

# Erythrocyte Acetylcholinesterase Levels and Hirschsprung Disease: A Case of Cautious Interpretation of Diagnostic Test Results?

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Hirschsprung disease is a rare congenital bowel motility disorder. Full thickness rectal biopsy remains the gold standard for diagnosis [1]. Given the invasive nature of rectal biopsy, attempts have been made to devise a non-invasive marker of the disease. However, these efforts have been unsuccessful due to several limitations of these markers, specially the sensitivity and specificity.

Kema et al in their recently published research article in JPMS have shown that erythrocyte cholinesterase can be a useful screening test in clinically suspected cases of Hirschsprung disease [2]. These findings are in conformity with some of the literature while contrasts with most of the published reports. Using the keywords "Hirschsprung AND erythrocyte acetylcholinesterase" retrieves seven titles in PubMed. Of these, the majority did not find any statistically significant correlation between erythrocyte acetylcholinesterase levels and Hirschsprung disease. Yanagihira et al showed that the erythrocyte cholinesterase levels correlate well with rectal cholinesterase levels [3]. She XY et al showed that the levels of erythrocyte acetylcholinesterase are significantly greater in Hirschsprung patients compared to the controls [4].

Kema et al have shown a comparatively high sensitivity (85%) and a specificity of 75% of erythrocyte acetylcholinesterase levels [2]. They suggest that the test can be useful when the disease is clinically suspected based on the presentation. However, the results of this test should be interpreted with caution. First is the concern of false negatives. Given the complications of Hirschsprung, missing the diagnosis is potentially dangerous. The test labeled 4 (out of 30) cases as "negatives" which were subsequently proven to be positive on biopsy (False negatives). One potential solution to increase the sensitivity (and to decrease the negative predictive value) is to identify a different cut off value. An receiver operator curve (ROC) is a tool that can help. It is

computed graphically with true positives (sensitivity) on the Y axis whereas the false positives (1-specificity) plotted on the X-axis. Hence, to increase the sensitivity, the curve will have to be shifted upward. This can decrease the false negatives. One caveat, however with the use of ROC's is that an increase in sensitivity is offset by decreased specificity.

Thus increasing the sensitivity of erythrocyte acetylcholinesterase test will automatically increase the number of false positive tests. With a cut off of 13 KU/L and a small sample size of 30 patients, Kema et al showed one false positive result [2]. The patient was identified having all clinical symptoms including high levels of erythrocyte cholinesterase but with a negative rectal biopsy. A false positive result besides being the limitation of the test is deleterious for two reasons. First a positive test will likely create anxiety in the patients. Secondly, this has to be followed by rectal biopsy which is an invasive procedure. However, this needs to be balanced by the risk of missing a case and providing false assurance to parents, a more complicated presentation later on, or mis-diagnosis.

The rarity of the disease (1:5000) decreases its positive predictive value and allows applicability only on definite inpatients presenting with clinical symptoms suggestive of Hirschsprung's disease [5]. This incidence also permits the sample size and results of the Kema et al study to be significant for a particular study site. Cheaper, easier and non-invasive use of this serological test inclines it more towards a screening tool in selected populations rather than a main diagnostic gold standard test. However more studies are required to inspect this test with appropriate cut off markers for better results. Using it as a screening tool may result in sparing a few who definitely do not have the disease and rest can undergo a confirmatory, more invasive, gold-standard test.

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