Alpha1 MZ Foundation - Information & Research

News & Research Update

Aug 10, 2024

Dear Subscribers,

This time, two very exciting subjects from research sources.

- A new therapeutics medication that corrects the Serpina 1 gene for us Alpha's
- The discovery of a B12-related antibody causing serious neurological issues, which may have a relationship with Alpha1 because of the autoimmune issues caused by the low AAT levels.

Intellia Therapeutics

Intellia Therapeutics recently announced that it received authorization to start its phase 1-2 clinical trial of NTLA-3001 in the second half of 2024.

NTLA-3001 is a potential **one-time gene editing** treatment that may normalize AAT protein levels and is Intellia's first CRISPR-based targeted gene insertion candidate to advance into clinical trials. NTLA-3001 is designed to precisely insert a healthy copy of the SERPINA1 gene, which encodes the AAT protein, with the potential to **restore permanent expression of functional AAT protein** to therapeutic levels after a single dose.

The Phase 1/2 study will be an international, multicenter, single-arm, open-label study of NTLA-3001 in adults with AATD-associated lung disease. The study will enroll up to 30 patients and consist of a dose-escalation phase, followed by a dose-expansion phase to confirm the recommended dose. The study will evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of NTLA-3001. See below the link to the press release.

https://ir.intelliatx.com/news-releases/news-release-details/intellia-therapeutics-receives-authorization-initiate-phase-12-0?fbclid=IwY2xjawEhnx1leHRuA2FlbQIxMQABHXyhL2GTSYVrb5XdM0uD0wDNjzyCGcIO4bl_qucWk9otc4wSgVkeS9AxaA_aem_QmJIXDhtcfr6ZjKdZrA3ag&sfnsn=scwspwa

Vitamin B12-related neurological issues caused by Autoimmune disease

This research article needs some introduction:
Our preliminary clinical study among Alpha1 MZ patients observed a very high prevalence of Alphas with Vitamin B12 deficiency, and we developed a Thesis that may explain the root cause of this deficiency among the MZ population.

The abstract of this study, shown below, suggests a possible alternative root cause, which may be affiliated with an Alpha1 Antitrypsin deficiency.

This research paper shows that a particular autoimmune issue may cause severe neurological problems caused by a B12 deficiency at the cell level while the blood B12 level is normal. We also know (based on research papers) that a low AAT will cause Autoimmune issues (Antibodies) in Alpha1 patients.

This paper is fascinating because it provides evidence that while your B12 blood level is completely normal, you may still have a serious B12 deficiency induced by Antibodies stopping B12 from

entering the cells where it has to do its work. This particular autoimmune issue is causing Transcobalamin (B12) receptor antibodies, which means that the B12 is not reaching the cells. (in this case, the brain) Adding high levels of B12 (something we see in our clinical practice) enabled an alternative pathway for B12 to enter the cells and, as such, provided a solution.
(Note: Many MZs use B12 injections to resolve neurological issues.)

Abstract of the paper

Vitamin B12 is critical for hematopoiesis (blood cell production) and myelination (formation of an isolation layer around a nerve). Deficiency can cause neurologic deficits, including loss of coordination and cognitive decline.
However, diagnosis relies on the measurement of vitamin B12 in the blood, which may not accurately reflect the concentration in the brain. We identified an autoantibody targeting the transcobalamin (B12) receptor (CD320) in a patient with progressive tremor, ataxia, and scanning speech. Anti-CD320 impaired cellular uptake of cobalamin (B12) in vitro by depleting its target from the cell surface. Despite a normal serum concentration, B12 was nearly undetectable in her cerebrospinal fluid (CSF). Immunosuppressive treatment and high-dose systemic B12 supplementation were associated with increased B12 in the CSF and clinical improvement.

Optofluidic screening enabled the isolation of a patient-derived monoclonal antibody that impaired B12 transport across an in vitro model of the blood-brain barrier (BBB). Autoantibodies targeting the same epitope of CD320 were identified in seven other patients with neurologic deficits of unknown etiology, 6% of healthy controls, and 21.4% of a cohort of patients with neuropsychiatric lupus. In 132 paired serum and CSF samples, the detection of anti-CD320 in the blood predicted B12 deficiency in the brain. However, these individuals did not display any hematologic signs of B12 deficiency despite systemic CD320 impairment. Using a genome-wide CRISPR screen, we found that the low-density lipoprotein receptor serves as an alternative B12 uptake pathway in hematopoietic cells. These findings dissect the tissue specificity of B12 transport and elucidate an autoimmune neurologic condition that may be amenable to immunomodulatory treatment and nutritional supplementation. Below is the link to the article.

https://www.medscape.com/viewarticle/form-b12-deficiency-affecting-central-nervous-system-may-be-2024a1000c5q

The key takeaway of the above is:

- Alpha 1 is known to cause autoimmune issues
- Autoimmune issues may lead to B12-related serious neurological issues
- You can have a B12 deficiency leading to severe neurological problems while the B12 level in your blood is normal.
- Adding high amounts of B12 (injections) resolved the deficiency by using an alternative path into the cell. (Which is currently used by many Alpha's)

And, like always, enjoy the ride !!

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