SYNGAP1-Related NSID

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General Discussion

Summary

Intellectual disability (ID) is a common disorder defined by the presence of significant limitations in both cognitive and adaptive behaviors with onset before the age of 18. ID is subdivided into syndromic intellectual disability, in which intellectual deficits and distinguishing morphologic, radiologic or metabolic features are present, and non-syndromic intellectual disability (NSID), in which intellectual deficits appear without these physical abnormalities. Mutations in the *SYNGAP1* gene are thought to be a relatively common cause of NSID. NSID patients, including those associated with *SYNGAP1* mutation, typically exhibit moderate to severe ID with a high prevalence of epilepsy and/or autism spectrum disorder (ASD) and may also have attention deficits, impulsivity, and/or mood disorders. *SYNGAP1*-related NSID patients with epilepsy usually respond well to medications, yet some are refractory (difficult to control even with multiple drugs). *SYNGAP1*-related NSID is a sporadic condition that is caused by *de novo* (spontaneous, noninherited) mutations. The use of genomic sequencing has dramatically increased the capacity of physicians to identify these mutations.

Introduction

SYNGAP1-related NSID in humans was first reported in 2009 and is one of the first genes found to be associated with NSID. Since initially described, an increasing number of children with *SYNGAP1*-related NSID have been identified, suggesting that it may represent one of the most common causes of ID.

Signs & Symptoms

Children with *SYNGAP1*-related NSID present with mild hypotonia (low muscle tone) and global developmental delay at the end of the first year or during the second year of life. They can start to walk at a normal age but more frequently later in life (range: 14 months to 30 months of age). Rarely, their gait is described as being ataxic (unstable). Language development is also variably impaired with some children speaking with isolated words, associations of two or three words or with simple short sentences, whereas others remain non-verbal. Some of the children show oral dyspraxia (oral motor dysfunction), which can result in drooling or eating difficulties.

While the primary symptom of *SYNGAP1*-related NSID is moderate to severe cognitive impairment, a large percentage of children are also diagnosed with autism spectrum

disorder (ASD). Other behavioral abnormalities include inattention, impulsivity, and physical aggression (hitting, biting). Mood swings, sullenness, and rigidity are also reported in many children.

Approximately 97% of children with *SYNGAP1*-related NSID develop epilepsy characterized by a variety of seizures including absences, myoclonia (brief, involuntary twitching of a group of muscles), generalized tonic-clonic seizures (grand mal seizures), and drop attacks. The seizures usually start during the first few years of life. Seizures are well controlled in most of the children with the administration of a single anti-epileptic drug but in some cases seizures are refractory.

The appearance and growth of children with *SYNGAP1*-related NSID are not unusual. Some children will develop microcephaly (smaller head circumference). The presence of this feature does not correlate with the severity of the cognitive impairment.

Children (and presumably adults) with *SYNGAP1*-related NSID continue to develop, progressing at their own pace. Unless their epilepsy is not well controlled, they do not regress or deteriorate and can always continue to learn.

Causes

The human genome is composed of approximately 20,000 genes. A great majority of these genes, including the *SYNGAP1* gene, are expressed as two copies (one copy inherited from each parent). Only a single abnormal copy of the *SYNGAP1* gene is sufficient to cause NSID (haploinsufficiency). The abnormal gene is usually the result of spontaneous mutation(s) (not inherited from either parent, also called *de novo* mutation) although in rare cases can be inherited from a non-affected parent due to a genetic phenomenon called gonadal mosaicism. The new mutations occur spontaneously in the sperm or egg cells of one of the parents.

The *SYNGAP1* gene encodes for the protein, SynGAP (brain-specific RAS GTPase-activating). Normal levels of SynGAP protein are essential for proper brain function and development. Within the brain, the protein is most often found at synapses (points of communication between neurons) where it regulates critical biochemical signaling pathways that support learning and memory capabilities.

Affected Populations

Intellectual disability caused by mutations in *SYNGAP1* appears to be equally prevalent in males and females. The disorder is recognizable early during childhood. No adult has yet been reported with a mutation in *SYNGAP1*. However, because affected children are generally healthy, this disorder may be as prevalent in the adult population as it is in children. *SYNGAP1*-related NSID is found in all ethnic groups, with the same prevalence.

Related Disorders

There are several genetic forms of global developmental delay or intellectual disability that can mimic *SYNGAP1*-related NSID. Distinguishing them on a clinical basis is difficult without genetic testing.

Diagnosis

Children with moderate to severe non-syndromic global developmental delay (GDD) or ID should be genetically screened for potential involvement of genes. The presence of a generalized form of epilepsy (recognizable by physicians by the type of seizures and the EEG pattern) is consistent with the diagnosis. Microcephaly, when present, is not congenital but acquired. Brain imaging techniques such as MRI usually do not show any specific neural abnormalities.

Because such a clinical presentation is common and associated with numerous genes, specific genetic testing for mutations in *SYNGAP1* results in a low yield. More recently, physicians are requesting genomic testing (the exploration of all genes at once) for the investigation of children with GDD/ID. By exploring the whole genome in this way, physicians aim to increase their chance of finding the gene causing their patient's disorder. They usually start with a genome-wide search for deletions or duplications that encompass single or multiple genes using array hybridization. If this analysis does not yield answers, the next step could be the sequencing of all the genes (whole-exome or whole-genome sequencing).

Standard Therapies

Clinical Testing and Workup

Genetic testing provides definitive diagnosis of *SYNGAP1*-related NISD. Medical assessment for the possibility of seizures, swallowing difficulties, ASD and other behavioral abnormalities is recommended. Because brain MRI does not typically show any abnormality in these children, it is not formally indicated to perform this exam. Neurologists, however, may request a brain MRI in children with seizures. The recommended evaluations for a child diagnosed with *SYNGAP1*-related NSID are summarized in the Management section of the following resource:

https://www.ncbi.nlm.nih.gov/books/NBK537721/

Treatment

Like other forms of intellectual disability, there are no known disease-altering treatments for *SYNGAP1*-related disorders. Current treatment for NSID in general is directed toward the specific symptoms that are apparent in each individual. Management may require the coordinated efforts of a team of specialists. Pediatricians, surgeons, pediatric neurologists, gastroenterologists, psychiatrists, speech pathologists, and other healthcare professionals may need to systematically and comprehensively plan an affected child's treatment.

Treatment options that may be used to treat individuals with an ID are complex and varied. The specific treatment plan will need to be highly individualized. Decisions concerning the use of specific treatments should be made by physicians and other members of the health care team in careful consultation with an affected child's parents or with an adult patient based upon the specifics of his or her case; a thorough discussion of the potential benefits and risks, including possible side effects and long-term effects; patient preference; and other appropriate factors.

Early developmental intervention is important to ensure that affected children reach their potential. Most affected children will benefit from occupational, physical and speech therapy. Various methods of rehabilitative and behavioral therapy may be beneficial. It is essential that therapies are continued on a year-round basis to promote development of new skills and to prevent regression. Additional medical, social and/or vocational services including special remedial education may be necessary. Psychosocial support for the entire family is essential as well. Other treatment is symptomatic and supportive. Additional therapies for an NSID syndrome depend upon the specific abnormalities present and generally follow standard guidelines. Anti-seizure medications are usually effective in treating seizures for those patients that present with epilepsy; however, in a subset of patients, these medications do not work (refractory seizures) requiring non-pharmacologic treatments such as epilepsy surgery or neurostimulation.

Genetic counseling is recommended for affected individuals and their families.

Investigational Therapies

There is a concerted, worldwide effort to develop personalized therapies for patients with genetic forms of NSID. With respect to *SYNGAP1*-related disorders, evidence indicates that pathogenic *SYNGAP1* mutations disrupt biochemical signaling pathways in neurons that promote cognitive ability. Thus, repairing these disrupted signaling pathways is a promising pre-clinical therapeutic avenue. One of the roles of SynGAP protein is to regulate synaptic plasticity and learning by controlling the Ras/ERK cell-signaling pathway in the brain. Indeed, evidence in the literature suggests that aberrantly elevated RAS/ERK signaling contributes to long-term cognitive deficits, further supporting the notion that this pathway is a valid pre-clinical therapeutic target in *SYNGAP1*-related disorders.

Pre-clinical studies in models of other intellectual disability syndromes suggest that cholesterol-lowering statin drugs (HMG CoA reductase inhibitors), such as Lovastatin (Mevacor) and Simvastatin (Zocor), can reduce elevated Ras/ERK signaling, with corresponding improvements in cognitive deficits. These FDA-approved statins are the focus of clinical trials for intellectual disability disorders caused by fragile X syndrome and neurofibromatosis type 1. As of 2019, these compounds have not yet showed enough promise to warrant FDA approval. However, research is ongoing in animal models of *SYNGAP1*-related disorders to determine if these cholesterol-lowering compounds can improve biochemical signaling, glutamatergic neuron function and cognitive ability in animal models. In addition, other pre-clinical strategies are being developed, such as the early phase discovery and testing of novel drug-like probes that can restore the function of SynGAP protein in neurons damaged by severe mutations.

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Tollfree: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

Some current clinical trials also are posted on the following page on the NORD website: https://rarediseases.org/for-patients-and-families/information-resources/info-clinical-trials-and-research-studies/

For information about clinical trials sponsored by private sources, contact: www.centerwatch.com.

For information about clinical trials conducted in Europe, contact: https://www.clinicaltrialsregister.eu/

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