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Editorial/Commentary

Short Takes

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Petty S and Gross RA. Special editorial: Neurology null hypothesis: A special supplement for negative, inconclusive, or confirmatory studies. Neurology. 2018:Epub2018 June 8

Flash Summary: The idea of this supplement is to publish manuscripts that increase transparency in science and medicine. The journal will seek negative, inconclusive and confirmatory studies. Such studies are currently not readily published in mainstream journals concerned about their impact factor.

Bottom Line: Most journals ask the reviewer to analyze whether the manuscript under review is new or confirmatory. New information always trumps both confirmatory and negative information in the current literature.

Petty and Gross believe that publishing even negative articles provides a real service. The publication of negative papers will allow authors to design studies that might improve on a published study that is negative.

Many negative studies need to be published and can be just as useful as a positive study. Hopefully, negative clinical trials funded by pharmaceutical companies can also be published. Let's be hopeful. It is a real waste for researchers to replicate completed clinical trials that were not published because they were negative.

Bigi S, Dulcey A, Gralla J, et al. Feasibility, Safety, and Outcome of Recanalization Treatment in Childhood Stroke. Ann Neurol. 2018;83:1125-132

Flash Summary: Intravenous thrombolysis and endovascular therapy (IVT/EVT) are evidence-based treatments for adults with stroke, but there are few data in childhood stroke. This was a retrospective study over a ten year period. It was a multicenter, population-based cohort of stroke in patients between one month and 16 years old. All had an arterial ischemic stroke (AIS) and all had a Pediatric National Institutes of Health Stroke Scale pedNIHSS of greater or equal to 4. Patients who underwent IVT/EVT were compared to children who underwent standard care. Outcome was assessed at six months after the stroke using the Pediatric Stroke Outcome Measure (PSOM). One hundred fifty patients with a mean age of seven years were included. Recanalization therapy was performed in 16. Patients receiving recanalization were older and sicker. Death and bleeding did not differ between the two groups. After multiple linear regression analyses, only higher NIHSS remained as a predictor of outcome.

Bottom line: This study shows that IVT and EVT are probably safe but there are no efficacy data here. EVT for now will be utilized on a case by case approach, but we are unlikely to ever have prospective data. With pediatric AIS and a clot, an individual EVT approach will be necessary. However, it should be used sparingly.

As for IVT, there are no efficacy data in children. Since IVT seems as safe in children as in adults, a study is necessary. A U.S. study was planned but failed in recruitment since it required the imaging of a clot to start IVT. This is just too cumbersome and resulted in too many exclusions of potential subjects. This is in contrast to adult studies which, when first performed, had simple inclusion criteria. A pediatric study should include IVT in patients with probable AIS and consistent MRI. This should be adequate for inclusion criteria resulting in better recruitment. This is sensitive but probably not as specific as in the adult population. IVT should be studied as a treatment trial after a clinical exam, history and fast MRI. The study can be done since there is equipoise as to the efficacy of IVT in the pediatric population. We only need simple and fast inclusion criteria.

Seong E, Insolera R, Dulovic M, et al. Mutations in VPS13D lead to a new recessive ataxia with spasticity and mitochondrial defects. Ann Neurol. 2018;83:1075-1088

Flash Summary: The study aimed to identify novel causes of recessive ataxias including spinocerebellar ataxia with saccadic intrusions, spastic ataxias and spastic paraplegia. This was an international collaboration; these authors performed exome sequencing in seven families with recessive ataxia and/or spastic paraplegia. The authors also evaluated a drosophila knockout model and assessed mitochondrial function associated with the mutation.

Exome sequencing identified a compound heterozygous mutation in VPS13D on chromosome 1. The phenotype for the

Editor's note: Short Takes offers a brief analysis by Steven G. Pavlakis of selected articles that may be of interest to child neurologists. Papers that strike the fancy of the analyst or the editors are selected for inclusion, but we welcome suggestions.

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mutation is variable between affected patients and includes ataxia and spasticity in some. Disease onset ranged from infancy to age 39 years. Symptoms were slowly progressive with a loss of ambulation in five individuals. Fibroblasts showed reduced energy production implicating mitochondrial function. All but two carried a loss of function.

The study demonstrates that a compound heterozygote mutation in VPS13D causes movement disorders along with ataxia and spasticity, making the VPS13D the fourth VPD13 paralog involved in neurological disease.

Bottom line: The hereditary ataxias are diverse with broad phenotypic variability. I remember seeing patients with Freidrich ataxia (FA) as a resident and the clinical phenotype at that time seemed very specific. With the determination of a mutation, I realized the phenotype was broader and patients might only have ataxia on presentation with FA. I sent a patient with progressive ataxia many years ago for genetic testing convinced that the patient did not have FA since the 11 year old boy only had cerebellar ataxia. Well, he did have FA and was mutation positive. Studies, however, need to define the mutation first with a more specific phenotype. Once the mutation is found clinical investigations can be performed to understand the full scope of the phenotype.

With the decreasing cost of sequencing and the improved availability, it is now clinically possible to evaluate ataxia patients in ways not even dreamt about ten years ago. Here, VP13D results in ataxia, spasticity and mitochondrial dysfunction resulting in a slowly progressive disease.

Over the next decade, we hope to have treatments that we can only speculate upon at present. Phenotypic-genetic studies will help us achieve this goal of improving patient care.

All these genetic phenotypic studies seem a bit tedious but are making important strides. Very careful and systematic genetic studies coupled with excellent phenotypic data are the way to go to understanding genetic disease. The phenotypic “splitting” approach works for initial gene finding studies and “lumping” does not.