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CHAPTER ONE

The putative etiology and prevention of autism

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Abstract

Since the initial psychological report by Leo Kanner in 1943, relatively little formal biochemical/neurological research on the cause of autism, other than peripheral searches for genomic mutations, had been carried until the end of the 20th century. As a result of studies on twin sets and the conclusion that autism was largely a hereditary defect, numerous investigations have sought various genetic faults in particular. However, such studies were able to reveal a plausible etiology for this malady in only a small percentage of instances.

Key bio-molecular characteristics of this syndrome have been uncovered when the potential roles of the glia were studied in depth. Findings related to biochemical deficiencies appearing early in the newborn, such as depressed IGF-1 (insulin-like growth factor #1) in neurogenesis/myelination, are becoming emphasized in many laboratories. Progress leading to timely diagnoses and subsequent prevention of central nervous system dysconnectivity now seems plausible. The tendency for an infant to develop autism may currently be determinable and preventable before irreversible psychosocial disturbances become established.

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These discussions about glial function will be inter-spersed with comments about their apparent relevance to autism. The concluding portion of this presentation will be a detailed review and summation of this diagnosis and prevention proposition.

Abbreviations

AKT protein kinase B
ALS acid labile-subunit
ASD autism spectrum disorder
BBB blood-brain barrier
BDNF brain-derived neurotrophic factor
CNS central nervous system
CSF cerebrospinal fluid
GSK3B glycogen synthase kinase-3-beta
fMRI functional magnetic resonance imaging
IGF insulin-like growth factor
IGFBP IGF binding protein
IGFR IGF receptor
IL interleukin
IRS insulin receptor substrate
mTOR mammalian target of rapamycin
NGF nerve growth factor
OL oligodendrocyte
Olig1 oligodendrocyte transcription factor 1
OPC oligodendrocyte precursor cell
P13K phosphoinositide-3-kinase
PNS peripheral nervous system
PROM premature rupture of membranes
PTEN phosphatase and tensin homolog
SNP single nucleotide polymorphism
VSGA very small for gestational age

1. Background

Beginning in 1943, reports began to appear authored by Leo Kanner and others which described an abnormal form of behavior starting in children around ages 1–4 years.[1] For several years, the phenomenon was considered to be a consequence of dysfunctional parenting. For example, the theory of the "refrigerator mom" blamed the abnormal behavior, which persisted into adulthood, as a lack of affectionate parental attention toward their youngsters displayed by non-tender mothers in particular.[2] Later, this concept was discredited.

Toward the end of the 20th century, attention turned toward genetics to explain this condition. In particular, many sets of monozygotic twins were both observed to display autistic behavior in up to 90% of the cases.[3] Thus, it was assumed that the etiology of *all* cases of autism had a genetic origin. However, extensive studies identified major mutations in only 5–10% of autism occurrences. On the other hand, some children with major genetic defects had some behavioral traits similar to autism but not a complete set of such traits as are found in classical autism.[4]

According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) published in May, 2013, autism was defined by cases which displayed at least three persistent deficits in the areas of

(1) Social and emotional reciprocity,
(2) Non-verbal communication behaviors,
(3) Developing and maintaining appropriate relationships,
(4) Repetitive speech, movements, or employing of objects,
(5) Excessive maintenance of routines, formalized patterns of verbal/nonverbal behavior, or excessive refusal to change,
(6) Highly restricted, unusual, fixated interests (e.g., strong preoccupation with atypical objects), and
(7) Hyper- or hypo-reactivity to sensory input or extraordinary interest in appreciated aspects of the environment.

Until that time, variations of autistic behavior were grouped by specific names such as Asperger's syndrome, autistic disorder, and childhood disintegrative disorder, with various levels of seriousness. From that point in time onward, the differing presentations of this condition were taken to be degrees of symptom severity of the same malady. Hence, ASD (autism spectrum disorder) was understood to mean a group of conditions of the same malady but of varying functionality and intensities of sign presentations[5] (see Sections 8 and 10).

In contradistinction, other ailments were defined by specific genetic errors which were like autism spectrum disorder (ASD) in only *some* of the characteristics they displayed (see Table 1). Although thought to be differing representations of ASD, they were reexamined because these distinct Mendelian human diseases made autism seem to be a similar but genetically not identical heterogeneous condition. In many such instances, rare or common varieties of multiple genes make their genomic profile markedly different from other so-called autism-like cases. For example, Rett syndrome has been considered a variation of ASD but displays markedly different characteristics.[6]

Table 1 Some key differences between Rett syndrome and autism.

Characteristic	Rett syndrome	True autism
Head	Microcephaly	Macrocephaly
Common gender	Female (nearly all)	Male (4:1)
Brain involvement	Frontal cortex	Cerebrum; cerebellum
Neurons affected	Cholinergic	Serotonergic

Based on Riikonen R. *Insulin-like growth factors—neurobiological regulators of brain growth in autism?* In AW, Zimmerman, ed., Autism Current Theories and Evidence, Totowa, NJ: Humana Press; 2008, Chapter 10, 233-244.

"Autism-like" syndromes (with major mutations noted in parentheses but not found in the vast majority of ASD cases) include Rett syndrome (MECP2—methyl CpG binding protein 2), Fragile X (FMR1—fragile X mental retardation), Tuberous Sclerosis (TSC1—tuberous sclerosis 1), and Phelan-McDermid syndrome (SHANK3—SH3 and multiple ankyrin repeat domain 3). By comparison, MECP2 has been identified in about 1% of all cases of true autism.[4]

IGF-1 (insulin-like growth factor-1) is a single-chain polypeptide containing 70 amino acids. The level of free (active) IGF-1, typically about 1% of the total in humans, is governed by:

(a) Total IGF synthesis—largely controlled by growth hormone,
(b) IGF binding proteins (the most common in the CNS being IGFBP-2, 3, 4, and 5), and IGFBP proteases,
(c) Drugs that inhibit protein-binding of IGF,
(d) IGF cell membrane receptors (IGFR),
(e) Amount of the acid-labile subunit ALS, and
(f) Supply of nutrients.[7–9]

Most IGF-1 (>98%) in the blood is bound to IGFBP-3 and ALS. After release of the binding protein by matrix metalloproteinase-9 (MMP9), the insulin-like growth factor-1 crosses the blood-brain barrier (BBB) through an interaction with endothelial transporter lipoprotein-related receptor-1 (LRP1).[10,11]

IGF-1 is produced primarily in the liver (after birth) and in the placenta (before birth) for endocrine distribution. This polypeptide can also be synthesized locally for paracrine/autocrine provision. IGF-1 acts through tyrosine kinase-bearing receptors (IGFR) and plays a key role in brain development in youngsters. IGF-1 increases dendritic branching of layer two pyramidal neurons and the formation of neo-cortical connections.

This agent has significant effects on fetal and neonatal brain growth (especially with myelination). Particularly sensitive to IGF-1 deficiency are oligodendrocytes, cerebellar Purkinje cells, and motor neurons. IGF-1 stimulates DNA synthesis, neurite growth, neurotransmitter secretion, bone maintenance, control of neurotrophic factors, apoptosis inhibition, and protection of oligodendrocyte precursors.[7]

Overall, the roles of IGF-1 in normal fetal and neonatal nerve development include preventing neuronal injury, reducing neuronal degeneration, and increasing myelination. IGF-1 is involved in neurogenesis and synaptic genesis, and exerts effects in brain repair after mild/moderate injury. IGF-1 is neuroprotective when made available within 2 h of a hypoxic event.[7,11]

2. Glia

As the emphasis on major mutations associated with true autism occurrences decreased in studies about ASD, increasing attention was paid to structural and chemical deviations found in these cases, especially in the brain development of the newborn. To comprehend this shift in focus, it is important to review the factors and interrelations of glia to the disease process. The human neuro-glial cells to be considered here are oligodendrocytes, astrocytes, microglia, and Schwann cells primarily.

Glial cells are part of the immune system, maintaining chemicals needed for synaptic function, producing myelin which insulates the neural axons, synthesizing cerebrospinal fluid, controlling inflammation, and eliminating waste products. Glial cells do not participate directly in electrical impulse transmission in the nerves or in synaptic interactions between axons and dendrites but do affect the speed of neural signal passage. Glia lack axons or dendrites and play no role in adhering nerve cells together. (The word "glia" is derived from an ancient term meaning glue, since early scientists in this area believed that adhesion was the primary function of these cells).[12]

Glia do adjust the ionic environment of nerves in order to transmit electrical signals in the neurons more effectively. Glial cells assist the healing of nerve injury. As will be noted below, glia found in the central nervous system (CNS) bear specific differences from glia in the peripheral nervous system (PNS) in this regard.

Although the figure is debated, the ratio of glia cells to neurons in the brain appears to be roughly 1:1.[13] Special importance in the forthcoming discussions of their functions in autism is the role of oligodendrocytes in

the CNS in particular in maintaining and strengthening a fixed nerve connectivity position once created and joined in the young brain; thereby, they reduce the potential of dysconnectivity occurring in infants. As will be described, this is highly dependent on the supply of insulin-like growth factor (IGF-1).

Glial cells in the PNS often promote the regeneration of lost neural function, although such recovery is not found in the CNS. In the central nervous system, nerve damage control is usually limited to apoptotic removal of affected components by astrocytes and microglia, in circumstances somewhat similar to reparable cases in the PNS.[12]

Infrequently, glia can serve as the origin of highly malignant glioblastomas, with no evidence of lower grade precursors. About 95% of cases cannot be related to any specific cause, such as heredity. Apoptosis does not occur in these aggressive tumors, which are difficult to treat or control. It is very uncommon for glioblastomas to spread beyond the brain.[12]

The glia to be examined here are listed in Table 2 in Section 7:

Some of these glia cells will now be discussed as they may relate to the genesis of autism.

3. Astrocytes and microglia (CNS)

Astrocytes and microglia are significantly involved in synapse maturation, maintenance of neural function, and synapse formation in the central nervous system. An astrocyte is typically in contact with many neurons simultaneously and could directly affect thousands of synapses.

The genesis of autism may be related to the release of cytokines such as TNFα, IL-1β, IL-2, IL-6, and IL-10 during infections such as Covid-19. Patterson proposed that such factors could lead to reduced prenatal production of insulin-like growth factor-1 (IGF-1) by the placenta during and following maternal infection, especially first trimester influenza.[14] In that case, the blood-brain barrier (BBB) becomes more permeable, possibly leading to neuro-inflammation. In this situation, microglia and astrocytes become more reactive. This reactive gliosis may affect the pruning of synapses and dendrites, especially by microglia.[12]

Microglia are among the brain's major responses to infection. They also direct post-infection reshaping of the brain cells. Microglia clear debris created by such an assault. Microglia act to restore some affected intra- and inter-cellular connections. Autistic disabilities may result from too few or too many removed connections post-infection in some cases. The role

of microglia also appears to be involved with proper brain reconnections. In summary, microglial and pro-inflammatory cytokine activation control brain cell rewiring, reshaping, matching, and restructuring following an insult. Such an attempt may result in brain dysfunction as found in autism, as happens in faulty pruning processes.[15–17]

Microglial progenitors occupy the developing spaces prior to the completion of the blood-brain barrier. In the very young, vitamin D deficiency may induce errors of repair and development by poorly mediated pro-inflammatory release from microglia. Neural dysfunction might be the consequence of aberrant microglia after the insults of imperfect synaptogenesis or dendritic augmentation which they were unable to prevent.[18]

Microglia are the primary macrophages of the CNS. Fetal neo-neurons may experience faulty epigenetic alterations by being exposed to nutritional deficiencies, chemical insults, or stress hormones. Microglia are unusually active in injured patients, especially those destined to develop persistent abnormalities. Primitive neural phagocytes uniquely originate in the embryonic yolk sac. These early microglia colonize the whole CNS. Later, they are derived from lone cells. These glia are found at all stages of brain development.[19]

About 50% of all neurons in the developing brain undergo programmed cell death. Corpses are phagocytized by microglia throughout life. Excluding extraordinary health situations, personal longevity occurs inversely to the quantity of IGF-1 present. For reasons yet to be determined, microglia can promote neuron and neural progenitor cell survival in some situations. Alternatively, microglia phagocytize exuberant synaptic connections by pruning.[20]

Microglia are abnormally active in autism patients, especially those destined to develop overtly this malady between 12 and 36 months of age. Inefficient dendritic pruning may explain enlarged head circumferences in some young autistic children. As noted earlier, maternal infections or inflammatory immune activation in pregnant women may actuate microglial factors and promote the release of pro-inflammatory cytokines.[21,22]

Microglia are able to produce IGF-1. This may reduce the number of babies destined to become autistic (see discussion below). Also, such glial cells engulf dead and dying neural cells everywhere in the developing brain. These glia regulate neuron system vascularization, synaptic connectivity, axon outgrowth, and synaptic maturation, as well as appear in the CNS before the development of blood vessels.[23]

Astrocytes are closely associated with synaptic function. They have segment control of impulse transmission and are essential for the establishment of synaptic connectivity. By their interaction with neuronal synapses, this modulates interneuron function.[24]

Astrocytes secrete thrombospondins, which increase the total number of neuronal synapses. These cells are important to the current timing of synapse formation. The total number of neurotransmitter receptors determines the postsynaptic strength.[25]

Astrocytes have phagocytic capacity for removing nonfunctional synapses. This is largely dependent on two receptors, MEGF10 and MERTK. Thus, in summary, the astrocyte-synapse interaction has several aspects: formation, function, and elimination. A number of autism-like neurological disorders are linked to astrocyte dysfunction: amyotrophic lateral sclerosis, Rett syndrome, Fragile X syndrome, and other psychiatric conditions.[26]

With increased neuronal activity, the demand for blood flow increases. Vasoactive metabolites of arachidonic acid are released from astrocyte endfeet onto the blood vessels. Prostaglandin E2 (PGE2) and epoxyeicosatrienoic acid (EET) dilate vessels. In contrast, 20-hydroxyeicosatetraenoic acid (20-HETE) and ATP constrict the vessels.[27]

Astrocytes supply the bulk of caloric need of the brain, control compensation of interstitial fluid, provide substrates and precursors for biosynthesis, and recycle neurotransmitters. These gliotransmitters include adenosine triphosphate, glutamate, homocysteic acid, taurine, atrial natriuretic factor, tumor necrosis factor-alpha, and gamma-aminobutyric acid. An astrocyte is polarized, with processes at one end making contact with the blood supply, and the other end creating contact with adjacent synapses.[28]

Biochemically, astrocytes perform most of the Kreb cycle utilization of blood-delivered glucose to provide energy to the neurons. Also, astrocytes can store chemical bond energy in the form of glycogen. Similarly, oligodendrocytes rely on aerobic glycolysis. Calcium ions have fundamental roles in this energy-providing process as well. Hence, astrocytes and the blood-brain barrier (BBB) act together as a governor and a barrier with size-selective permeability.[29]

An example of the filter role of the BBB is the case of IGF-1 (see Section 7 for details). The level of IGF in an individual's cerebrospinal fluid (CSF) is directly related to its concentration in the blood; increase in systemic IGF-1 increases its passage into the cerebrospinal fluid. In cerebellar granule cell cultures, added IGF-1 increases cell survival, and withdrawal

results in neuronal death. Young children (<4 y.o.) with autism have reduced levels of IGF in their CSF, as noted earlier. This is thought to be the cause of reduced numbers of Purkinje cells in the cerebellum.[30]

This selective role of the BBB can be affected by hypoxia/ischemia and stroke. Astrocyte dysfunction (astrogliosis) in the face of pathologic challenges in the form of injury and disease from CNS insults can extend to microglia and oligodendrocyte progenitors. In such cases, the glia cells can then generate negative effects via cytokines, chemokines, prostaglandins, and other agents. Perhaps the most detrimental effect of astrogliosis is inhibition of axon regeneration. In the presence of astrogliosis, genetic polymorphism (to be discussed later) could change the future of the astrocytes as well. Blindness and paralysis may result in extreme cases. On the other hand, control of inflammation, BBB repair, and neuroprotection depend on the roles played by astrocytes so as to preserve viable tissue and function. [31,32]

4. Oligodendrocytes (CNS)

Ventricular zones of the brain are the sites of origin of oligodendrocyte precursor cells (OPC). They migrate from there to the developing CNS, where they become active oligodendrocyte (OL) units. The rate of OL production can accelerate to replace lost myelin in the presence of injury, advanced age, or disease. The ability to transition from OPC to OL begins shortly before birth and continues for several months thereafter. The mammalian OPCs produce platelet-derived regulators to survive and proliferate.[33]

Of particular interest to the latter discussion here on autism is the manner in which IGF-1 affects proliferation, differentiation, and survival of OLs. Additional agents also able to promote this activity include neuregulins, Wnts, neurotrophin-2, chemokines, and thyroid hormone, among others. OPCs thrive *in vitro* with media containing platelet-derived growth factor (Pdgf). Thyroid hormone promotes differentiation and Pdgf sustains this activity.[33]

In adults, the number of OPCs stays reasonably constant until a demyelination occurs. OL development continues lifelong. This is necessary for normal brain function as well as repair following periodic demyelination events, as needed. It is a result of the balance between inhibitory extracellular signals, such as Notch signaling and differentiation promoters like Olig2. Following OL differentiation, genes controlling myelin-associated

proteins such as PLP (proteolipid protein), MAG (myelin-associated glycoprotein), CNP (2′:3′-cyclic nucleotide-3′-phosphodiesterase), and MBP (myelin basic protein) are strongly induced. Myelin-regulator factor (Myrf) is generated as needed to aid in OL maturation and myelination. Epigenesis is also involved in this control process, including histone modification, chromatin remodeling, noncoding RNAs, and DNA methylation.[34]

Myelin production is the main role of oligodendrocytes. Because of its high lipid content (80% vs 20% protein), myelin is poorly hydrated but very stable for prolonged periods. The myelin sheets encircle the axons of nerves several times, to enhance packing density. In this way, Van der Waal's forces strongly promote the potency of this unit. The surface area of each flattened myelin unit is estimated to total up to 50×10^3 μm^2.[34]

The sequence of axonal wrapping with myelin is:

(1) Proliferation and migration of OPCs,
(2) Axon-glia recognition,
(3) Differentiation of OPCs to OLs,
(4) Axonal wrapping, and
(5) Myelin compaction.

In addition, oligodendrocytes and axons are joined metabolically. Aggregate cultures of fetal rat brain treated with IGF show marked increases of CNP (2′,3′-cyclic nucleotide-3′-phosphodiesterase) and oligodendrocytes. The emergence of enhanced MBP (myelin basic protein) can also serve as a marker for this transition.[35]

Oligodendrocytes provide support and insulation to CNS neurons. This is achieved by developing a myelin sheath around the neuronal axon. This covering material insulates the neuronal axons, accelerates the passage of nerve impulses from source to objective, and sustains/supports the functional pathways of these units once interneuron connections are formed. In this manner, dysconnectivity in the brain is minimized. The increased velocity over myelinated axons is due to reduced ion leakage, improved synaptic function, saltatory impulse movement, and decreased cell membrane capacitance.[35] (The neurons in the PNS are myelinated by Schwann cells and will be discussed separately.)

Functionality of the axonal portion of the neurons depends in large part if it is myelinated, and, if so, to what extent. This can be identified by the level of axonal myelination. Two-thirds of all the axons in the body are unmyelinated. Such axons in the CNS have radii of 0.05–0.6 μm and

conduction speeds of $1.8\sqrt{a}$, where a is the axonal radius. In contrast, myelinated axons typically have overall radii of 0.5–10 μm and conduction speeds of 12(a + b), where b is the myelin sheath thickness. The impulse velocities in unmyelinated axons are typically 0.5–10 m/s; in myelinated axons they can be up to 150 m/s. A typical adult brain has about 100 billion neurons.[36]

Myelination of new neurons in the CNS of the human fetus begins in 24–25 weeks post-conception. The rate peaks at 1-year postpartum and tapers off gradually until about 25–30 years of life. Oligodendrocyte precursors arise from pluripotent cells in neurogenesis. OPCs are highly migratory, proliferative, hardy, and vigorously myelogenic. However, if the level of IGF-1 is reduced, the differentiation of OPCs to generate functional oligodendrocytes is diminished, and rapid cell death ensues. Oligodendrocyte loss results in demyelination. This can lead to impaired neurologic functions such as those changes seen in multiple sclerosis and autism.[35]

In the CNS, functional oligodendrocytes, a type of neuroglia, can be linked to as many as 50 axons for the purpose of creating and maintaining myelogenesis. In the fetal brain, the first wave of OPC formation occurs in the medial ganglionic eminence; the second wave develops in the medial forebrain; and the third wave, near the time of birth, extends from the dorsal and subventricular zones. The dysconnectivity characteristic of autism typically affects the posterior-to-anterior neural pathways, among others, in the brain.[34]

Oligodendrocytes are the last cells to be produced in the CNS. The overall role for oligodendrocytes is a supporting and trophic one, like all the other glia. In this function, they produce GDNF (glial cell line-derived neurotrophic factor), BDNF (brain-derived neurotrophic factor), and supplemental IGF-1.[35]

The impulses carried by the myelinated neurons have spatial insulating gaps, the nodes of Ranvier, which are voltage-gated sodium channel clusters. By promoting saltatory node-to-node impulse passage, the velocity is increased by as much as 100x. Areas of the brain populated by dense collections of myelinated neurons are known as white matter, whereas the nonmyelinated areas are called gray matter. People with high IQs have been found to have greater white matter than average.[35]

Demyelinating diseases such as multiple sclerosis and various leukodystrophies as well as spinal cord injuries and hypoxic episodes can be a

stimulus to reduced myelination. The efficiency of remyelination decreases with age or toxin-induction because of less effective OPC recruitment and differentiation (progenitor failure). Transplanted OPCs can ameliorate dysmyelinated cases. Loss of normal homeostatic functions and increases of toxic actions may help explain the neuro-degradation and pathophysiology in Parkinson's disease, Huntington's disease, Alzheimer's disease, and amyotrophic lateral sclerosis.[35]

5. Schwann cells (PNS)

In the PNS, myelination is carried out by Schwann cells rather than oligodendrocytes. These glial cell bodies here are located inside the nerve itself, unlike OLs. Schwann cells evolve as follows:

Neural crest → precursor → immature → promyelin → mature

In sharp contrast to oligodendrocytes in the CNS, Schwann cell function and survival are strongly dependent on IGF-2 instead of IGF-1.[36,37] Neuregulin (NRG1), an epidermal growth factor, is a key regulator of axon myelination in the PNS. (This will have important relevance in the later discussion about autism.)

Peripheral nerve regeneration is dependent on the presence of viable Schwann cells, glial cells that associate synapses of the PNS with nerve fibers. Myelination of these nerve fibers is essential to achieve accelerated propagation of action potentials by saltatory conduction, much like the nerves of the CNS. Diseases specifically of the myelin itself are limited to the PNS (e.g., multiple sclerosis). The internodal portion of the axon is about 99% of its length overall. In this way, myelin provides a high-resistance, low capacitance neural sheath to enhance impulse speed. Like the CNS oligodendrocyte, myelination of the PNS nerves by Schwann cells is subjected in part to epigenetic regulation.[38]

6. Myelination and IGF-1

One of the first studies to relate IGF-1 to autism utilized a hospital-based collection of juvenile spinal tap surpluses. Although the number of cases was relatively small, a clear difference was found in samples from children aged 1 to 4 years. The aliquots from youngsters diagnosed as autistic by conventional psychological methods displayed IGF-1 concentrations of the CSF that were lower than for neurologically normal children of similar ages (normal mean = 0.4; autistic = 0.2 μg/L).[6]

A number of other reported observations pertained to a plausible connection between autism and IGF levels. For example, a study was carried out on an equal number of African American and Caucasian girls, matched for age, body mass index, socioeconomic status, and pubertal stage. Each was tested for serum IGF-1. The African American girls were found in 2000 to have greater total IGF-1 ($p < 0.001$) and free IGF-1 ($p < 0.01$) than their paired white teammates.[39] In a related study of 8-year-old children in 2002–10, the prevalence of ASD among Caucasians was 6.7 and for African Americans was 5.9 per 1000 (95% CI).[40] This would support the deduction that the higher the IGF-1 level, the lower is the potential for autism.

During pregnancy, placental GH (growth hormone) is believed to be the impetus for the rise in fetal serum IGF-1. Especially during the second trimester, the level of IGF-1 in the amniotic fluid increases steadily. Women carrying female fetuses also display a significantly higher placental GH level in their own blood than those bearing male gestations (e.g., 14% difference at 28 weeks gestation). This is consistent with the lower incidence of autism in female offspring than male. Placental (fetal) GH can be distinguished analytically from maternal pituitary GH.[41,42]

Inadequate placental production of IGF-1 can reduce the transfer of nutrients across the placenta to the fetus. Very-small-for-gestational-age (VSGA) newborns eventually have a higher incidence of autism than children who were normal weight at birth.[43]

Increased risk for autism in the offspring is linked in many cases to antepartum maternal infection. Maternal immune activity (MIA) increases in response to infectious challenges, such as influenza and herpes. As a result, the level of interleukin-6 (IL6) rises, whereby the activity of placental JAK/STAT3 (Janus kinase/signal transducer and activator of transcription proteins) escalates. In turn, this reduces the amount of IGF-1 released by the placenta to the developing fetus (see Fig. 1). As a consequence, autism results more often if chorioamnionitis occurs. Hence, MIA (e.g., with premature rupture of membranes—PROM) could serve as a trigger for lowering the neonate's IGF-1 available to aid in neoneuronal myelination, independent of the maternal level of IGF-1. In line with this, IL6 is markedly elevated in the cord bloods of preterm newborn whose mothers had presented in prodromal labor with PROM vs those with intact membranes. IL6 is increased in the cerebellum of many autistic children.[14]

If not fully myelinated, nerve cell transmission is likely to be much slower than normal. Infant responses to environmental stimuli will be diminished,

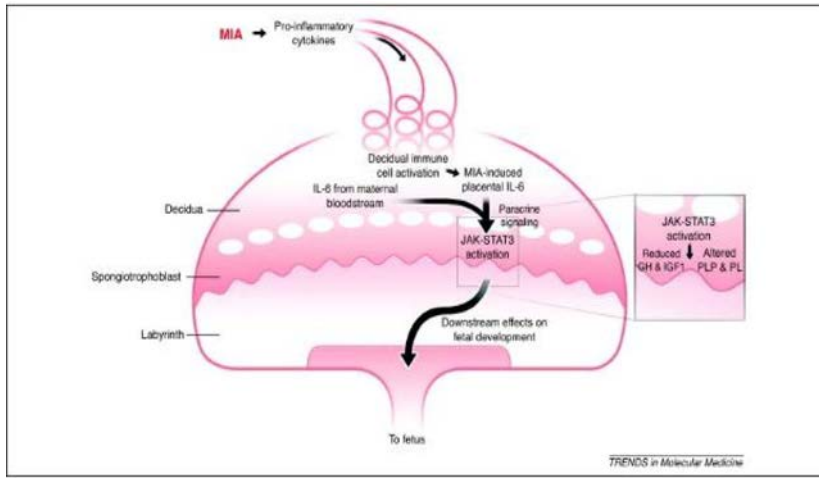

Fig. 1 Maternal immunologic activation, secondary to an inflammatory process, promotes the release of IL6. The cytokine depresses IGF-1 production and release to the fetus. EY Hsiao, pH Patterson. Activation of the maternal immune system induces endocrine changes in the placenta via IL-6. *Published in Brain Behav. Immun. 25 (2011). This diagram is reproduced here with the kind permission of Elsevier Publishers.*

as a result. Reduced IGF-1 in the very young neonates decreases differentiation of oligodendrocytes, causing diminished neuronal myelination, the hallmark of autism in the brain. In autism, brain tissue displays abnormally thin axon myelin coats, as observed by MRI and direct biopsy,[28,44] thereby promoting reduced neural function and impulse transmission. This supports the observation that one of the primary pathologic processes in autism is deficient IGF-mediated myelination in the developing central neural pathways in the white matter of the brain. This becomes overtly evident in the baby's behavior at 1–4 years of age.[7–11,45]

7. Autism etiology

The observations noted so far suggest that supplementation of IGF-1 in the newborn could reduce or eliminate neurologic defects, especially the eventual development of ASD. This condition in particular is to be differentiated from less common syndromic neuro-pathologies which bear some of the characteristics of ASD but are distinguishable from it (see Table 1). For example, repetitive movements are found in both true autism and Rett syndrome (RS); however, as noted earlier, RS is almost unique to girls but ASD is much more common in boys (4:1). RS has a distinguishing

major genetic mutation (MECP2), whereas autism does not. Autism can coexist with other genetic disorders such as Downs syndrome in about 10% of the cases.[46]

There is increasing evidence that the etiology of autism is related to disorders of the **IGF1/IGFR/IRS1/PI3K/AKT/mTOR** intracellular signaling pathway. In particular, this conduit effects the translation of IGF-1 to promote myelogenesis. Activation of the tyrosine kinase receptor sites of IGFR, the junction between the extracellular and intracellular milieux, affects a number of signaling pathways, inducing vasomotor and metabolic effects. In contradistinction, phosphorylated AKT is decreased in the autistic brain.[47–49] This could happen if the cellular environment contained a reduced amount of IGF and/or if the IRS1 in the PI3K/AKT chain were polymorphic (rs1801123—see Section 10). As will be noted in Section 11, supplemental dietary IGF-1 could ameliorate either problem.

Another anabolic role of IGF1 in the nervous system relates to an additional application of the PI3K/AKT chain. When stimulated, this chain can also inhibit GSK3B (glycogen synthase kinase-3-beta), which would otherwise prevent the synthesis of glycogen and proteins in the brain.[50] Thus, deficiency of insulin-like growth factor-1 (IGF-1) can reduce anabolic function promoted by this sequence.

Rather than being due to a major genetic defect, the dysconnectivity characteristic of autism appears to be the result of diminished effect of IGF-1 on neonatal neurogenesis and myelogenesis, secondary to impediments in the PI3K/AKT pathway or to insufficient IGF-1 initially.

Autism is currently referred to as ASD—autistic spectrum disorder. Instead of occurring as a conglomerate of several different entities with some shared characteristics, the *spectrum* of ASD may be a single malady with a range of intensities determined by the degree of neonatal IGF-1 deficiency (see Section 10). This would yield a scope of degrees of activity determined by the level of phosphorylation (or inaction) of the PI3K/AKT cellular pathway.[48]

Further supporting the IGF hypothesis is the observation that the rate of cancer in autistic patients is about one-third that of neurologically normal individuals. This may be due to the lower level of IGF in children and adults with ASD. In contradistinction, elevated amounts of IGF are typically accompanied by shortened longevity of life. One of the characteristics of IGF-1 is its mitogenic property. Similarly, the tumor suppressor PTEN also acts to reduce the activity of PI3K, thereby diminishing the active translation of IGF. This could also lessen neuronal myelination in children

destined to display autistic behavior later. On the other hand, chemical inhibition of PTEN could enhance myelination.[51–53]

In comparison, the PI3K/AKT/mTOR pathway is a key player in the Schwann cell initiation of myelination. PTEN is a lipid phosphatase with the effect of opposing this PI3K pathway in the PNS environment and preventing the resumption of myelination. Loss of OLs in the CNS, leading to demyelination, can be repaired and restored by remyelination. Such myelin is necessary for axon survival, which requires intact OPCs and oligodendrocytes. Available IGF-1 and Olig1 are utilized for this purpose. Effective remyelination also needs removal of prior myelin debris by glial macrophages. With aging, there is a decrease in OPC recruitment and differentiation.[48]

As noted, nucleotide polymorphic limitation of the cellular IRS-1 factor can retard the translation of the IGF signal. Overall, IGF stimulation of oligodendrocytes is essential for axonal myelination and synaptic development in the prenatal and neonatal stages, especially in the brain. Thus, it is important to enhance the total activity in the CNS and PNS of biologically operational IGF early in a newborn's development. The primary objective is to avoid unalterable dysconnectivity (mis-wiring) in the crucial neonatal stages of brain neural circuit genesis, especially with the long-range posterior-to-anterior connections. In contradistinction, reduced IGF-1 levels in early life can increase the overall lifespan. However, deficiency of this growth factor in the adult negatively affects neurovascular and cognitive function.[51]

As it relates to the avoidance of autism, the level of IGF-1 in the newborn appears to be the most pertinent. During the first 4 years of life, the serum IGF-1 concentration remains reasonably constant unless it is augmented pharmacologically or nutritionally.

Suppressed serum IGF-1 levels, due to a variety of reasons, such as prematurity, can cause dysmyelination of neo-neurons. It is at this stage, especially in the first year of extrauterine life, that irreparable brain mis-wiring could occur at a critical time since the active formation of new nerve tracts is taking place.[46]

In general, IGF-1 promotes protective surveillance of existing brain cells to prevent neuronal derangement. As noted earlier, nuclear polymorphisms can down-regulate the promotion by this factor. Knockout mice which lack the ability to synthesize sufficient IGF-1 have reduced axonal diameters and decreased nerve conduction velocities. In contradistinction, transgenic mice with enhanced IGF1 produce up to 130% the normal

amount of myelin. Untreated autistic children between birth and 4 years of age have lower levels of this growth factor in their cerebrospinal fluid than unaffected youngsters.[6] These findings in affected persons are consistent with diminished myelination in early neurogenesis.[50]

The neuronal growth cones (axon precursors) are guided to sites of need (e.g., muscles) by non-diffusible biochemical factors in the vicinity of the target tissues. To refine the path, both chemo-attractive (such as netrins) and chemo-repulsive (such as semaphorins) agents are appropriately placed within the receiving tissues. Once the axon reaches a suitable dendritic or organ target, synapse formation ensues. Such trophic interactions begin before birth and continue postnatally.[46,52,53]

8. Connectivity

With time, neurons in the developing neonate display increasing numbers of synapses. The fittest of them survive and the less functional in the remainder are eliminated by apoptosis. The most effective connections are retained peripherally and in the brain. This is promoted by agents such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). According to the Hebb's Postulate, active, functional interplay between a presynaptic axon and a postsynaptic target fortifies the synaptic link overall. Such strengthening promotes persistence of the joining of neurons with terminal tissues. Conversely, weakly associated unions eventually resolve and disappear.[53–60] (See figs. 24.1 and 24.2B in Ref. 53.)

Postnatal brain development is dependent on enhancement of functional synapse formation. This is promoted by strong, timely impulses sent to the target via the presynaptic axon. For proper, efficient, coordinated, and rapid neural connectivity (circuitry) to develop between regions of the neonatal brain, early, comprehensive myelination of the participating axons is essential to retain the most functional course. In contradistinction, autistic brains have been observed to display heterogeneity, with various areas of increased and of decreased connectivity. This is especially evident in imaging studies of the corpus callosum, where autistic individuals exhibit changes in white matter myelination related to decreased interhemispheric connectivity. Such studies include fMRI (functional magnetic resonance imaging) and EEG (electroencephalography).[60–62]

Attracted by CX3CR1 chemokine receptor, microglia colonize and become ready for nerve development prior to the appearance of other

Table 2 Summary of glial cell types.

Glia	Site	Main functions
Astrocytes	CNS	Link neurons to blood supply; secrete neurogenic factors, neurotransmitters, and neuromodulators
Microglia	CNS	Prune synapses/dendrites; release CX3CR1/neurotrophic BDNF
Oligodendrocyte	CNS	Produce myelin sheath
Ependymal cells	CNS	Secrete cerebrospinal fluid
Radial cells	CNS	Matrix to assist neo-neuron migration
Schwann cells	PNS	Myelination; clear cellular debris
Satellite cells	PNS	Regulate chemical environment

BDNF, brain-derived neurotrophic factor; CX3CR1, fractalkine receptor in microglia migration. Table based on Barres, BA, Freeman, MR, and Stevens B, eds. *Glia*, Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press; 2015, sections 1,2,4.

nervous system cells. From there, synaptic junctioning and related axon outgrowth ensue (see Table 2).

Protective myelination in humans reaches its peak growth rate by 1 year of age. Psychosocial behavioral symptoms of autism typically appear between 1 and 4 years after birth. In the brains of autistic children, myelination has been shown by imaging studies and biopsy to be deficient compared to unaffected children.[28,44] Such a diminution would weaken the operation of the axon-target synapse, thereby accounting for the malfunction of areas of the brain involved in comportment. This would include the brain's prefrontal and temporal areas.[60,63]

"Pruning" of excessive neural synapses and dendrites by microglia (autophagy) to enhance the functionality of the retained circuitry has been found in the CNS of children up to the age of 1 year. During this time, the estimated number of synapses increases by a factor of 10. In unaffected individuals, dendrite exuberance normally occurs as the need for high velocity impulse delivery is met by myelinated presynaptic axons. On the other hand, disproportionate processing is the consequence of hypomyelination. Compounding this could be neuronal cell signaling impediments in the PI3K/AKT/mTOR pathway.[32,62]

Initially, brain dysconnectivity in autism was discerned in 2004 to be between frontal and posterior compromised areas. In the absence of effective connectivity (e.g., parietal nerve tract union with frontal zones),

functional combinations of nerves would be diminished. Such circuitry disorders could result from abnormalities such as:

(a) arrested OPC development,
(b) OL dysfunction, and
(c) axonal disorders disrupting normal impulse signaling.

As a result of such dysconnectivity and consequential neurological defects, normal brain function would be disrupted, especially in aspects of behavioral issues. This results from myelination deficits causing cerebral white matter hypoplasia, decreased neural connectivity, and impaired or disrupted impulse conduction synchronization between cerebral sites as a consequence of insufficient IGF-1.[63]

Brain connectivity denotes networks that are functionally connected to each other to result in meaningful psychological and physical actions. White matter inflammation can induce a reactive response (of the microglia and/or astrocytes), leading to disordered myelination. Being a prelude to autism, this typically occurs in the first postpartum year without overt signs. The dysconnectivity approach to explain the etiology of autism replaces the previous emphasis on genetic defects as a more germane perspective.[64]

Examination of autistic patients by fMRI has revealed functional underconnectivity in at least five areas (prefrontal, parieto-occipital, motor, somatosensory, and temporal). In contrast is the parallel observation of tempero-thalamic hyperconnectivity in other cephalic areas in the autism group, compared to unaffected individuals of a similar age. The overconnectivity regions are apparently due to incomplete dendritic pruning by glia, especially within medial motor and orbito-frontal zones, whereas underconnectivity is due to hypomyelination in other brain areas. It was concluded that such abnormalities could explain socio-communicative and cognitive impairments in autism.[64,65]

In general, the exposure of children to new concepts, as found in the classroom, acts to stimulate new memory functions. However, therapeutic attempts have so far been marginally successful, at best, to promote correction of neural dysconnectivity in autistic children. Such reduced "normal" brain connectivity in childhood autism is due to aberrant long-range connections of neural networks secondary to hypomyelination.

Autism can be seen as a dysconnection (mis-wiring) syndrome. In other words, children with autism possess a pathology emanating from reduced brain networking at psychosocial levels. As of today, no treatment is available to reverse this error once established. Central to this problem is inadequate myelination able to hold developing nerve circuits fully ligated

and aligned together by effective, functional synapses. Similarly, reduced fractional anisotropy near the corpus callosum may be due to reduced myelination of adjacent fiber tracts or to defective early neural migration, synaptogenesis, or dendritic/axonal pruning.[64–67]

Autism becomes symptomatic around ages 1–2 years in many cases. This happens to be approximately contemporaneous with the first 6–14 months of postpartum life when cephalic synaptogenesis, dendritic arborization, and myelination are very active. Dysconnectivity-related behavior would become noticeably apparent near the end of this inaugural period. Generally, hypoconnectivity in autism relates to disrupted neural communication between distant regions (e.g., frontal and parietal lobes bearing complex cognitive and social functions); in contradistinction, hyperconnectivity involves neural contact between local brain regions.

In the first stage of axon/target union, on or about the time of birth, each of many axonal branches of a single neuron may develop synaptic connections with several targets. A large percentage of these multiple rudimentary neuronal innervations are subsequently eliminated. Most susceptible to such early dissolution are those neurons with hypomyelination and low velocity impulse transmission. In such cases, the chance of a functional persistence or reconnection to another site is reduced from the final mature ones.[53]

Because autistic dysconnectivity often encompasses synaptic dysfunction (i.e., synaptic connection problems rather than regional issues), it has been recommended that related studies should consider the possible single nucleotide polymorphisms (SNPs).[63–67]

9. Polymorphism and biomarkers

As of now, autism is largely an irreversible condition once it can be recognized explicitly through psychological testing. In some cases, autistic symptoms may improve to some degree with early psychotherapeutic intervention. The behavior traits characteristic of autism are believed to be the results of brain dysconnectivity developed during the infantile and early childhood years.

ELISA quantitation of deficient serum IGF-1 in umbilical cord blood collected at delivery, for example, may foster early initiation of specific nutrient supplementation to minimize subsequent development of primary symptoms of autism. It might also define where on the spectrum the malady would lie, if left untreated promptly. Antepartum diagnostic cordocentesis

could potentially be employed in highly suspicious cases, especially in gravid women with one or more prior affected offspring. Also, fetal SNPs could be identified in the maternal circulation before birth.[67–75]

Most SNPs are silent since 98% occur in the intron or intergeneic regions of the DNA. However, some have been identified in variably symptomatic conditions such as autism. To be classified as a polymorphism, the least common pathognomonic allele must have an occurrence frequency of 1% or more. Each may or may not display overt changes of medical importance. Some of the SNPs possibly relevant to identifying potential autism development include:

(1) Insulin receptor-like growth factor (IRS-1)—G972R
(2) Dual specificity DESP15—rs3746599
(3) IGF1/TasI and IGF1/SmaBI
(4) IGF-1 (Chinese)—rs1520220
(5) IRS-1 (Korean)—rs1801123
(6) FOXP2—rs2056202; rs2292813
(7) GSBRB3—rs878960.

In particular, polymorphic IRS-1 (#5 in the above list) reduces the rate of translation of IGF-1. (See the discussions about the intracellular PI3K/AKT chain noted in Section 8.) Allele frequency analysis determines if a statistically significant association between the incidence of this SNP and autism exists. The presence of this SNP is often correlated with enhanced autism potential in Korean children.[69] However, a SNP allele that is frequent in one ethnic group, as it was in this reported introductory study, may be rarer overall in mixed groups. Thus, investigations of this allele in several locales in the world are necessary before it can be utilized on a regular screening basis.[67–75]

Rett syndrome and Fragile X, for example, which resemble autism in only some physiological and psychosocial characteristics, occur much less frequently than ASD (see Section 2). The present report has enumerated biochemical features of true autism cases, which distinguish them from less common disorders bearing some, but not all, analogous characteristics. One or more early-warning biomarkers detected at birth (or previously) could be anticipatory for the later appearance of authentic autistic disease:

(1) Deficient serum IGF-1
(2) Elevated anti-myelin basic protein
(3) Elevated serotonin
(4) SNP rs1801123
(5) SNP rs878960.

Timely detection could conceivably allow prompt correction of the biochemical flaw(s) before permanent neuro-psychological abnormalities appear.[7,45,69,71] For example, one mathematical approach using three of these blood factors together can help predict at birth which newborn have increased probabilities of displaying autistic characteristics at a later age:

1—IGF1, 2—anti-myelin basic protein (anti-MBP), and 3—serotonin.[45] With these quantities can be calculated an *Autism Index* (AI), where p = weighted probability of variation of the biomarker from normal in autism, and n = absolute percentage (expressed as a decimal) deviation of the biomarker from normal:

$$AI = [p_1n_1 + p_2n_2 + p_3n_3]/0.1$$

AI = 0.00 would be an example of an unaffected newborn, whereas AI more or less than zero would raise the possibility of future appearance of autistic features and the current need for preventative intervention.[46]

10. Autism prevention

Ingestion of milk raises a human's serum level of IGF-1. Human milk increases a baby's IGF-1 level more than bovine milk or formula.[76] In a study performed on adults, it was found that a daily intake of 600 mL of milk for 12 weeks raised the mean serum IGF level by 10% in total.[77,78] On the other hand, vegan women who consume no animal products (e.g., bovine milk) have serum IGF levels that are 13% on average lower than in omnivores.[79] Although ingested IGF is a polypeptide, it apparently survives passage through the stomach because of casein shielding.[80,81]

Special imaging study approaches have shown autistic children with the most unmanageable social interaction skills to have significantly lower global MWF (myelin water fraction) scores when compared with normal control individuals.[82] MRI brain scans of children who have been breast-fed as infants displayed increased white matter in frontal and associated brain regions.[83] The longer a group of babies were breast-fed, the less frequent was the occurrence of autism later.[76] This was again confirmed in a meta-analysis from several sources.[84]

Also, ingestion of vitamin D enhances the benefit of IGF-1 by increasing IGFR receptors. Mothers of autistic children have a 1-in-5 chance of delivering another affected child, whereas those with no previous autistic offspring have a 1-in-60 possibility.[7,85] It is twice as common in siblings as in half-siblings. Vitamin D supplementation of gravid mothers with

prior autistic children significantly reduced the chance of bearing another affected child. Such nutritional additives might diminish the possibility of autism in babies in general.

Hence, plausible preventive treatments include:

(1) Human breast milk feeding of the newborn for up to 1 year in order to raise the serum level of IGF-1 of the baby. Children breast-fed exclusively for the first several months of life present a significantly lower incidence of autism than those fed bovine milk or formula. The longer a baby is breast-fed exclusively, the lower is the chance that it will display autistic characteristics later.[76,84] Another means for elevating blood IGF-1 in the neonate is massage therapy, although prolonged treatment in conjunction with autism has not been studied as yet.[86,87]

(2) Oral supplementation of vitamin D increases the circulating level of IGF-1 significantly. Gravid women who were deficient in vitamin D at mid-gestation were twice as likely to deliver children who eventually developed autism than those who were normal in this nutrient. When women who had previously delivered autistic children were given vitamin D supplement in a following gestation, the rate of affected subsequent offspring dropped from 20% to 5%.[88–91]

(3) Modified forms of IGF (such as Des-IGF, $IGF_{1–3,}$ or cGP), one of which can be administered orally, show potential for use in these cases. They more easily cross the BBB (blood-brain barrier) and bind less strongly with IGFBPs (IGF binding proteins), thereby requiring administration of less in the active, unbound form. The ultimate purpose is to raise the level of free IGF-1 and prevent the type of autistic brain changes secondary to hypomyelination found on biopsy.[46,92–97]

$$IGFBP_3\text{-}IGF_1 + cGP \rightarrow IGFBP_3\text{-}cGP + IGF_1$$

(4) Influenza vaccination should be administered seasonally to all non-allergic women contemplating a new pregnancy.[14]

Irreversible CNS dysconnectivity developing with overt symptoms in the first year or two of neonatal life may be the consequence of an uncorrected biochemical deficiency secondary to a nucleotide polymorphism. This is comparable to a partially inhibited enzyme. The initial step of the PI3K chain is the interaction of the IGFR (receptor) with free IGF (see Section 8). The higher the concentration of unbound IGF-1 in the surrounding serum/extracellular milieu, the more rapid would be the signal

transfer to IRS1. However, if this IRS1 has a functional polymorphic change from normal IRS1 (e.g., rs1801123), the slower would be the passage of the message to PI3K, the next member of the chain.

Consequently, there may be at least three processes for slowing the PI3K/AKT chain activation of myelination: reduced IGF-1 in the cellular environment or IRS1 polymorphism in the transmembrane chain. Either problem could be compensated kinetically by an increase in the provision of IGF-1, such as with breastfeeding.

(a) Dephosphorylation[98]
(b) IRS1 polymorphism[69]
(c) Selective inhibition of elements of the P13K/AKT pathway[99]

Any of these problems could be compensated kinetically by an increase in the provision of IGF-1, such as with breast-feeding.

Examples of the association of a SNP with autism are rs1801123 and rs878960, as discussed earlier. The observed kinetics of IGF1 translation via the PI3K/AKT chain when comparing affected from neurologically normal individuals would support the purported association of these SNPs in particular with autism. Such an applicable SNP departure from normal (rs878960) could serve as a parameter to assess anticipated symptom severity (i.e., spectrum position) as well. The three alleles of SNP rs878960 in GABRB3 (gamma-aminobutyric acid receptor subunit beta-3) can distinguish severe cases of autism from mild/moderate ones.[71]

Early prevention of autism development could be initiated by measuring IGF-1 in umbilical cord blood at delivery. This would determine the advisability of IGF augmentation for at least one full postpartum year to overcome by biochemical kinetics the neurogenic deficiency of autism. Timely action is necessary because myelination of brain neurons is nearly complete by the child's second birthday.[9,100]

Although the concept of dysconnectivity in autism was proposed as early as 2004, no inclusive mechanism for its origin and prevention has been advanced until now. As described previously in the present discussion, it would appear that reduced myelination due to inadequate provision or deficient translation of IGF-1 by oligodendrocytes explains the basis of dysconnectivity beginning in affected infants. Furthermore, it creates the framework for minimizing the negative effect on connectivity development in the affected newborn.[15,63,96–100]

In Fig. 2 are seen several summarized aspects of postulated faulty metabolism in autistic people, especially young children. Starting from the top, insufficient IGF-1 produced in the liver would diminish the velocity of the PI3K/AKT chain, followed by reduced stimulation of oligodendrocytes

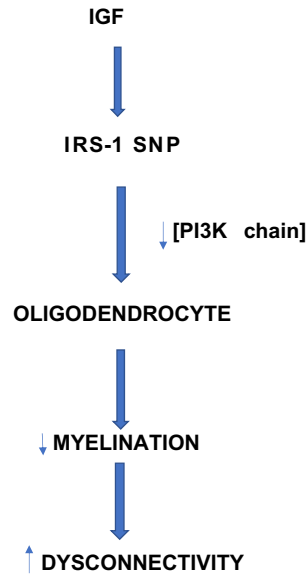

Fig. 2 IGF-1 stimulates oligodendrocytes to supply myelin to the neo-neuron. IGF-1 enhances the velocity of the **IGF1/IGFR/IRS1/PI3K/AKT/mTOR** intracellular chain. In the presence of the polymorphic form of IRS-1 gene or reduced IGF-1, the rate of myelin production is reduced, myelination of new nerves is slowed, and connectivity of new circuits is inadequate to meet the needs of the developing infantile brain. As a result, permanent mis-wiring ensues, especially with long distance connections (e.g., parietal-to-frontal).

to myelinate neo-neurons. The same lowered production would result if there were an IRS-1 SNP in the chain. Impaired guidance of nerve circuit generation in the young brain would lead to overall dysconnectivity.

Related to this is the vitamin D_3 receptor (VDR) gene polymorphism which may explain the enhanced utility of this vitamin in reducing the incidence of autism. Alleles of the VDR gene (T allele at position Taq-1 and α allele at position Apa-I), when present, modulate the ASD incidence for a given level of vitamin D.[101]

The analyses to diagnose and appreciate the various underlying events related to the etiology of autism (Fig. 2) would synopsize the putative cause and effect of this transformed biological pathway. Correction of this insufficiency could be achieved by dietary increase of the amount of IGF-1 to replace deficient amounts produced in the liver or to overcome the decreased kinetics of the PI3K/AKT pathway due to a polymorphic form of one or more components of this reaction sequence. An additional diagnostic test that could be made at delivery is myelin basic protein or its antibody (Tables 3 and 4).[41,45,100]

Table 3 Mean serum IGF-1 level of young children (μg/mL) born at term.

Children (μg/mL) born at term		
Age (months)	**Girls**	**Boys**
2.5–12	103	91
21–39	132	108
45–51	164	114

Note that within each age grouping, boys have a lower mean level of serum IGF-1 than girls. This may account for the greater occurrence of autism in boys than girls (4–1). See Section 7 and Ref. 42 concerning corresponding fetal placental growth hormone (GH) differences by gender.

Based on Yuksel, B, Nuiozbek, M, Mungan, NO, et al. Serum IGF-1 & IGFBP-3 levels in healthy children between 0 and 6 years of age. *J Clin Res Pediatr Endo*. 2011;3(2):84–88.

Table 4 Associated test results[a].

Neonate/infant source:	Unaffected	Autistic
CSF IGF (age 1–4 years)	Normal	Low
Serum IGF (neonate, VSGA)	Low normal	Low
Serum IGF (via maternal infection)	Normal	Low (↑IL6)
Polymorphic IRS1	Negative	Positive
Phosphorylatd AKT	Positive	Negative
Brain dysconnectivity (fMRI)	Negative	Positive
Neuron impulse velocity	Normal	Reduced
Dendritic mass (MRI)	Normal	Excessive
Cerebral white matter (MRI)	Normal	Hypoplastic
Serum IGF[b]	Normal	Low
Serum serotonin[b]	Normal	Elevated
Anti-myelin basic protein[b]	Normal	Elevated

[a]Based in part on Refs. 7, 12, 14, 46, 93; practicable for evaluation in addition to psychological diagnostic testing in infants (Ref. 5).
[b]See Ref. 46 for a perinatal score which includes these three blood parameters.

This review of glial functions and their bidirectional association with neural activity aids in the understanding of autism's etiology. This is especially true in myelination. The central nervous system network depends to a large extent on the abilities of the glia to support essential roles fundamental to neuronal generation, operation, turnover, and cleanup.[102,103]

Valproic acid (VPA) is an effective anti-epileptic drug. If given to seizure-prone gravidas, it may lead to an increased incidence of autism in their offspring. Studies in laboratory animals exposed to VPA display decreased OL-lineage cells and hypomyelination. If no alternative drug is found effective during the pregnancy, IGF prophylaxis postpartum in the neonate would appear to be indicated.[104]

As reviewed early in this chapter, speculation into the cause(s) of autism which began with the "refrigerator mom" proposal[2] was followed by numerous etiologic proposals. In recent years, ASD has been correlated with major genetic mutations, but such prominent flaws were found in no more than 10% of the autism cases.[4]

Lately, cesarean section has joined the group of putative associations with ASD. The odds ratio distinction of c/sections followed by autism as a postpartum complication (1.34), compared to less often affected vaginally delivered infants, is most pronounced in the gestational range of 39–41 weeks.[105] *Before* primary operative delivery is elected and executed, a term fetus's endurance is tested most while encountering prodromal and active labor stress, especially due to dystocia. The varying risks to the baby are often evidenced by non-reassuring fetal heart rate tracings of fluctuating degrees (mild to severe). This may be due to undiagnosed preexisting IGF deficiency, making hypomyelinated CNS neo-neurons exquisitely sensitive to pre-labor, antepartum, and intrapartum hypoxic impairment as found in stressed deliveries. Affected neurons may be removed by microglia in such cases.

As recommended here for all deliveries, every newborn should be tested for serum IGF level at birth via umbilical cord or heel-stick blood. Neonates scoring positive for deficient IGF-1 should be started immediately on quantified breast-feeding or insulin-like growth factor supplement. (The exact doses remain to be determined.)

11. Challenge

Using the data that 1-in-60 of all neonates develop autism and that 3,853,000 babies were born in the United States in 2017 would average

out to another 165 newborn children in America who would develop a form of this disease *every day* of that year. It is estimated that it typically would be in the range of an additional $3,000,000 to raise such an affected child.[7,100] Therefore, research to solve the autism enigma is urgently needed for both humanitarian and medical reasons.

Numerous etiologic theories for autism have been proposed without proven basis (e.g., pollutant exposure,[106] major genetic mutations,[107] and digestive tract changes).[108] The currently entertained model incorporating glia cells, myelination, dysconnectivity, and IGF-1 could explain atypical connectivity. Such a defect is principally found in the frontal networks and corpus callosum, and seems to be most viable inclusive scheme proposed thus far[46,109] (see Section 8 and Fig. 2).

Just as diminished serum IGF-1 parallels poor postpartum brain growth and is a major indicator of depressed CNS development in preterm infants,[103] so too, it relates directly to potential brain dysconnectivity in autistic full-term children. IGF-1 augmentation can diminish brain injury after hypoxic events, much like the benefit of breastfeeding neonates as it relates to autism.

At birth, the baby's cord blood IGF-1 concentration is largely independent of the mother's level.[110] Depressed neonatal serum IGF-1 may result in poor postpartum brain growth, especially in SGA (small for gestational age) babies. It is a predictor of reduced or delayed CNS development, especially in preterm infants.[111] Deficiency of this growth factor can cause autistic brain dysconnectivity if left untreated. What remains to be determined is the umbilical cord serum IGF-1 limit below which aggressive postpartum growth factor replacement is indicated, as well as the minimum breast milk IGF-1 concentration that can be remedial in this regard.

Recent studies have demonstrated encouraging results using IGF derivatives to treat maladies such as Rett and Fragile X syndromes.[112,113] It has been proposed that IGF-1 and IGF derivatives are able to reduce synaptic defects in established cases. Also, these pharmaceuticals may alleviate neurotoxicity present in the AKT/mTOR pathway in affected microglia.[114]

As yet, no study has reported an antepartum or postpartum method which prevents or diminishes the development of classical autism in the infant other than prolonged breastfeeding *from birth* exclusively.[76,83,84,115–117] Although the pathologic processes in autism begin around birth, behavioral symptoms usually do not appear until ages 1–4 years. This could portend the futility of IGF-1 administration to psychologically symptomatic autistic patients, once the malady is well established.

Recent events have centered around the Covid-19 pandemic. To be investigated is if this virus has any effect on the developing fetuses, such as autism.[118]

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