASD.

Elemental and Co-factor Deficiencies

Children with ASDs often have inadequate dietary intake or gastrointestinal malabsorption, leading to vitamin and mineral deficiencies, which can further compound impairment of brain development or exacerbate underlying metabolic disorders [49, 50]. Additionally, certain pharmacological therapies can lead to nutritional or micronutrient deficiencies.

Hormonal Integrity

Disruption of the hypothalamic-pituitary-adrenal (HPA) axis during fetal and/or early childhood brain development has been implicated in autism. Deficiency of thyroid hormones during critical brain development is a well-recognized cause in children with mental retardation, psychomotor delay and deafness. Animal models have shown that fetal or neonatal thyroid deficiency can cause behavioral and neuropathological findings consistent with autism [55, 56]. Iodine deficiency, dietary antithyroid agents, and environmental toxins can affect maternal thyroid function during pregnancy and go undetected. Some

common plant isoflavonoids and environmental toxins such as herbicides, bisphenol A, and phthalates are gaining interest as being thyrotoxic or neurotoxic [57]. Dysfunction of the HPA axis may be causative or contributory to the pathogenesis of some ASD phenotypes, and is often treatable.

Autonomic Nervous System

Dysregulation of the autonomic nervous system (ANS) can exacerbate underlying maladaptive behavioral tendencies, or be a complication of adjunctive pharmacological therapies [58]. Autonomic dysregulation may be incorrectly labeled as a sensory processing disorder [1]. Clinicians treating ASD often overlook ANS over-responsivity, which in some instances can be related to mitochondrial dysfunction and/or channelopathies [28, 59]. Research has demonstrated that children with ASD can have blunted autonomic arousal to visual or auditory social stimuli, for example, as measured by cardiac and galvanic skin responses [60]. There is also evidence for increased sympathetic tone or parasympathetic hypofunction in ASDs with or without clinical complaints of autonomic dysfunction occurring as young as three years of age [61, 62]. Symptoms of mood disorder, anxiety, sensory over-responsiveness, poor attention span, sleep disorders, and gastrointestinal dysfunction are among the frequent manifestations of autonomic dysfunction in ASDs, and can be part of the symptom complex of mitochondrial disorders or channelopathies [28, 61].

Sleep Disorders

Sleep disorders and disturbances are very common in children with ASDs. The prevalence of sleep disorders in ASD is reported to be between 44 % and 83 % including difficulty in settling to sleep, lengthy episodes of night waking with or without confusion, crying or screaming during sleep (sleep terror), bruxism, enuresis, REM sleep behavior disorder, early morning awakening, shortened night sleep, day time sleepiness and irregularities of the circadian rhythm [63, 64]. Unrecognized and untreated sleep disorders can be causative or exacerbate maladaptive behavior patterns [65, 66]. Additionally, insomnia and night awakenings cause loss of sleep in other family members, affecting their health and abilities as a caretaker. Problematic sleep patterns such as sleep onset and maintenance insomnia, and reduced sleep efficiency have been reported in pre-school children with autism by questionnaire and actigraphic studies [67]. Circadian rhythm dysfunction may contribute to the insomnia observed in ASD based on the abnormal melatonin levels in ASD and favorable effect of melatonin in treating insomnia in ASD children [68]. These types of sleep disorders may be a surrogate marker for underlying metabolic disorders and channelopathies [67].

Genotyping

There is a genetic etiological predisposition for most of the causes and complications of ASD. Genotype-phenotype relationships can not only identify new and novel biological mechanisms of ASDs, but also can eliminate unnecessary diagnostic testing; change clinical management through improved diagnostic acumen, thus reducing the reliance on ineffective therapies; alert clinicians to potential deleterious involvement of other organ systems; and inform pragmatic interventions based on genotype-phenotype relationships. Although cost and accessibility of genetic testing laboratories can be a barrier, these tests are proving to be cost effective [30]. Additionally, NextGen sequencing is uncovering pathogenic variants that are likely causative or contributory to ASD in over 40 % of cases, and even higher rates of "actionable" findings ("actionable" being defined as identifying potential treatment interventions with medications or specific metabolic/enzymatic supplements or dietary options, triggering additional diagnostic investigations/testing, providing a presumed biological cause or contributor to the patients phenotype, alerting to other organ system involvement, or indicating avoidance of certain medications) [28, 69–71].

Metabolomics

Biologically driven maladaptive behaviors are increasingly being recognized as concomitants of mitochondrial disorders and channelopathies in ASDs with intellectual disabilities, as are many psychiatric disorders [72–76]. Mitochondrial disorders and/or channelopathies are increasingly being recognized as causative or contributory to the development and maintenance of epilepsy, which is a common concomitant of ASD, and may share pathophysiological origins [77, 78]. Mitochondrial disorders/dysfunction can cause gastrointestinal dysmotility and be associated with cyclical vomiting syndrome and migraine [59, 79, 80]. Inflammation can aggravate and/or exacerbate underlying mitochondrial disorders or channelopathies, and mitochondrial integrity is crucial for immune system functioning, and may be causal in triggering the ASD phenotype [76]. Also, certain inborn errors of metabolism respond to vitamin/co-factor supplementation, such as folinic acid for cerebral folate deficiency and anti-oxidants, carnitine, and other types of supplements for forms of mitochondrial disorders [76, 81–83]. Thus, clinical, laboratory, enzymological, and genetic metabolomics assessments are an important component of the biological phenotyping and clinical profiling of ASD.

Neuroimaging

Although structural [computed tomography (CT), magnetic resonance imaging (MRI)] and functional [functional MRI

Table 5 Biological sub-phenotyping and clinical profiling for autism spectrum disorders

A. Neurological Evaluation/Examination
B. General Physical Examination
C. Neurophysiological Testing
D Assessment for Co-morbid/Co-occurring Conditions
1) Sleep Disorders
2) Autonomic Nervous System/Dysautonomia
3) Gastrointestinal/Nutritional Assessment
4) Endocrinological Integrity
5) Co-factors/Elemental Deficiencies
6) Inflammatory/Immunological/Infectious Complications
7) Neuropsychiatric Disorders
E. Neuropsychological Evaluation
F. Functional Behavior Analysis
G. Laboratory Assessments
1) Metabolomics
2) Hormonal analysis
3) Genotyping
H. Neuroimaging

(fMRI), positron emission tomography (PET), and other modalities] neuroimaging research has identified changes consistent with neural network disorganization and disconnectivity, neuroimaging is of clinical utility in only select cases [24]. Neuroimaging should be considered when there are focal, new or progressive abnormalities detected on clinical neurological examination or neurophysiological (EEG) testing. Neuroimaging should also be considered in cases of ASD with concomitant/co-morbid epilepsy, brain diseases associated with autism (Tuberous Sclerosis for example), or if there are clinical suspicions of cerebrovascular disease or other structural brain abnormalities.

Conclusions

The slow recognition of ASD as a neurobiological disorder and the limited abilities of the medical community to reverse the progression or core features of autism have created a population vulnerable to manipulation and deception by charlatans. Or, as Paul Offit has written, patients with ASD and their families can fall prey to "False Prophets" who preach about unproven cures and forms of "snake oil" [84]. However, the understanding of autism has evolved, and we are now at a crossroad whereby ASD can be understood and defined by a fusion of genetics, epigenetics, metabolomics, neurophysiology, neurology, immunology, endocrinology, and gastroenterology that can explain the aberrant behavioral, neurodevelopmental and intellectual manifestations of autism. The advent of understanding the biological sub-phenotypes of ASD, along with targeted medical therapies, coupled with a multimodal therapeutic approach that encompasses behavioral, educational, social, speech, occupational, creative arts, and other forms of therapies has created a new and exciting era for individuals with ASD and there families: "personalized" and "precision" medical care based upon underlying biological sub-phenotypes and clinical profiles (Table 5). The identification and understanding of ASD is crucial, as earlier interventions are associated with improved outcomes [85, 86]. Although much more research and progress is needed, for many individuals and their families dealing with the scourge of autism, their long and frustrating diagnostic journey and quest for effective, pragmatic therapies is beginning to come to an end, with a hope for improved outcomes and quality of life.

Compliance with Ethical Standards

Conflict of Interest Dr. Mintz serves on the editorial boards of the Journal of Child Neurology and Vision Development and Rehabilitation; has functioned as Principal Investigator for clinical trials research contracted through the Clinical Research Center of New Jersey, LLC (CRCNJ) sponsored by the following companies: Sunovion, Pfizer, Shire, Eisai, Inc, and Allergan; is the principle investigator for research funded by the State of New Jersey through the Governor's Council for Medical Research and Treatment of Autism; is President, CEO, and Founder of The Center for Neurological and Neurodevelopmental Health, LLC, (CNNH) and CRCNJ; and is President of NeurAbilities, a 501(3)c Public Charity.

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References

1. Rapin I, Tuchman RF. Where we are: overview and definitions. In: Tuchman R, Rapin I, editors. Autism: A Neurological Disorder of Early Brain Development, International Child Neurology Association. London: Mac Keith Press; 2006. p. 1–18.
2. Frazier TW, Youngstrom EA, Speer L, et al. Validation of proposed DSM-5 criteria for autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2012;51:28–40.e3.
3. Mandy WP, Charman T, Skuse DH. Testing the construct validity of proposed criteria for DSM-5 autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2012;51:41–50.
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed.-text revision (TR). Washington, DC: American Psychiatric Association; 2000.
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
7. Volkmar FR, Reichow B, McParland J. Classification of autism and related conditions: progress, challenges, and opportunities. Dialogues Clin Neurosci. 2012;14:229–37.

8. Volkmar FR, State M, Klin A. Autism and autism spectrum disorders: diagnostic issues for the coming decade. J Child Psychol Psychiatry. 2009;50:108–15.
9. Kanner L. Autistic disturbances of affective contact. Nervous Child. 1943;2:217–50.
10. Olmsted D, Blaxill M. Leo Kanner's mention of 1938 in his report on autism refers to his first patient. J Autism Dev Disord. 2016;46: 340–1.
11. Asperger H. Die autistischen psychopathen im Kindesalter. Arch fur Psychiatrie und Nerven Krankheiten. 1944;117:76–136.
12. Heilpädagogik AH. Einführung in die psychopathologie des KindesfürÄrzte, Lehrer, psychologen und Fürsorgerinnen. Wien: Springer; 1952.
13. Fellowes S. Did Kanner actually describe the first account of autism? The mystery of 1938. J Autism Dev Disord. 2015;45:2274–6.
14. Frith U, Morton J, Leslie AM. The cognitive basis of a biological disorder: autism. Trends Neurosci. 1991;14:433–8.
15. Brumback RA, Harper CR, Weinberg WA. Nonverbal learning disabilities, Asperger's syndrome, pervasive developmental disorder: should we care? J Child Neurol. 1996;11:427–9.
16. Klin A, Volkmar FR, Sparrow SS, Cicchetti DV, Rourke BP. Validity and neuropsychological characterization of Asperger syndrome: convergence with nonverbal learning disabilities syndrome. J Child Psychol Psychiatry Allied Discipl. 1995;36:1127–40.
17. Rourke BP, Tsatsanis KD. Nonverbal learning disabilities and Asperger syndrome. In: Klin A, Volkmar FR, editors. Asperger syndrome. New York, NY: The Guilford Press; 2000. p. 231–53.
18. Baker JP. Autism at 70 -redrawing the boundaries. N Engl J Med. 2013;369:1089–91.
19. Volkmar FR, Nelson DS. Seizure disorders in autism. J Am Acad Child Adolesc Psychiatry. 1990;29:127–9.
20. Folstein SE. Genetic aspects of infantile autism. Annu Rev Med. 1985;36:415–9.
21. Rutter M. Childhood schizophrenia reconsidered. J Autism Child Schizophrenia. 1972;2:315–37.
22. Kolvin I. Studies in the childhood psychoses. I. Diagnostic criteria and classification. Br J Psychiatry. 1971;118:381–4.
23. Johnston MV, Blue ME. Neurobiology of autism. In: Tuchman R, Rapin I, editors. Autism: A Neurological Disorder of Early Brain Development, International Child Neurology Association. London: Mac Keith Press; 2006. p. 79–92.
24. Herbert MR, Caviness VS. Neuroanatomy and imaging studies. In: Tuchman R, Rapin I, editors. Autism: A Neurological Disorder of Early Brain Development, International Child Neurology Association. London: Mac Keith Press; 2006. p. 115–40.
25. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington, DC: American Psychiatric Association; 1980.
26. Hippler K, Klicpera C. A retrospective analysis of the clinical case records of 'autistic psychopaths' diagnosed by Hans Asperger and his team at the university Children's hospital, Vienna. Philos Trans R Soc Lond Biol Sci. 2003;358:291–301.
27. Kirk SA, Kutchins H. The myth of the reliability of DSM. J Mind Behav. 1994;15:71–86.
28. Mintz M, Chadehumbe M, Barabas R, et al. The clinical utility of relevant exome panels for autism spectrum disorders and intellectual disabilities. Ann Neurol. 2014;76:S246. (Poster Presentation at the 43rd Annual Meeting of the Child Neurology Society, Columbus, Ohio, 2014).
29. Eapen V, Črnčec R, Walter A. Exploring links between genotypes, phenotypes, and clinical predictors of response to early intensive behavioral intervention in autism spectrum disorder. Front Hum Neurosci. 2013;7:567.
30. Soden SE, Saunders CJ, Willig LK, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. Sci Transl Med. 2014;6:265ra168.
31. Mintz M, Allesandri M, Curatolo P. Treatment approaches for autistic spectrum disorders. In: Tuchman R, Rapin I, editors. Autism: A Neurological Disorder of Early Brain Development, International Child Neurology Association. London: Mac Keith Press; 2006. p. 281–307.
32. Iwata BA, Dorsey MF, Slifer KJ, Bauman KE, Richman GS. Toward a functional analysis of self-injury. J Appl Behav Anal. 1994;27:197–209.
33. Beavers GA, Iwata BA, Lerman DC. Thirty years of research on the functional analysis of problem behavior. J Appl Behav Anal. 2013;46:1–21.
34. Kasari C, Brady N, Lord C, Tager-Flusberg H. Assessing the minimally verbal school-aged child with autism spectrum disorder. Autism Res. 2013;6:479–93.
35. Visser EM, Berger HJ, Van Schrojenstein Lantman-De valk HM, et al. Cognitive shifting and externalising problem behaviour in intellectual disability and autism spectrum disorder. J Intellect Disabil Res. 2015;59:755–66.
36. Sansa G, Carlson C, Doyle W, et al. Medically refractory epilepsy in autism. Epilepsia. 2011;52:1071–5.
37. Roulet-Perez E, Deonna. Autism, Epilepsy and EEG Epileptiform Activity. In: Tuchman RF, Rapin I, editors. Autism: A Neurological Disorder of Early Brain Development, International Child Neurology Association. London: Mac Keith Press; 2006. p. 174–88.
38. Yasuhara A. Correlation between EEG abnormalities and symptoms of autism spectrum disorder (ASD). Brain Dev. 2010;32: 791–8.
39. Mintz M, LeGoff D, Scornaienchi J, et al. The underrecognized epilepsy spectrum: the effects of levetiracetam on neuropsychological functioning in relation to subclinical spike production. J Child Neurol. 2009;24:807–15.
40. Mintz M, Szklarski L, Chadehumbe M, et al. Unexpected subclinical spikes: clinical and neurophysiological correlations. Abstract No. 2.016. In: American Epilepsy Society annual meeting, www.aesnet.org. Washington: Seattle; 2014.
41. Tuchman RF, Rapin I. Regression in pervasive developmental disorders: seizures and epileptiform electroencephalogram correlates. Pediatrics. 1997;99:560–6.
42. Nass R, Devinsky O. Autistic regression with rolandic spikes. Neuropsychiatry Neuropsychol Behav Neurol. 1999;12:193–7.
43. Sanchez Fernandez I, Loddenkemper T, Galanopoulou AS, Moshe SL. Should epileptiform discharges be treated? Epilepsia. 2015;56: 1492–504.
44. Chapman KE, Specchio N, Shinnar S, Holmes GL. Seizing control of epileptic activity can improve outcome. Epilepsia. 2015;56: 1482–5.
45. Szklarski L, Mintz M. Dense-array electroencephalography (dEEG) improves compliance and acquisition without sedation or restraint for children and adults with behavioral challenges. Abstract No. 3.133. In: American Epilepsy Society Annual Meeting, www.aesnet.org. Pennsylvania: Philadelphia; 2015.
46. Nikolov RN, Bearss KE, Lettinga J, et al. Gastrointestinal symptoms in a sample of children with pervasive developmental disorders. J Autism Dev Disord. 2009;39:405–13.
47. Valicenti-McDermott MD, McVicar K, Cohen HJ, et al. Gastrointestinal symptoms in children with an autism spectrum disorder and language regression. Pediatr Neurol. 2008;39:392–8.
48. Buie T, Campbell DB, Fuchs GJ 3rd, et al. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. Pediatrics. 2010;125:S1–18.
49. Buie T, Fuchs GJ 3rd, Furuta GT, et al. Recommendations for evaluation and treatment of common gastrointestinal problems in children with ASDs. Pediatrics. 2010a;125:S19–29.
50. Buie T. Potential etiologic factors of microbiome disruption in autism. Clin Ther. 2015;37:976–83.

51. Zimmerman AW, Connors SL, Matteson KJ, et al. Maternal antibrain antibodies in autism. Brain Behav Immun. 2007;21: 351–7.
52. Fatemi SH, Stary JM, Halt AR, Reatmuto GR. Dysregulation of reelin and bcl-2 proteins in autistic cerebellum. J Autism Dev Disord. 2001;31:529–35.
53. Jyonouchi H, Sun S, Itokazu N. Innate immunity associated with inflammatory responses and cytokine production against common dietary proteins in patients with autism spectrum disorders. Neuropsychobiology. 2002;46:76–84.
54. Jyonouchi H, Geng L, Ruby A, et al. Dysregulated innate immune responses in young children with autism spectrum disorders: their relationship to gastrointestinal symptoms and dietary intervention. Neuropsychobiology. 2005;51:77–85.
55. Sadamatsu M, Kanai H, Xu X, et al. Review of animal models for autism: implication of thyroid hormone. Congenit Anom. 2006;46: 1–9.
56. Roman GC. Autism: transient in utero hypothyroxinemia related to maternal flavonoid ingestion during pregnancy and to other environmental antithyroid agents. J Neurol Sci. 2007;262:15–26.
57. Stein TP, Schluter MD, Steer RA, et al. Bisphenol A exposure in children with autism spectrum disorders. Autism Res. 2015;8:272–83.
58. Ming X, Julu PO, Brimacombe M, Connor S, Daniels ML. Reduced cardiac parasympathetic activity in children with autism. Brain Dev. 2005;27:509–16.
59. Zaki EA, Freilinger T, Klopstock T. Two common mitochondrial DNA polymorphisms are highly associated with migraine headache and cyclic vomiting syndrome. Cephalalgia. 2009;29:719–28.
60. van Engeland H. The electrodermal orienting response to auditive stimuli in autistic children, normal children, mentally retarded children, and child psychiatric patients. J Autism Dev Disord. 1984;14: 261–79.
61. Ming X, Brimacombe M, Chaaban J, Zimmerman-Bier B, Wganer GG. Autism spectrum disorders: concurrent clinical disorders. J Child Neurol. 2008;23:6–13.
62. Ming X, Stein TP, Barnes V, Rhodes N, Guo L. Metabolic perturbance in autism spectrum disorders: a metabolomics study. J Proteome Res. 2012;11:5856–62.
63. Williams PG, Sears LL, Allard A. Sleep problems in children with autism. J Sleep Res. 2004;13:265–8.
64. Malow BA, Marzec ML, McGrew SG, et al. Characterizing sleep in children with autism spectrum disorders: a multidimensional approach. Sleep. 2006;29:1563–71.
65. Schreck KA, Mulick JA, Smith AF. Sleep problems as possible predictors of intensified symptoms of autism. Res Dev Disabil. 2004;25:57–66.
66. Ming X, Walters AS. Autism spectrum disorders, attention deficit/ hyperactivity disorder, and sleep disorders. Curr Opin Pulm Med. 2009;15:578–84.
67. Wiggs L, Stores G. Sleep patterns and sleep disorders in children with autistic spectrum disorders: insights using parent report and actigraphy. Dev Med Child Neurol. 2004;46:372–80.
68. Johnson KP, Malow BA. Sleep in children with autism spectrum disorders. Curr Neurol Neurosci Rep. 2008;8:155–61.
69. Lu JT, Campeau PM, Lee BH. Genotype-phenotype correlation-promiscuity in the era of next-generation sequencing. N Engl J Med. 2014;371:593–6.
70. Srivastava S, Cohen JS, Vernon H, et al. Clinical whole exome sequencing in child neurology practice. Ann Neurol. 2014;76: 473–83.
71. Yang Y, Muzny DM, Reid JG, et al. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. N Engl J Med. 2013;369:1502–11.
72. Gardner A, Boles RG. Comment on treatment of psychiatric illness in patients with mitochondrial disease. Psychosomatics. 2011;52: 497–8.
73. Verge B, Alonso Y, Miralles C. New evidence for the involvement of mitochondrial inheritance in schizophrenia: results from a cross-sectional study evaluating the risk of illness in relatives of schizophrenia patients. J Clin Psychiatry. 2012;73:684–90.
74. Gardner A, Boles RG. Mitochondrial energy depletion in depression with somatization. Psychother Psychosom. 2008;77:127–9.
75. Burnett BB, Gardner A, Boles RG. Mitochondrial inheritance in depression, dysmotility and migraine? J Affect Disord. 2005;88: 109–16.
76. Legido A, Jethva R, Goldenthal MJ. Mitochondrial dysfunction in autism. Semin Pediatr Neurol. 2013;20:163–75.
77. Singh NA, Pappas C, Dahle EJ, et al. A role of SCN9A in human epilepsies, as a case of febrile seizure and as a potential modifier of Dravet syndrome. PLoS Genet. 2009;5:1–12.
78. Goldenthal MJ, Kuruvilla T, Damle S, et al. Non-invasive evaluation of buccal respiratory chain enzyme dysfunction in mitochondrial disease: comparison with studies in muscle biopsy. Mol Genet Metab. 2012;105:457–62.
79. Camilleri M, Carlson P, Zinsmeister AR, et al. Mitochondrial DNA and gastrointestinal motor and sensory functions in health and functional gastrointestinal disorders. Am J Physiol Gastrointest Liver Physiol. 2009;296:G510–6.
80. Boles RG. High degree of efficacy in the treatment of cyclic vomiting syndrome with combined co-enzyme Q10, L-carnitine and amitriptyline, a case series. BMC Neurol. 2011;11:102.
81. Curtis LT, Patel K. Nutritional and environmental approaches to preventing and treating autism and attention deficit hyperactivity disorder (ADHD): a review. J Altern Complement Med. 2008;14: 79–85.
82. Frye RE, Sequeira JM, Quadros EV, James SJ, Rossignol DA. Cerebral folate receptor autoantibodies in autism spectrum disorder. Mol Psychiatry. 2013;18:369–81.
83. Frye RE, Delatorre R, Taylor H, et al. Redox metabolism abnormalities in autistic children associated with mitochondrial disease. Transl Psychiatry. 2013;3:e273.
84. Offit PA. Autism's false prophets. New York: Columbia University Press; 2008.
85. Zwaigenbaum L, Bauman ML, Fein D, et al. Early screening of autism spectrum disorder: recommendations for practice and research. Pediatrics. 2015;136:S41.
86. Zwaigenbaum L, Bauman ML, Choueiri R, et al. Early intervention for children with autism spectrum disorder under 3 years of age: recommendations for practice and research. Pediatrics. 2015;136: S60-81.