A framework for autism

Individuals with autism or Asperger syndrome come with many problems. They are diagnosed because of their poor social relations, including all forms of human communication. They also have restricted interests and inappropriate, rigid patterns of behavior. They may have abnormal responses to sensory stimuli. In the case of autism, these children have major language abnormalities, including muteness or severe delays obvious by three years of age. The majority of children called autistic are classified as retarded when they reach school age, although this is not always accurate. Individuals with Asperger syndrome are less obvious as young children because their language usually is not delayed, but contains odd characteristics such as being very formal with a peculiar voice; they usually are not classified as retarded. Both children with autism and Asperger syndrome may be savants. Most of the subgroups within the autism/Asperger syndrome are predominantly male.

The autistic/Asperger children may have many associated problems. A difficult one is food faddism, such as food refusal, food fads and pica. Unusual sleep patterns haunt their parents. The children can be aggressive toward others or continually injure themselves.

However in spite of the suffering of these children and their families, a certain haphazardness can be observed in the approach to medical therapies for individuals with such serious brain problems. This is due to the fact that if ever there was a field of medicine that was in a state of major confusion and contradictions, it is autism/Asperger today. This has happened in spite of a generation of careful standardization of criteria. The results from major centers with reputations for excellence often contradict each other regarding which areas of neuroanatomy are affected as deduced from brain imaging, what kind of pathology underlies this symptom complex and exactly what is the electrophysiology. The accepted pattern of publication in medicine of a first study being confirmed by a second one does happen, but is still unusual. There is even a dispute regarding whether the patients should receive a medical work-up in the first place in order to establish a rational approach to treatment. Badly needed are some guidelines for clinicians, researchers and parents – a framework inside which to reorder the older information and place new studies. This paper attempts to address this problem and proposes one such framework.

Norman Geschwind, a brilliant behavioral neurologist of the twentieth century, introduced the concept of the cerebral disconnection syndromes as central to the classic syndromes of behavioral neurology[1]. For example, the signature syndromes of the brain, such a Wernicke's aphasia or Broca's aphasia, were originally based on reports of the effect of lesions in a localized brain area. But it is unlikely that neuropsychiatric disorders are limited to a single anatomical location; they reflect the dysfunction of one or more neural circuits which pass through several different areas of the brain[2]. Research studies document that the complex behavioral domains are coordinated by large-scale distributed networks and damage to any network component can impair behavior in the relevant domain[3]. Focal brain lesions that interfere with these processing streams lead to Geschwind's disconnection syndromes, such as apraxia, prosopagnosia, color anomia, amnesia etc.

Regarding the behavioral symptoms of autism, there is evidence of interference of the behavior domain circuits all the way from the prefrontal cortex down to the cerebellum. It appears that the pathways can be interrupted at a number of different anatomical levels or at a variety of synaptic sites. But autism is more than a disconnection of functional existing pathways. Based on evidence from functional MRI and other imaging studies[4) 5) 6)], abnormal neural pathways may have been formed during prenatal neurodevelopment in many children with autistic symptoms. The information about behavioral circuits has been gathered from the many different diseases that have autistic symptoms in their spectrum *(Table 1, Table 2, Table 3, Table 4)*.

Some of these studies closely match changes in the neural circuits as described in the cerebellar cognitive affective syndrome, which is based on a study of diseases confined to the cerebellum.[7)] The major pathological studies in autism which included the Purkinje cells of cerebellum actually do replicate each other showing a decreased density of these cells in most cases[8) 9) 10)] – in an exception to the rule of failed replication of autism studies. One such neural circuit is the dentato-thalamo-cortical pathway which has been found impaired in a number of studies in autism[11)]. It is pos-

Table One: **The majority of patients have core autistic symptoms long term**

- Chromosome 15q11–13 syndrome
- Infantile autistic bipolar disorder (IABD)
- Miles-Hillman subgroup of nonstigmatized phenotypes
- Majority «still undiagnosed»

Table Two: **The majority of patients have transient symptoms of autism**

- Transient until improved:

  Zappella dysmaturational syndrome with familial complex tics

- Transient until further deterioration:

  The Rett Complex

Table Three: **The minority of patients have autistic symptoms**

- Toxic fetal encephalopathies: – alcohol, cocaine, lead, thalidomide, valproate
- Perinatal toxicity: – ROP (retinopathy of prematurity)
- Infectious fetal encephalopathies: – rubella, herpes simplex
- Space-occupying lesions: – cysts, brain tumors
- Genetic and MAS/MR disease entities:
  - Angelman syndrome
  - Anorexia nervosa
  - CATCH 22
  - Charge Association
  - Cohen syndrome
  - Cole-Hughes macrocephaly syndrome
  - Cowden syndrome
  - DeLange syndrome
  - Down syndrome
  - Ehlers-Danlos syndrome
  - Fragile X syndrome
  - Goldenhar syndrome
  - Hypomelanosis of Ito
  - Joubert syndrome
  - Leber congential amaurosis
  - Lujan-Fryan syndrome
  - Moebius sequence
  - Neurofibromatosis 1
  - Neuroaxonal dystrophy
  - Noonan syndrome
  - Smith-Magenis syndrome
  - Sotos syndrome
  - Steinert's myotonic dystrophy
  - Tourette syndrome
  - Tuberous sclerosis complex
  - Turner syndrome
  - Williams syndrome

sible that this pathway will stand the test of time as one of the circuits that is dysfunctional in some individuals with autistic symptoms.

The process of cortical ontogeny in the human is complex with each of the events of brain development having its own critical period, a time period before or after birth during which a particular set of enabling factors is essential for normal cortical development. Take the example of the neurotrophins, a category of related growth-promoting substances that are essential for normal cortical development and plasticity by being a factor in the regulation of synaptogenesis and synaptic transmission[12]. In a study of archived neonatal blood of children who later were diagnosed as autistic, Nelson and colleagues found very elevated levels of certain neurotrophins and also certain neuropeptides – BDNF, NT4/5, VIP and CGRP – in 99% of the children with autism compared to controls[13]. The Rett syndrome gene MECP2 has been shown to regulate expression of BDNF and maternal infections also affect BDNF expression in the fetus[14]. The study by Nelson and colleagues was found similar elevations of the neurotrophins and neuropeptides in 97% of the children with later mental retardation, including those with Down syndrome. It is great interest that no measure distinguished the children with autism from those with mental retardation. This study could be construed as additional evidence that the autistic syndrome, like the mental retardation syndromes, begins prior to birth in the overwhelming number of cases.

Table Four: **Metabolic disorders which sometimes have autistic symptoms**

- Adenylosuccinate lyase deficiency
- Cytosolic 5' nucleotidase abnormality
- Metachromatic leukodystrophy
- Mucopolysaccharidosis
- Peroxisomal disorders
- Phenylketonuria
- Pyridoxine-dependency syndrome
- Succinic semialdehyde dehydrogenase deficiency

In fact the autistic syndrome shares many of the characteristics of the mental retardation syndrome. They both impair the brain in almost all cases during the gestational neurodevelopmental time frame and they are both present at birth but not clinically apparent. Although both syndromes have

a percentage of children who develop epilepsy, the autistic syndrome actually has a higher prevalence of children with seizure disorders than a population with severe mental retardation[15]. Low-functioning children with autism do not have the same neuropsychological profile as youngsters classified as retarded; nevertheless, IQ is the single best predictor of outcome in both[16]. It is not unreasonable to suppose that, like mental retardation, the autistic syndrome probably is another syndrome of many different underlying disease entities. If autism is such a diverse syndrome, then each medical center working with autistic patients is likely to be studying a different mix of underlying disease entities; this would account for the failure of these centers to replicate each others work.

Thus, in summary as a working framework, autism/Asperger might be considered a syndrome of many disease entities whose behavioral symptoms occur due to malfunction of the distributed behavioral neural networks. This malfunction is due to aberrant prenatal neurodevelopment, leading either to 1) abnormally formed neural circuits or to 2) dysfunction of network components of standard neural pathways.

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