An Evolutionary Medicine Perspective on Treatment of Pediatric Functional Abdominal Pain

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Abstract: In a recent issue, Kovacic et al. analyze data from a randomized sham-controlled trial and show that pretreatment vagal efficiency, an index related to respiratory sinus arrhythmia, is a predictor of pain improvement in adolescents with functional abdominal pain when treated with auricular percutaneous electrical nerve field stimulation. The underlying premise is the polyvagal hypothesis, an explanatory framework for the evolution of the mammalian autonomic nervous system, which proposes that functional gastrointestinal disorders can result from a chronic maladaptive state of autonomic neural control mechanisms after traumatic stress. This is an opportunity for us to stimulate physicians' interest in evolutionary medicine.

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Effective therapy for functional abdominal pain disorders (FAPDs) is limited, especially in children, and patient response is largely unpredictable. Symptom clusters are not specific and sensitive enough as predictors of treatment response (i.e., effect modifiers), and no reliable biomarkers for response have been identified. Our limited understanding of the pathophysiology of these diseases complicates the proposal of clinical or biological effect modifiers for investigation. Inversely, if a credible and accurate effect modifier were found, this knowledge could lead to basic and applied research, which could boost our understanding of underlying disease mechanisms and reveal new treatment targets and effect modifiers. Therefore, progress requires either a reliable effect modifier or a valid explanatory model. The study by Kovacic et al. (1) in a recent issue of *The American Journal of Gastroenterology* may indicate advances in both aspects: it proposes an effect modifier in adolescents with FAPDs while its underlying premise, the polyvagal hypothesis, provides a fascinating explanatory model for FAPDs.

Building on the preclinical evidence that vagal afferents project to the auricle and percutaneous electrical nerve field stimulation (PENFS) modulates central pain pathways, Kovacic et al. recently conducted a randomized, double-blind, sham-controlled trial of auricular PENFS in 115 adolescents meeting Rome III FAPDs criteria at a US tertiary center. This low-risk-of-bias trial showed that 4 weeks of auricular PENFS significantly reduced abdominal pain (measured as worst pain or composite pain score) (2). Subsequently, they published a *post hoc* analysis restricted to 50 patients with irritable bowel syndrome, showing that a ≥30% reduction in worst abdominal pain was more frequently achieved with PENFS (59%) compared with sham stimulation (26%) (3). This led to a marketing authorization by the US Food and Drug Administration for the auricular PENFS device in adolescents with irritable bowel syndrome (4).

Kovacic et al. analyzed data from their original randomized trial on pretreatment values of respiratory sinus arrhythmia (RSA, variation in heart rate during each breathing cycle), heart period (time between heart beats), and vagal efficiency (VE, a related index calculated through the association between RSA and heart rate) (5). They determined that VE, but not RSA or heart period, was a predictor of pain improvement at week 3 among adolescents with FAPDs treated with PENFS. The lower the pretreatment VE, the more the pain improved.

As always, novel predictors of treatment response should be viewed with caution because attempts to replicate such results in subsequent randomized trials are typically unsuccessful (6). Application of the Instrument for the Credibility of Effect Modification Analyses (7) reveals low confidence that the apparent effect modification is true and not due to chance or bias for various reasons. The registered protocol in ClinicalTrials.gov did not mention data collection or analyses for effect modification. There was no adjustment for other potential effect modifiers (e.g., age, sex, magnitude of gastrointestinal symptoms and/or physiological or psychological stress during RSA measurement, or specific FAPD or subtype). The *P* value was significant (0.011) but did not reach the stringent threshold of 0.005, which is required for effect modification analyses. The R^2 was 0.1521, meaning that only 15% of the variability of the treatment effect was explained by the value of VE, whereas 85% of the variability remained unaccounted for; this is far from a strong correlation and, judging from figure Y (1), it is unlikely that baseline VE is sensitive or specific enough to guide a physician to treat an individual patient with PENFS. No sensitivity analyses assessed the robustness of the assumptions, e.g., using related outcomes, such as worse pain. There was a high risk of attrition bias, as 11.3% of participants were excluded because of treatment discontinuation, missing data, or being considered extreme outliers. Still, this is an important study with potentially huge impact if replicated in other trials because VE would be the first biomarker that predicts response to a treatment. Moreover, its measurement is noninvasive, relatively simple, and inexpensive.

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Table 1. Pathways by which evolutionary processes can affect disease risk (from Gluckman et al. (11) with permission)

1. An evolutionary mismatched or novel environment: The individual has been exposed to an environment beyond their evolved capacity to adapt or to an entirely different environment or challenge
2. Life history-associated factors
3. Excessive or uncontrolled defense mechanisms: Evolved processes that are normally adaptive become inappropriate and harm the individual
4. Losing the evolutionary arms race against other species
5. Results of evolutionary ("design") constraints
6. An apparently harmful allele is maintained by balancing selection
7. Sexual selection and competition and their consequences
8. The outcomes of demographic history

Notably, the Kovacic et al. article (1) calls attention to the polyvagal hypothesis, proposed by coauthor Stephen W. Porges 25 years ago and based on an evolutionary medicine viewpoint. The polyvagal hypothesis explains the evolution of the mammalian autonomic nervous system and the bidirectional brain–body interactions, including the brain–gut connection (8). It proposes that the dampened RSA that is frequently observed in patients with irritable bowel syndrome or other functional gastrointestinal disorders can expose a chronic maladaptive state of the neural (mainly vagal) control mechanisms, which is evident when acute neural defense responses that are adaptive and beneficial in the short term are maintained chronically after exposure to severe traumatic stress or abuse (9). Despite emerging evidence of the pitfalls of heart rate variability and related indices as markers of autonomic nervous system function (10), the polyvagal hypothesis remains a valuable model for basic and clinical research that could lead to important discoveries for patients with functional gastrointestinal disorders.

This is an opportunity for us to stimulate physicians' interest in evolutionary medicine. Other disciplines have long used evolutionary perspectives to explain observations, e.g., biologists' and anthropologists' assessments of reproductive strategies across species and cultural differences among human groups, respectively. By contrast, physicians have been slow to use an evolutionary perspective to understand disease. An evolutionary perspective considers causation of health and disease at 2 levels (11). *Proximate* causes are the immediate pathways (molecular, anatomical, and physiological mechanisms), e.g., the mechanisms by which *Helicobacter pylori* infection increases the risk of gastric cancer. *Ultimate* causes are the evolutionary explanations for why humans (or some individuals more than others) are more susceptible than other species to a specific disease and when and why a disease appeared during the evolution of our species. Table 1 summarizes pathways through which evolutionary processes act. Pathway number 3 is particularly relevant to the polyvagal hypothesis. A key concept is that the evolutionary processes operate to maximize biological fitness (reproductive success within a lineage), not health or longevity. In fact, maximum biological fitness is often achieved by trading off health or longevity. This approach can facilitate interpreting whether a specific aspect of the pathophysiology of a disease is adaptive or maladaptive. For example, in patients with chronic bacterial infections, is iron deficiency the result of bacterial virulence factors, an undesirable side effect of host defensive mechanisms, or a deliberate defensive mechanism that creates an iron-depleted, bacteriostatic environment? Each of these alternative explanations would have profoundly different implications for research and clinical practice. Overall, an evolutionary approach does not instantly solve long-standing pathophysiological mysteries and therapeutic or diagnostic challenges in medicine, but it adds an additional dimension to our explanatory frameworks of specific human diseases and expedites the identification of targets for basic and clinical research, some of which will be eventually translated into improved clinical practice.

CONFLICTS OF INTEREST

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