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Pediatric Multiple Sclerosis - Characterizing a Rare Disease

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This study provides some insight into how one approaches understanding a relatively rare disease, using standardized disease scoring and monitoring logged into large registries.

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Source: Iaffaldano P, Simone M, Lucisano G, et al. Prognostic indicators in pediatric clinically isolated syndrome. **Ann Neurol. 2017;81(5):729–739**; doi:10.1002/ana.24938. See **AAP Grand Rounds commentary by Dr. David Urion** (subscription required).

Oh, and did I mention this is one of the most complex statistical analyses for a study I've reviewed on these pages in the last 7 years? Don't worry, I won't get you too bogged down in the details!

This study struck me as very illustrative of how researchers approach gathering information about relatively rare diseases. Any meaningful data ideally would involve a large number of participants, so for rare diseases that would involve multiple centers. It's tough to coordinate that for a prospective randomized controlled trial of a treatment intervention, but maybe a bit easier (still tough!) to gather data. That's usually done by having national or international disease registries, where clinicians can enter selected data about their patients, ultimately to be analyzed and reported by a central coordinating team.

The current study pertained to "pediatric Clinically Isolated Syndrome (pCIS)," defined as a "monofocal or multifocal clinical central nervous system event of presumed inflammatory demyelinating cause with acute or subacute onset in the absence of encephalopathy, not explained by fever or systemic illness" and not meeting certain criteria for other disorders such as multiple sclerosis or acute disseminated encephalomyelitis. pCIS tends to recur and may be a harbinger of pediatric-onset multiple sclerosis. Prior studies had suggested that use of disease-modifying drugs (DMDs; e.g. interferon-beta, monoclonal antibody drugs) were associated with lower risk of recurrent neurologic events.

Researchers used 2 different pCIS registries, one based in Italy and the other more international, and subjects for this study were drawn from 76 different centers around the world (none from the US). Based on

their analysis of 770 patients, they found that DMD use was associated with a lower rate of second attacks and of disability.

A few take-home points: this was a retrospective observational study, though the authors termed it a "retrospective observational study performed on prospectively acquired data." What I take that to mean is that clinicians entered data about their patients prospectively, but not every patient had all the data items available. For example, not all children had cerebrospinal fluid analysis performed. That becomes a problem when one tries to analyze the results looking at different variables (multivariate analysis). If some of the data points are missing, it doesn't work. A way around this is a form of legitimate fudging called imputation or bootstrapping. We've talked about this **before**, and I noted even our beloved US Census Bureau has used the technique when they are unable to get full data with their mail and door-to-door surveys. It's a method to "assume" what the missing data would have been, based on the rest of the dataset. It may send a bit sketchy on the surface, but it is a validated statistical method.

As I indicated at the top, other aspects of the statistical methodology are well beyond my expertise; 1 is of particular interest, a computerized methodology for **recursive partitioning** called Recursive Partitioning and Amalgamation (RECPAM) methodology. If you can fully understand it, please contact me so I can learn too!

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