



## A New Pharmacologic Approach for the Potential Reduction of Autism and Multiple Sclerosis

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### Abstract

Multiple sclerosis and autism bear significant neuropathologic similarities such as reduced myelination and elevated anti-myelin basic protein (anti-MBP). However, the ages at which multiple sclerosis and autism are first diagnostically apparent are typically quite different. Therefore, we are proposing a single therapeutic model that may be beneficial for both conditions using glatiramer to modulate the antibody to MBP, and insulin-like growth factor to stimulate the myelination of neurons. This new approach needs to be evaluated in future clinical studies.

### Background and Relevant Associations

When comparing autism spectrum disorder (ASD) and multiple sclerosis (MS), similarities and differences can be noted [1,2]. Both are maladies of myelination. Both display elevated titers of myelin basic protein antibodies. However, the pathology of autism begins in infancy and mainly involves reduced neo-neurogenesis of the central nervous system (CNS). In contradistinction, the neuromuscular manifestations of MS most often first appear in adulthood.

Studies of brain biopsies from cases of ASD have identified symmetrically reduced myelination of newly formed neurons, whereas myelin sheaths in unaffected individuals are uniformly thicker [3]. The neurologic symptoms of the disease are thought to be related to altered synaptic function in the young central nervous system. Loss of Purkinje cell cerebellar tracts has been detected in autistic children by MRI tractography [4]. In contradistinction, demyelination of established neurons in MS is patchy and irregular. This presentation is apparently a consequence of specific local autoimmune degradation of established myelin components; mature nerves exhibit diminished velocity of impulse transmission and, subsequently, muscle degeneration occurs [5].

Because of the age of onset, brain dysconnectivity could account for the behavioral problems encountered with childhood ASD but not with MS, which typically appears first in adults [6]. Besides ASD, dysconnectivity has been implicated in other neuropathies such as Friedreich's ataxia and schizophrenia [7,8]. In the latter,

miswiring is related to aberrant synaptic plasticity due to abnormal receptor function. Significant dysconnectivity is identified in treatment-resistant schizophrenics when compared with their healthy siblings [9].

The 70-amino acid polypeptide, insulin-like growth factor-I (IGF), is thought to be a key parameter in the genesis of ASD because of:

- A. Reduced IGF in the cerebrospinal fluid (CSF) of young autistic children [10];
- B. IGF activation of myelination via oligodendrocytes [11];
- C. Laboratory mice altered to exhibit autism-like behavior improve when given IGF [12];
- D. Milk, especially from human sources, contains significant levels of IGF. Groups of babies breast-fed (in contradistinction to formula) for extended periods later display a lower overall incidence of autism than the general population [13];
- E. Very-small-for-gestational-age (VSGA), very premature newborn commonly have lower levels of IGF in their

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blood than normal-sized babies. Such small children also exhibit a higher incidence of ASD later [14,15];

- F. In addition to IGF, two other bioactive factors are often elevated in autistic individuals: one is serotonin and the second is anti-myelin basic protein IgG (anti-MBP). The latter may be acting to retard production of functional new neurons through myelin deficiency. It has been proposed [16,17] that the serum concentrations of these three factors can be combined at birth to determine the Autism Index (AI) to predict the likelihood of later development of autism. (Future studies may show that the magnitude of AI defines the position of a given case on the Autism Spectrum):

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

Where, p = weighted probability; n = percent departure from normal; 1 = IGF; 2 = anti-MBP; 3 = serotonin concentration.

## Hypothesis

### Enhancing pharmacologic efficacy in autism

Giving IGF to autistic patients to alleviate symptoms has been proposed [18]. However, myelin defects already established in older affected individuals (especially brain dysconnectivity) may be beyond functional repair [19,20], with the possible exception of mesenchymal stem cell therapy [21]. IGF *in vivo* has numerous additional control functions such as modulating skeletal growth rate, longevity, and tumor enlargement [22], which may be problematic. Thus, it could be advantageous to chemically isolate the portion of the IGF macromolecule able to promote a specific neurologic benefit exclusively or predominately.

One might consider a newborn's random motions as a trial-and-error experiment in identifying the most beneficial neuromuscular mechanisms for use in life. Once a utilitarian neuronal pathway is defined, it is made permanent. This "cementing" is promoted by myelination. A large portion of these neural roadmaps are established within the first year of life. Based on behavioral changes, ASD becomes evident and is typically diagnosed between the ages of 1 and 4 years [23,24]. In that the irreversible neurologic damage characteristic of autism is largely sustained in the first 1-2 years of postpartum life, early diagnosis and preventive therapy must begin before symptoms arise.

Serum IGF reaches a peak concentration at the time of the teenage growth spurt and decreases steadily thereafter [25]. Little or no symptom resolution in autistic individuals typically occurs by that time because of the infantile onset of central dysconnectivity. If one of the prime factors in this process (IGF) is deficient

since birth, unsupported efforts by the body to correct psychosocial defects beyond the first year of life are futile. Therefore, timely augmentation of IGF supply and the promotion of myelin generation in the neonate are both essential.

Concerning the putative association of immunologic factors and autism, maternally derived anti-brain autoantibodies have been found in as many as 20% of mothers with children at risk for ASD [26,27]. Autism has been identified in the offspring of mothers with MS. This suggests the possibility of fetal exposure to immune assault *in utero*.

To corroborate this proposed pharmacologic bimodality approach to ASD, an appropriate initial clinical study would be to measure the serum IGF level at birth and to psychologically test each untreated child a one year or two later for signs and symptoms of autism. This would establish peripartum cord blood test limits to differentiate normal from deficient and clarify if such a distinction exists. A second phase of such a study would be a double-blind investigation where 50% of the neonates would be given IGF augmentation and the rest placebos. After the first year of life, children who had received the IGF supplement would be compared to those who did not, for the incidence of autism as it may relate to the neonatal IGF level. (Increlex<sup>®</sup> is a synthetic analogue of IGF that has been approved for human use by the FDA.) As an immunomodulator of anti-MBP, glatiramer added in this setting should augment myelin biosynthesis.

### Enhancing pharmacologic efficacy in multiple sclerosis

A drug which is widely utilized to lengthen the time between relapses in MS is glatiramer acetate (Copaxone<sup>®</sup>), a random amino acid polymer similar in composition to MBP [28]. It is believed that glatiramer produces its benefit by complexing with the anti-MBP antibodies and reducing T-cell attack, thereby raising the level of the free MBP available for the regeneration and organization of functional myelin. The primary benefit of this drug in relapsing MS, for example, is to extend the time between attacks; in the long term, the disease typically eludes improvement under this regimen, however.

The observation that the symptoms of MS exacerbate with a patient's age, and that the serum IGF level in all humans normally falls with age, further supports the contention that demyelination in this disease is related to the total quantity of free IGF available [24-29]. The variation in the rate of decrease of IGF activity is believed due in part to polymorphism of the IGF gene on chromosome 12, mRNA heterogeneity, and

concentrations of the growth factor's six binding proteins [29-33]. Hypomyelination caused by growth hormone deficiency can be reversed by IGF-1 in transgenic mice [34]. Thus, the potential for spontaneous remyelination of denuded axons in MS patient's decreases with age [5], unless additional IGF can be supplied parenterally.

IGF alone given to MS patients has proven ineffective [35]. This may be due to the concurrent up-regulation of one or more of its six binding proteins (IGFBPs), thereby limiting the level of free IGF. Some species of truncated IGF have weakened adherence to IGFBPs and, as a result, increased activity [36,37]. Of particular value would be an IGF analogue which seeks growth factor receptors but interacts only weakly with IGFBPs.

In current MS therapy, glatiramer by itself would appear to diminish the immunologic degradation of myelin basic protein, a fundamental building block of myelin [28]. To promote the reparative function of glatiramer could be the incorporation of the oligodendrocyte stimulator, insulin-like growth factor-1. Glatiramer advances oligodendrogenesis *in vitro* by Th2 lymphocyte stimulation of IGF biosynthesis, but apparently not enough to overcome the effects of demyelination in test animals or affected humans [38-40]. It would seem more appropriate to treat multiple sclerosis cases with both parenterally administered glatiramer and IGF (or one of its truncated forms) together. In this way, the availability of free MBP and activated oligodendrocytes would be enhanced to achieve more neurologic rescue.

Another 2-agent approach for treating demyelination diseases has been studied. Using mesenchymal stem cells for neuro-restoration synergistically with a protein kinase inhibitor, such as Fasudil<sup>®</sup>, the combination had a benefit superior to either modality alone [41]. Multi-functional pharmaceutical combinations (e.g., Atripla<sup>®</sup>) have been especially efficacious in arresting very high HIV RNA concentrations [42].

## Discussion and Propositions

From the discussions reviewed above and from definitive or suggestive prior research already reported, it would appear that ASD and MS have characteristics in common:

1. Defective myelination of new (in the fetus and/or neonate) or established (in the adult) neurons;
2. Autoantibodies that prevent the initial generation or participate in the subsequent damage of functional myelin sheaths;
3. Diminished ability to create new or repaired myelin through the constructive effects of IGF or similar agents; and

4. Both conditions have been attributed to genetic polymorphisms, although a comparison of the two diseases in this aspect remains to be investigated. Polymorphism found in the IGF gene is related in some cases to suppressed levels of the growth factor. Gene studies have validated associations between multiple sclerosis and polymorphic nuclear variants [43,44].

The present hypothesis would appear to resolve some shortcomings of previous therapeutic attempts. MBP is needed for constructing and assembling myelin. The presence of anti-MBP in ASD and in MS may well be a consequence of a viral infection in either the mother before parturition or in the postpartum infant since IL6 can act as an immunologic stimulus [1,45-48].

It is therefore proposed that the combination of glatiramer to reduce anti-MBP activity and IGF to promote neo myelination would enhance the pharmacologic benefit in treating both diseases for similar reasons:

1. Neutralizing the anti-MBP in either malady would enhance the effective concentration of this essential protein component in subsequent myelin synthesis.
2. The inclusion of IGF in treating both diseases would stimulate oligodendrocytes to promote the biosynthesis of myelin for neogenesis or repair. Early initiation of the combination of the drugs would appear to more effectively retard the development of neuropathologic symptoms than either pharmaceutical alone.
3. If serum IGF levels at birth do indeed predict the subsequent development of autistic symptoms, then treatment with a selective synthetic analogue of IGF and glatiramer may well alleviate at least the most serious aspects of the disease.

Clinical studies to corroborate this hypothesis in the case of both MS and ASD should now be undertaken. Such a combination of the two drugs may bear increased benefit in treating both ASD and MS. However, it must be emphasized that this regimen is not intended to reverse all of the pathology created by either malady. It will probably not change already existent dysconnectivity in ASD and not reestablish fully functional musculature in MS.

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