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The Gray Zone of Periodic Fevers

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Last week I wrote about a retrospective case series study that could change clinical practice, but for this week's study of a similar design I would argue the reverse. Both studies are well-done, so why the difference in applying the results?

Source: Lantto U, Koivunen P, Tapiainen T, et al. Long-term outcome of classic and incomplete PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis) syndrome after tonsillectomy. J Pediatr. 2016; 179:172-7. doi:10.1016/j.jpeds.2016.08.097. See AAP Grand Rounds commentary by Dr. Rebecca Brady (subscription required). required).

The study is a look-back at a large cohort (n = 108) of Finnish children with periodic fevers, specifically those who had classic (n = 58) or partial (n = 50) Periodic Fever, Aphthous stomatitis, Pharyngitis, and Adenitis (PFAPA) syndrome and underwent tonsillectomy. The "partial" group had at least 5 "regularly recurring" fever episodes but not associated with any of the 3 clinical findings (stomatitis, pharyngitis, adenitis), or they had onset of PFAPA-like illness after 5 years of age. Given that PFAPA has no conclusive diagnostic test, it's a bit tough to make the diagnosis, since this illness pattern certainly could be due to recurrent viral illnesses. Another feature of PFAPA, complicating any evaluation of treatment, is that it eventually resolves without intervention or apparent sequelae. In classic PFAPA, however, randomized controlled trials have strongly suggested that tonsillectomy results in earlier resolution of PFAPA symptoms.

The main focus of the study was to describe the effects of tonsillectomy on these 2 groups of patients, and the authors found that virtually all the patients, regardless of group, had immediate (defined as within 2 months of the procedure) resolution of the fever episodes. So, if this is a well-designed study, why shouldn't we jump on the tonsillectomy bandwagon for all these patients?

I can think of 3 main reasons to reserve judgment. First, it's difficult to define the patient population, as mentioned above. If some of the children have had an unlucky and unusual run of recurrent viral infections, of course that pattern will resolve eventually, and thus any intervention (including none) will appear to be highly effective. Second, it has all the problems with retrospective studies, including in particular here the problem of recall bias (if you think tonsillectomy is likely to help your child, maybe you'll ignore/forget about some febrile episodes). With a prospective study, at least the parents could be instructed to keep a fever and symptom diary and receive regular follow up. Third, remember that even classic PFAPA resolves spontaneously, meaning that the inclusion of a control group (no tonsillectomy) is highly important.

Which takes me back to the mention of randomized controlled trials of tonsillectomy in PFAPA. Notice that I didn't include the terms "placebo-controlled" or "double-blinded." Those are 2 features of prospective randomized controlled trials that help eliminate bias in the results, but they are virtually impossible to implement for tonsillectomy in PFAPA. First of all, a placebo group, which would need to feature some sort of sham operative procedure in children, is unethical. Secondly, the best one could do is single-blinding in such a study. Parents and children certainly know if a tonsillectomy was performed, but one could still ensure that the follow-up clinicians weren't aware of the treatment assignment. (Of course, a look in the oropharynx would reveal whether the child had undergone tonsillectomy.) Even for relatively objective outcome measures like fever and presence of aphthous stomatitis, pharyngitis, or adenitis, knowing the treatment assignment of a study patient can still introduce bias in how outcomes are recorded.

For this and other reasons (e.g. translating findings from a relatively genetically homogeneous population to my own diverse patient population), I'll wait for the randomized controlled trial of tonsillectomy in this partial PFAPA population; currently, there is nothing planned in ClinicalTrials.gov on this topic. I suspect that eventually someone will figure out the gene(s) responsible for this disorder and then our path will be clearer.

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