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Editorial/Commentary

Short Takes

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Data-driven analyses revealed the comorbidity landscape of tuberous sclerosis complex. Yu K, Miron O, Palmer N, et al. Neurology 2018; 91:974-976

Flash summary: This study, using *International Classification of Diseases, Ninth Revision* (ICD-9) codes in an Aetna database, identified patients with tuberous sclerosis complex (TSC) between 2008 and 2016. Using a nationwide insurance database, the authors were able to access a clinical database of over 3000 patients with TSC and compare these to a non-TSC patient cohort who served as age- and sex-matched controls. The investigators examined differences in phenotype between 3131 patients with TSC and 500 patients without TSC with a mean TSC age of 34 years, S.D. of 23 years. No genetic data were included. The authors found that patients younger than 20 years of age were statistically more likely to exhibit benign kidney tumors, brain neoplasms, epilepsy, psychiatric disorders, and autism.

Bottom line: Using a nationwide insurance database, the authors were able to group over 3000 patients, defined phenotypically by ICD-9 codes. The use of big data is rational in constructing phenotypes of rare diseases. More interesting would be a phenotype-genotype comparison, especially in other rare diseases, but this is more difficult because data are often not available and institutional review board clearance would be more difficult.

There is nothing terribly new here. I did not know that ulcerative colitis was associated with TSC, but this association is one of the weaker TSC comorbidities. This study is commendable, but I wonder how robust the phenotypic data are in an insurance ICD-9 study. I have to admit that I often only use one ICD code (now ICD, *Tenth Revision*). So, for example, I might use epilepsy in patients with TSC who primarily have epilepsy without coding for TSC. I tend to use the patient time for billing purposes because it is easier for me to enter the data for billable entries. As such, I may not include all the potential ICD codes. Let us face it; the authors are using an electronic medical record that is primarily a billing tool to extract phenotypic data.

Once Sidney Carter, one of the pioneers of our field, said to me "Bad data in, bad results out." He used much more colorful words that I cannot repeat in this journal. My guess is that using ICD data is very limited, and even though the data may not be bad, they might be very limited. So I would conclude limited data in, limited conclusions out. All the fancy statistical analysis in the world cannot change the fundamental fact that the data in are key to good results and conclusions.

Long-term treatment effect in cerebrotendinous xanthomatosis depends on age at treatment start. Stelten BML, Huidekoper HH, van de Warrenburg BPC, et al. Neurology 2019; 92:e83-e95. Doi:10.1212/WNL.0000000000006731

Flash summary: The authors attempted to determine whether chenodeoxycholic acid (CDCA) treatment affects the progression of neurological disability in cerebrotendinous xanthomatosis (CTX). The study reviewed data from 56 Dutch patients with CTX and examined whether age at diagnosis and initiation of chenodeoxycholic acid treatment correlated with the clinical characteristics and the changes in biochemical and functional scales. The median follow-up was eight years. Compared with participants diagnosed after age 24 years, those diagnosed before age 24 years had a better functional outcome. The authors conclude that early treatment improves the functional neurological outcome.

Bottom line: CTX is a rare autosomal recessive disorder caused by an abnormality in the *CYP27A1* gene. This results in a deficiency of the mitochondrial enzyme sterol 27-hydroxylase, even though the genetic abnormality is nuclear not mitochondrial. Here cholesterol and cholesterol deposits occur in the nervous system. Patients may have early diarrhea and cataracts during childhood. Some develop fatty tendinous xanthomas. The disease often leads to progressive neurological degeneration with ataxia, dementia, and spinal problems and the accumulation of the deposits in the nervous system.

I have never seen this disease, although it is always possible that I have seen a patient with CTX and missed the diagnosis. This study is limited by its retrospective nature, large age range (10 days to 51 years), and variable follow-up intervals (six months to 31 years). As a result, a few patients can skew the outcome

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

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statistics. In addition, patients who were not deemed compliant were excluded from analysis, producing yet another potential bias. Having said this, with such a rare disease, we may need to compromise on study design. The study in my opinion provides compelling data for treatment efficacy. As this is similar to a leukodystrophy and storage disease, it seems rational that early treatment improves neurological outcome more than delayed treatment. Another confounder is the phenotypic heterogeneity, which makes any treatment trial difficult. As with many genetic disorders, phenotypic variability, even within a family, may be profound.

Studies of rare diseases are difficult. However, a good clinical retrospective study from one center may be as good as one can do. The treatment effect described seems reasonable. We need to be flexible with trials of rare diseases and conclusions gleaned from what is available.