

Sandroni P, Low PA, et al Complex Regional Pain Syndrome I (CRPS I): Prospective Study and Laboratory Evaluation. Clin J Pain 1998;14:282-9.

Design: Prospective study of a diagnostic test

Population/sample size/setting:

- 102 consecutive patients (76 women, 26 men, mean age 45) referred to the Mayo Clinic for evaluation of chronic limb pain (41 upper, 61 lower extremity) to confirm or rule out CRPS
- Exclusionary criteria were the presence of another obvious explanation of the pain, previous sympathectomy, or medications known to affect autonomic function

Main outcome measures:

- Evaluation consisted of two parts: clinical and laboratory
- Clinical evaluation consisted of two parts: a questionnaire completed by the patient, and a neurologic examination parallel to the patient questionnaire
 - o The clinical score depended on allodynia (touch, pressure, movement) and vasomotor signs and symptoms
 - o The clinical score can range from 0 to 7; a score of 0-1 is not CRPS; a score of 2-3 is possible CRPS, 4-6 is probable CRPS, and 7 is definite CRPS
 - o The total clinical score was the CRPS-Sx for that patient
- Laboratory evaluation consisted of 3 parts, two for sudomotor function and one for vasomotor function
 - o Sudomotor function was evaluated with resting sweat output (RSO) and quantitative sudomotor axon reflex test (QSART)
 - o RSO and QSART recordings were done bilaterally and simultaneously at several sites on both extremities
 - o RSO was measured for 5 minutes on the unstimulated limb
 - o QSART was measured on the stimulated limb following iontophoresis of 10% acetylcholine; both the amount of sweat and the latency of the response were recorded and used to determine the QSART response
 - o Vasomotor response was determined by infrared thermometry, with skin temperatures averaged over six areas in both limbs
 - o The laboratory score ranged from 0 to 9; 0-1 is doubtful, 2-3 possible CRPS, 4-6 probable CRPS, and 6-9 definite CRPS
 - o The total score was the CRPS-Lab for that patient
- Clinically, sweat abnormalities were not reported as symptoms in 67% of patients, and were not reported as abnormal in 84% of clinical examinations
- QSART was normal in 38% of patients and abnormal in 62% (reduced in 38% and increased in 24%)
- RSO was normal in 71% of patients and abnormal in 29% (reduced in 22% and increased in 7%)
- Vasomotor function as measured by skin temperature was normal in 42% and abnormal in 58% (reduced in 39% and increased in 19%)

- RSO correlated significantly with QSART ($p < .001$) and with temperature reduction ($p = .032$)
- QSART correlated significantly with temperature reduction ($p = .02$)
- CRPS-Sx and CRPS-Lab were significantly correlated ($p = .035$)
- CRPS-Sx correlated with QSART reduction ($p = .025$), with RSO ($p = .049$) and with the combination of RSO + QSART ($p = .009$)
- The allodynia score correlated with QSART reduction ($p = .04$), RSO reduction ($p = .01$), and temperature reduction ($p = .007$)
- CRPS-Sx was < 2 in 31% of patients, 2-3 in 45%, 4 in 8%, and > 4 in 15%
- CRPS-Lab was < 2 in 29%, 2-3 in 29%, 4 in 20%, and > 4 in 22%

Authors' conclusions:

- There are close correlations of indices among clinical symptoms, signs, and laboratory measurements which are manifestations of a common perturbation of autonomic function, such as sympathetic sudomotor and vasomotor overactivity
- Allodynia and vasomotor clinical scores are well correlated
- CRPS-Sx and CRPS-Lab are well correlated
- A combined clinical and laboratory approach to the diagnosis of CRPS-I should emphasize (1) severity of pain out of proportion with the presenting clinical signs, (2) diffuse and distal distribution of pain, and (3) allodynia
- The components of CRPS-Sx and CRPS-Lab should be combined to yield a CRPS probability scale
 - o Definite CRPS= allodynia to touch, pressure, and movement + asymmetry of QSART or RSO at 2 or more sites
 - o Probable CRPS= Probable CRPS-Sx + CRPS-Lab with (a) asymmetry of QSART or RSO at 2 or more sites, or (b) QSART asymmetry at 1 site + RSO at 1 site and skin temperature asymmetry
 - o Possible CRPS= chronic limb pain + QSART asymmetry at 1 site or RSO asymmetry at 1 site or skin temperature asymmetry

Comments:

- The gestalt of a combination of clinical and laboratory findings appears to be a reasonable approach to the diagnosis of CRPS
- However, the presentation of data to support the diagnostic approach is unsatisfactory in several ways
 - o The associations are all reported as p values for correlation coefficients
 - o Correlation coefficients are estimates of the strength of a linear relationship between variables, but their p values are sadly uninformative
 - o P values reject the null hypothesis that there is zero correlation between scores on different scales, but this is not what is needed
- The presentation of data leaves important questions unanswered, for example
 - o How many patients with definite CRPS-Sx also had definite CRPS-Lab, and vice versa?

- How many patients had definite and probable CRPS-Sx and CRPS-Lab?
- Table 8 does not even allow this question to be answered, since it collapses all scores >4 into a single category; this combines scores of 5 and 6 (probable CRPS-Sx) with scores of 7 (definite CRPS-Sx); for CRPS-Lab, scores of 7, 8, and 9 are definite CRPS, but they are mixed in with scores of 5 and 6 in Table 8
- How many patients with clinical sweating also had asymmetrical QSART or RSO, and at how many sites?
- Therefore, the basic measures of a diagnostic test (sensitivity and specificity) cannot be estimated for QSART, RSO, or their combination
- A previous retrospective Mayo study of QSART reported that QSART was predictive of response to sympathetic block; the opportunity to study this relationship prospectively was not taken in this study
- Relationship between correlation coefficient and t distribution makes it possible to infer correlation coefficients from reported p values in sample of 102 patients, as below:
- Bonferroni adjusted p value of correlation between CRPS-Sx and CRPS-Lab was .035; if there were 4 comparisons made (CRPS-Sx with CRPS-Lab, QSART reduction, RSO, and RSO+QSART, then unadjusted p value would be .00875, which would correspond to a t statistic of 2.674, which in a sample of 102 patients would correspond to correlation coefficient r of .258, which would mean that r square is 0.067, which means that the variation in CRPS-Sx explains only 6.7% of the variation in CRPS-Lab, which means that a **statistically significant correlation represents a rather weak effect size**)
- Therefore, the data do not seem to support hypothesis that there is a strong relationship between clinical signs and autonomic function measurements

Assessment: Inadequate for evidence that QSART and RSO are diagnostic tests for CRPS