ESSAY

Differential Diagnosis in Pediatrics: A Probabilistic Approach

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How physicians arrive at a diagnosis has been the subject of much debate. Pattern recognition is used extensively by experts and is the most common method used by pediatricians. Many of the diagnostic questions posed in certification and self-study examinations developed by the American Board of Pediatrics and the American Academy of Pediatrics require the test taker to recognize a pattern of symptoms and laboratory tests and draw a conclusion about the most likely diagnosis. This method of diagnosis involves paralleling familiar situations independent of explicit hypothesis testing.[1] Sackett et al describe this process as "the instantaneous realization that the patient's presentation conforms to a previously learned picture or pattern of disease."[2]

Pattern recognition has several shortcomings. First, the method is highly dependent on the clinician's experience; novices are at a distinct disadvantage. Second, lists may vary from specialty to specialty. A pediatric infectious disease specialist may have a different list for acute childhood arthritis from that of a pediatric rheumatologist. Finally, the method fails when confronted with a defined clinical problem lacking distinguishing features, such as neonatal cholestatic jaundice or non–cystic fibrosis bronchiectasis.

An alternative diagnostic strategy is the hypothetico-deductive method.[2] This method requires the clinician to generate a short list of likely diagnoses rather than a single diagnosis and develop a strategy for eliminating or confirming each diagnosis. The diagnostic list is based on personal experience, described by Sackett et al as "explanatory ideas" that are generated by pattern recognition and developed into a list of possibilities as opposed to a single diagnostic possibility.[2] The ordering of the different diagnoses may vary from individual to individual, and the ranking is not quantitative.

Richardson and colleagues[3,4] have proposed that this diagnostic list be evidence based and quantitative. The term "pretest probabilities" is from Bayes' theorem and describes the probabilities assigned to each diagnostic possibility. Although a discussion of the formal mathematics is beyond the scope of this commentary, the posterior probability (a measure of the strength of belief in a given diagnosis for a specific clinical problem after the consideration of one or more diagnostic tests) is the product of the test characteristics (likelihood ratio) and the probability of a specific diagnosis, given the clinical problem (pretest probability). Consider the following example.

A 10-day-old female infant with an unremarkable perinatal and neonatal history is admitted for the evaluation of direct hyperbilirubinemia (total bilirubin 8.0 mg/dL; direct bilirubin 6.0 mg/dL). She is breastfeeding and gaining weight appropriately, and her neurodevelopment is normal. Her physical examination is remarkable for scleral icterus,

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cutaneous icterus to the level of the chest, and a palpable liver. Her liver function tests are within normal limits, but her newborn screen for galactosemia is positive (total blood galactose concentration ≥20 mg/dL and galactose-1-phosphate uridylyltransferase concentration ≤40 μmol/l).[5] What is the probability that this child has galactosemia? What is the most likely diagnosis?

A simplified form of Bayes theorem permits a comparison of two mutually exclusive hypotheses: the patient has galactosemia or the patient does not. Three simple formulae are required:

$$\text{odds} = \text{probability of event} / (1 - \text{probability of event}) \quad (1)$$

$$\text{probability} = \text{odds of the event} / (1 + \text{odds of the event}) \quad (2)$$

and

$$\text{ODDS}_{\text{posttest}} = \text{ODDS}_{\text{pretest}} \times \text{LR}+, \quad (3)$$

where LR+ is the positive likelihood ratio defined as the true-positive rate of the test divided by the false-positive rate of the test.

From Gottesman et al,[6] the pretest probability of metabolic disorder causing neonatal cholestatic jaundice is 0.044, and the pretest probability of galactosemia as the metabolic disorder is 0.365. From Freer et al,[5] the true-positive rate of galactosemia screening is 1.00, and the false-positive rate is 0.89.

Calculations of $\text{ODDS}_{\text{pretest}}$ and LR+:

$\text{Pretest probability}_{\text{galactosemia}} = 0.044 \times 0.365 = 0.016$ or 1.6%

$\text{ODDS}_{\text{pretest}} = 0.016/0.984 = 0.016$

$\text{LR}+ = 1/0.89 = 1.12$

Calculation of posterior probability:

$\text{ODDS}_{\text{posttest}} = 0.016 \times 1.12 = 0.018$

$\text{Probability}_{\text{posttest}} = 0.018/1.018 = 0.018$ or 1.8%

From Gottesman et al,[6] the probability that a neonate with cholestatic jaundice has idiopathic neonatal hepatitis is 0.260 or 26%, and the probability of extrahepatic biliary atresia is 0.259 or 25.9%.[6] Thus, in spite of a positive screening test for galactosemia, it is more likely that this patient has idiopathic hepatitis or extrahepatic biliary atresia. These and other diagnoses should be explored.

Richardson et al provide guidelines for assessing the validity of research that may supply these pretest probabilities: (1) the clinical problem should be clearly defined; (2) the patient sample should be broad, ideally drawn from a diverse geographic area and from consecutive patients; (3) the criteria for the final diagnosis should be explicit and widely accepted; (4) the diagnostic work-up should be comprehensive and universally applied; and (5) the results should be expressed as specifically as possible with accompanying probabilities.[3] Although these types of studies are plentiful in the adult literature, large, well-done, diagnostic studies are uncommon in pediatrics.

Just as systematic reviews and meta-analyses combine small, clinical trials to give an overall estimate of clinical effectiveness, rigorous systematic reviews can combine data from small studies to provide pretest probabilities for clinical problems. Systematic reviews have addressed the differential diagnoses of non–cystic fibrosis bronchiectasis in children and childhood stroke.[7,8] All systematic reviews have recognized limitations. The diagnostic approach to subgroups of patients varies and may not be complete or fully described. Variations in individual study size may bias data, particularly if narrow geographic areas are involved. Nomenclature is inconsistent. Nevertheless, rigorously performed systematic reviews of etiologies of defined clinical problems provide a logical, evidence-based starting point for differential diagnosis. These data, combined with evidence addressing the utility of a given diagnostic test, allow the clinician to estimate the degree of uncertainty associated with a specific diagnostic possibility.

In summary, there are a variety of diagnostic strategies used by pediatricians. Pattern recognition is used most often but has its limitations. In certain cases, systematic reviews or large case series can provide an evidence-based, probability-ordered differential diagnosis, increasing the likelihood of identifying the correct diagnosis in a timely fashion.

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