Combination of the Schirmer I and Phenol Red Thread Tests as a Rescue Strategy for Diagnosis of Ocular Dryness Associated with Sjögren's Syndrome

Ivan de Monchy,[1] *Gaël Gendron,*[1] *Corinne Miceli,*[2] *Nicolas Pogorzalek,*[1] *Xavier Mariette,*[2] *and Marc Labetoulle*[1,3]

Purpose. To define a combination of the Schirmer I and phenol red thread (PRT) tests that improves the screening of patients with ocular sicca syndrome.

Methods. The PRT test was performed before (PRT1) and after (PRT2) the Schirmer I test, in both eyes of 143 patients complaining of ocular dryness secondary to Sjögren's syndrome or sicca asthenia polyalgia syndrome (SAPS; 72 and 71 patients, respectively), and in 40 control patients. Groups were matched by age and sex. After determining the best cutoff values using the receiver operating characteristic procedure, several combinations of PRT and Schirmer I were assessed to improve the predictive values of the procedure.

Results. The best cutoff value for PRT2, estimated at 15 mm, provided a satisfying match between sensitivity and specificity indexes (68% and 90%, respectively), similar to those obtained with the Schirmer I test. If PRT1 alone was ineffective to screen SGS from control patients, the comparison between PRT1 and PRT2 (so-called "DeltaPRT") was found as a good marker to detect patients with persistent tear reflex. Interestingly, the combination of positive Schirmer I, PRT 2, and/or ΔPRT tests was found to be highly predictive of severe ocular sicca syndrome.

Conclusions. The combination of the Schirmer I and PRT tests strongly improves the screening procedure to detect patients with ocular dryness related to Sjögren's syndrome or SAPS. It could be more widely used in daily clinical practice, aside from the Schirmer I test, to optimize the work-up of patients presenting with dry-eye subjective signs. (*Invest Ophthalmol Vis Sci.* 2011;52:5167–5173) DOI:10.1167/iovs.10-6671

Ocular dryness is suspected in the presence of subjective signs, such as burning, itching, sensation of foreign body, or more generally the sensation of tear insufficiency.[1,2] However, the diagnosis must be supported by objective assessment. Despite an increasing knowledge on the pathogeny of dry eye over the last decade and multiple efforts to outline a battery of diagnostic procedures, no single test is considered to be the criterion standard for dry eye diagnosis.[3–5] Even though the Schirmer I test is used as one of the six major criteria for Sjögren's syndrome (SS) diagnosis,[6] the difficulty in the interpretation of the results limits its interest. Indeed, the Schirmer I test (i.e., without anesthesia) reflects various data, among which the volume of the lachrymal meniscus and basal and reflex tear secretion. This likely explains the low repeatability and sensitivity of the Schirmer I test.[4,5,7–9]

With the aim of developing a new way to assess tear production, Kurihashi[10] and Hamano et al.[11] described in the early 1980s the phenol red thread (PRT) test, which is currently available as Zone-Quick (Menicon, London, UK). The thread of cotton is soaked with phenol red, a pH-sensitive dye. When dry, the thread is yellow, and the thread turns orange when wetted by tears, as a consequence of the physiological pH of tears (from 7 to 8). Because of the very few amounts of pH indicator soaked on the thread, it is probable that the irritating effect of PRT test is minimal, as shown by the important repeatability of multiple PRT tests performed during the same session.[12] Indeed, phenol red is a vital dye, and is therefore suitable for use in living organisms. It is used in humans to test in vivo kidney function and renal blood flow, and as a carrier base material in several vaccines; both of these properties indicate a low level of toxicity on human tissues and cells.

The PRT test is fast (15 seconds to be performed) and painless,[13,14] and stimulates a low degree of reflex tearing.[12] While the first studies on PRT did not find a much better power of this test for the diagnosis of severe ocular dryness in comparison to the Schirmer I test,[12,13–16] the estimation of a correct cutoff value using a conventional statistical method such as the receiver operating characteristic (ROC) procedure has not been performed. Moreover, the hypothesis of a potential interest of a combined modus operandi between PRT and the Schirmer I test has not been tested. We retrospectively reviewed the results of PRT and Schirmer I tests in 143 patients suffering from either SS or sicca asthenia polyalgia syndrome (SAPS), and we compared these results with those of 40 patients with no sign of ocular sicca syndrome. We observed that a correct combination of the PRT and Schirmer I tests leads to a highly effective screening procedure.

Materials and Methods

One hundred eighty-three patients were included in this study between January 2002 and December 2008, among which 143 had been consequently referred by the rheumatology department (National Reference Centre for Sjögren's Syndrome) for a multidisciplinary assessment of a presumed inflammatory disease. At the time of the ocular procedures, the final result of the work-up was not known, but all them had a definite ocular dryness with subjective (burning, itching, sensation of foreign body, or sensation of lack of tears) and objective signs (corneal and conjunctival punctuates after fluorescein and Lissa-

From the Departments of [1]Ophthalmology and [2]Rheumatology, Hôpital de Bicêtre, Assistance Publique-Hôpitaux de Paris, Université Paris Sud, Le Kremlin-Bicêtre Cedex; and [3]Laboratoire de Virologie Moléculaire et Structurale, Centre National de la Recherche Scientifique, Gif-sur-Yvette Cedex, France.

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Corresponding author: Marc Labetoulle, Service d'Ophtalmologie, Hôpital de Bicêtre, 94275, Le Kremlin-Bicêtre Cedex, France; marc.labetoulle@bct.aphp.fr.

Table 1. Demographic Characteristics of Patients Included in the Study

Group	Patients (*n*)	Mean Age (y)	95% CI of Mean	% Female	χ^2 Test for Sex Ratio
SS	72	57.5	(54.5–60.5)	94%	$P > 0.7$
SAPS	71	57.1	(54.2–60.1)	91.5%	$P > 0.7$
Control	40	53.6	(49.5–57.7)	92.5%	$P > 0.7$

The three groups of patients were comparable for age (ANOVA; $P = 0.33$) and sex (χ^2 test; $P >$ 0.7 for each 2-group comparison). CI, confidence interval; SAPS, sicca asthenia polyalgia syndrome; SS, Sjögren's syndrome.

mine green staining). Finally, 72 patients (144 eyes) fulfilled the international criteria of SS[6] and were therefore classified in the SS group. The 71 remaining patients had objective and subjective signs of dry eye with no biologic or histologic abnormalities (no anti-SSA or anti-SSB antibodies and Chisholm's classification <3), and were therefore classified in the SAPS group.[17] The control group included 40 patients referred to the Ophthalmology Department for cataract, presbyopia, and refractive error during the same period (2002–2006). They were matched for sex and age (in ±3 years) with dry eye patients. Clinical evaluation confirmed that they neither had subjective nor objective signs of ocular dryness. No control patient was treated with drugs interfering with tear secretion (e.g., β-blockers or any drugs with antimuscarinic effects).

All procedures complied with the Declaration of Helsinki as revised in 2000, and were approved by the local institutional review board. After obtaining informed consent, both eyes were consecutively subjected to a first PRT test (PRT1), a Schirmer I test, and a second PRT test (PRT2). The first PRT test was performed at least 5 minutes after slit lamp eye examination, and then the maximum delay between two consecutive tests (PRT1 to Schirmer I and Schirmer I to PRT2) was 10 seconds. No topical anesthesia was used. As described in previous studies[15,18] and by manufacturers, the tip of the thread (Zone-Quick; Menicon), or the strip (Schirmer-plus; GECIS, P Gouchet, Neung sur Beuvron, France), was placed in the lower conjunctival cul de sac near the outer canthus. Careful attention was given to avoid contact of the device with the cornea. After 5 minutes for the Schirmer I strip or 15 seconds for the PRT thread, the device was carefully withdrawn and the length of wetted strip or thread was measured with a millimeter ruler.

Data were anonymously recorded before processing to retrospective statistical analysis using STATA software (StatacorpLP, College Station, TX). Categorical variables were analyzed using the χ^2 test, and continuous variables were analyzed using Student's *t*-test. Statistical significance was defined as $P < 0.05$ (2-tailed). For each of the three tests of tear secretion (PRT1, PRT2, and Schirmer I test), both eyes were tested. Because a preliminary comparison revealed some asymmetry between the right and left eyes in all groups of patients (see Results section), the minimal result of each pair of values was used for determining the best cutoff value and the optimized combined procedure.

The optimal cutoff value of the PRT1, PRT2, and Schirmer tests was estimated with the ROC procedure. Each theoretical cutoff value (i.e., from the lowest to the highest value observed in the study population) was used to estimate the sensitivity and the specificity of the test. Results were then graphed with the sensitivity as a function of (1-specificity). This conventional method of representing the relationship between the putative cutoff values and the effectiveness of the test provides a convenient way for selecting the threshold that finally provides the best combination between sensitivity and specificity (the optimal cutoff value is usually chosen as the hinge point of the curve).

Finally, to optimize the global effectiveness of the evaluation of tear production to distinguish normal subjects from SS or SAPS patients, several combinations of Schirmer I, PRT1, and PRT2 tests were tested for their positive and negative predictive values.[19]

Results

Comparison of Groups

The three groups of patients were comparable for age (ANOVA; $P = 0.33$) and for sex ($\div^2$ test; $P > 0.7$ for each 2-group comparison). Demographic characteristics are described in Table 1.

Comparison of Mean Values of Tear Production Tests

Mean values of right and left eyes were similar for the three tests in each of the three groups (matched Student's *t*-test; $P > 0.10$), ruling out a side effect. However, for a given test, the lowest and the highest data were significantly different (matched Student's *t*-test; $P < 0.001$), revealing some asymmetry between the right and left eyes for a given patient. Because the lowest value was presumably the most clinically relevant for dry eye screening, we selected the minimal result of each test for further statistical analysis. The results of the PRT1, PRT2, and Schirmer I tests (Table 2) were not influenced by age in each group (correlation coefficient $R = 0.02$ to 0.16; $P > 0.16$) or sex ($\div^2$ test; $P > 0.7$).

Assessment of Cutoff Values with the ROC Procedure

According to the ROC procedure, optimal cutoff value is usually chosen as the hinge point of the curve between sensitivity and specificity for each of the observed values in the study population.

As a control for the relevance of this method in our field of interest, we assessed the most pertinent cutoff value of the Schirmer I test to distinguish control patients from SS or SAPS patients. We found it to be 10 mm (sensitivity, 77.8%; specificity, 82.5%; Fig. 1), a threshold that is commonly accepted in most of clinical trials on ocular sicca syndrome.[3]

The ROC procedure for the PRT1 test showed no obvious hinge point clearly distinguishable on the curve (Fig. 2); this was the consequence of low specificity and sensitivity indexes whatever the selected threshold. This suggested that PRT1 could not be considered a relevant test when used alone for the evaluation of tear production.

In contrast, the analysis of the ROC curve for PRT2 clearly showed that 15 mm could be used as the optimal cutoff value for screening SS from control patients (Fig. 3), providing a

Table 2. Average Values of Lachrymal Tests Performed in the Three Groups of Patients

	SS Group (Mean ± SE)	SAPS Group (Mean ± SE)	Control Group (Mean ± SE)
PRT1, mm	14.47 ± 2.53	16.29 ± 1.48	19.12 ± 2.32
Schirmer I, mm	7.07 ± 1.90	12.36 ± 2.31	20.65 ± 2.58
PRT2, mm	13.65 ± 1.75	17.32 ± 1.62	22.85 ± 1.90
Differences between PRT1 and PRT2	$P = 0.24$	$P = 0.15$	$P = 0.002$

Briefly, patients underwent a phenol red thread test (PRT1), a Schirmer I test, and a second phenol red thread test (PRT2) in succession. For each test, only the lowest value (corresponding to either the right or left eye) was selected for final calculations. In the control group, the mean value of PRT2 was significantly higher than PRT1, suggesting that a persistent production of tears was induced by the Schirmer I procedure in normal subjects but not in patients with Sjögren's syndrome or sicca asthenia polyalgia syndrome syndrome. In contrast, this difference was not observed in the SS and SAPS groups. SAPS, sicca asthenia polyalgia syndrome; SE, standard error; SS, Sjögren's syndrome.

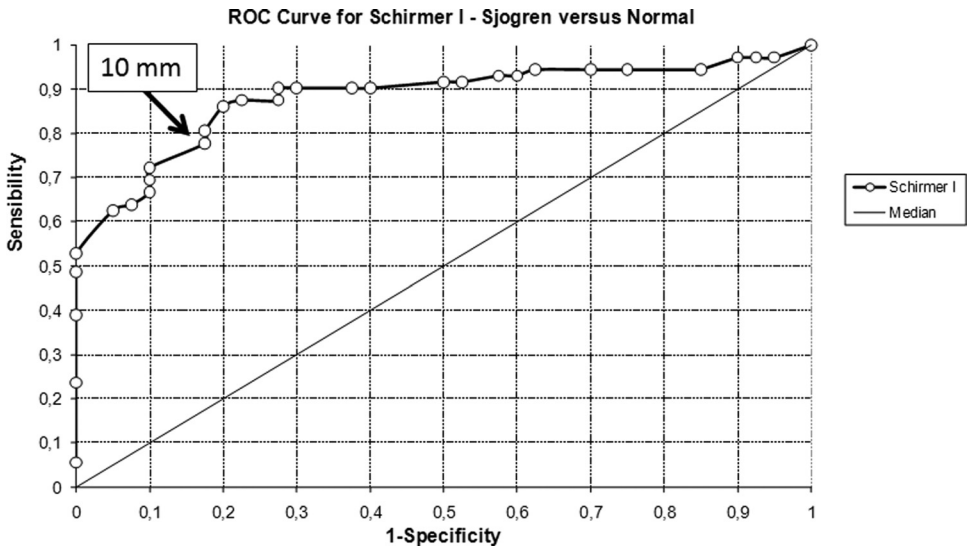

FIGURE 1. Receiver operating characteristic (ROC) curve showing the relationship between sensitivity and specificity of the Schirmer I test (Sjögren's syndrome vs. control patients) according to theoretical thresholds. For each of the values of the Schirmer I test observed in the study population (i.e., from the lowest to the highest in either Sjögren's syndrome patients or the control group), the sensitivity and sensibility indexes have been calculated and reported in the graph. According to the ROC procedure—in which the optimal cutoff value is usually chosen as the hinge point of the curve—the value of 10 mm *(arrow)* for the Schirmer I test has been selected as the best threshold to distinguish Sjögren's syndrome from normal patients, with sensitivity and specificity indexes at 77.8% and 82.5%, respectively.

satisfying match between sensitivity (68%) and specificity (90%). The effectiveness of PRT2 was moreover similar to the one of the Schirmer I test, as revealed by the equivalence of areas under curves for ROC procedure (Fig. 4). In contrast, distinguishing SAPS from either control or SS group was difficult whatever the test: PRT2 and Schirmer I tests shared a good specificity (78% and 83%, respectively) but a weak sensitivity (38% and 54%), both of them being equivalent in terms of selectiveness (no significant difference between ROC curves; $P = 0.82$).

Combining the Tests to Improve Sensitivity and Specificity

Because we observed that most SS or SAPS patients had a PRT2 lower or equal to PRT1 results—while the opposite was observed in control patients (Table 2)—we defined the variable "DeltaPRT" (ΔPRT) as PRT2 – PRT1, to assess the difference in PRT before and immediately after the stimulation of the lachrymal reflex because of the Schirmer I procedure. A positive ΔPRT therefore reflected a persistent production of tears once the conjunctiva had been stimulated (strip of the Schirmer I test), whereas a null or negative value suggested that the reflex tear production by the lachrymal gland was poor, even after a prolonged stimulation of the eye surface.

When DeltaPRT test was used alone to differentiate SS from control subjects, sensitivity and specificity were 61% and 75%, respectively (i.e., in the same order of magnitude as the PRT2 or Schirmer I tests alone; Table 3). The pertinence of this new variable was much higher, however, when considered in a combined process with the Schirmer I and/or the PRT2 results (Table 4). For example, the combination of a positive Schirmer I test (≤10 mm) and a positive PRT2 test (≤15 mm) was highly specific (95%) for screening SS patients from control subjects, as was the combination between a positive Schirmer I test (≤10 mm) and a negative value of ΔPRT (specificity, 92.5%). If both the Schirmer I and PRT2 tests were positive, a negative value of ΔPRT raised the combination to an excellent specificity (97.5%; Table 4). Finally, if only one of either the Schirmer I or PRT2 tests was below the threshold, a negative value of ΔPRT raised the specificity of the combination to 92.5% (Table 4). To obtain a better idea of the effectiveness of the combinations of test in clinical practice, we evaluated the positive predictive value (PPV; i.e., the probability of being classified as ill when the test is positive) and the negative predictive value

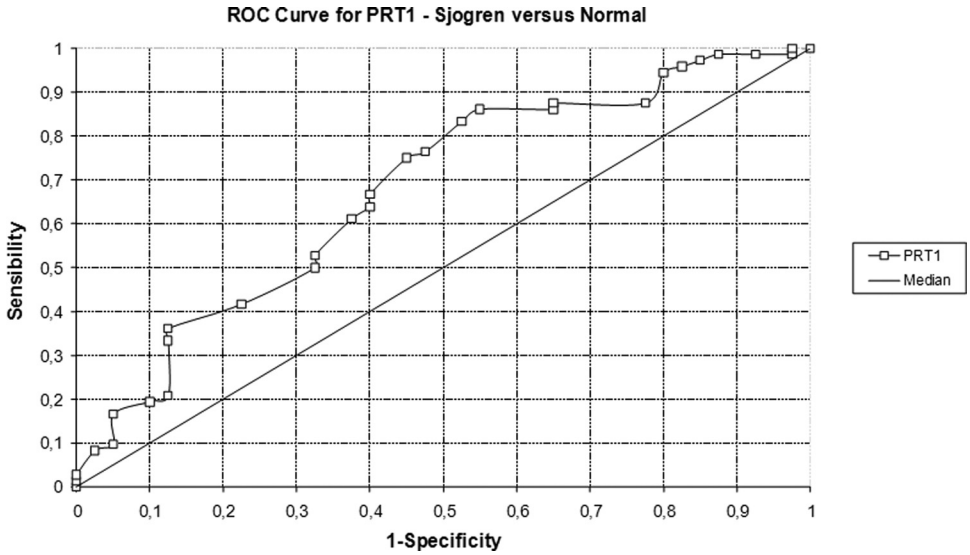

FIGURE 2. Receiver operating characteristic (ROC) curve showing the relationship between sensitivity and specificity of the phenol red thread test when used before the Schirmer I test (PRT1). The method for obtaining the graph was the same as that for Fig. 1, with the exception that PRT1 values were used. Because there was no hinge point clearly distinguishable on the curve, no optimal cutoff value was obvious using the ROC procedure in the case of PRT1.

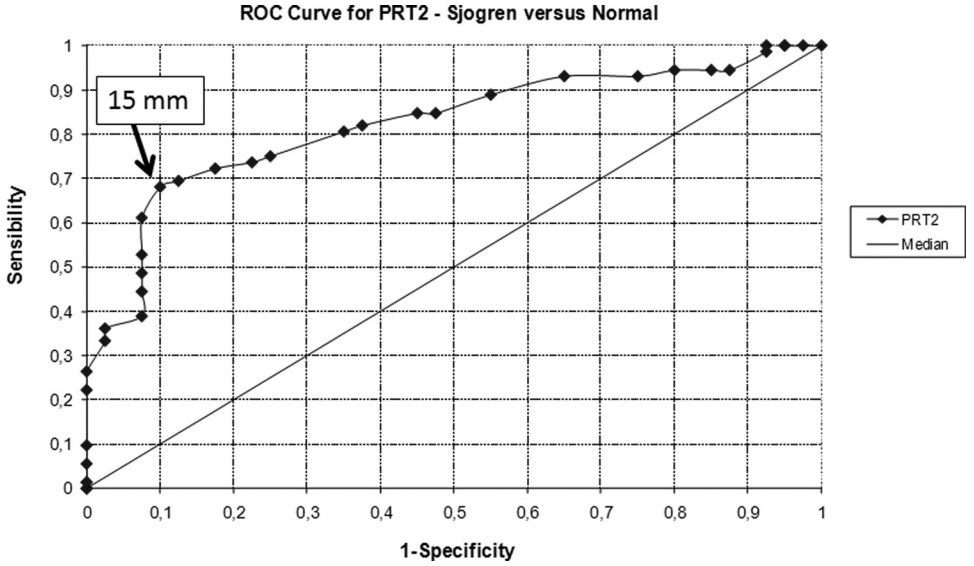

FIGURE 3. Receiver operating characteristic curve showing the relationship between sensitivity and specificity of the phenol red thread test, when used after the Schirmer I test (PRT2). The method for obtaining the graph was the same as that for Fig. 1, with the exception that PRT2 values were used. Because the hinge point of the curve corresponded to 15 millimeters *(arrow)*, this value of PRT2 was selected as the best threshold to distinguish Sjögren's syndrome patients from normal patients, with sensitivity and specificity indexes at 68% and 90%, respectively.

(NPV; i.e., the probability of being classified as normal when the test is negative), by initiating the analysis with the Schirmer I results (Figs. 5, 6). For example, the probability of being finally classified as a SS patient is only 55.5% when the Schirmer I test is positive (≤10 mm), with a remaining 7% of probability to be finally considered as "normal." If PRT tests are concomitantly performed, obtaining both a PRT2 ≤15 mm and a negative ΔPRT increases the probability of being finally classified as a SS patient to 73.3%, with only 2.2% of probability to be finally considered "normal."

Inversely, the probability of being finally classified as a normal patient is 40.2% when the Schirmer I test is negative (>10 mm). If the PRT2 test is concomitantly below 15 mm, the probability of being classified as "normal" is reduced to 15.4%, and its association with a negative ΔPRT result virtually classifies the subject as either an SS or SAPS patient (Fig. 6).

DISCUSSION

The standardized PRT test (Zone-Quick; Menicon) is of recent availability for clinical practice, but its real place in the diagnostic procedures remains to be clearly defined.[3,20] The main advantage of this tear production test is the lack of pain during the procedure, while this is the main inconvenience of the Schirmer I test, even when durations of tests shorter than 5 minutes are used.[21,22] The nature of the PRT test, a cotton thread soaked with phenol red, explains the excellent tolerability.[10,23] However, several questions have been raised on the reproducibility, normal values, and clinical relevance of this test. The mean results may slightly differ with sex and ethnic in normal volunteers,[13,18,24] but they do not appear to be influenced by age or the level of humidity in the examination room.[13] The experimental PRT test was found more reproducible than the Schirmer I test in normal subjects,[25] with a difference of <3 mm between two measures made in an interval of 24 hours in 68% of patients.[18,26] Even if some interexaminer variations may exist,[27] no significant difference was found between multiple measurements during the same session.[12] The PRT test is currently available in several countries (including Japan and the United States), but not at the moment in Europe, because of a 2009 revision of European standard (EN 11,137; sterilization by irradiation) that imposed a fair amount of new tests before reengaging marketing.

Our study confirms these first published results. The mean PRT values in our control group (19.12 ± 2.32 mm for PRT1 and 22.85 ± 1.71 mm for PRT2) were similar to those de-

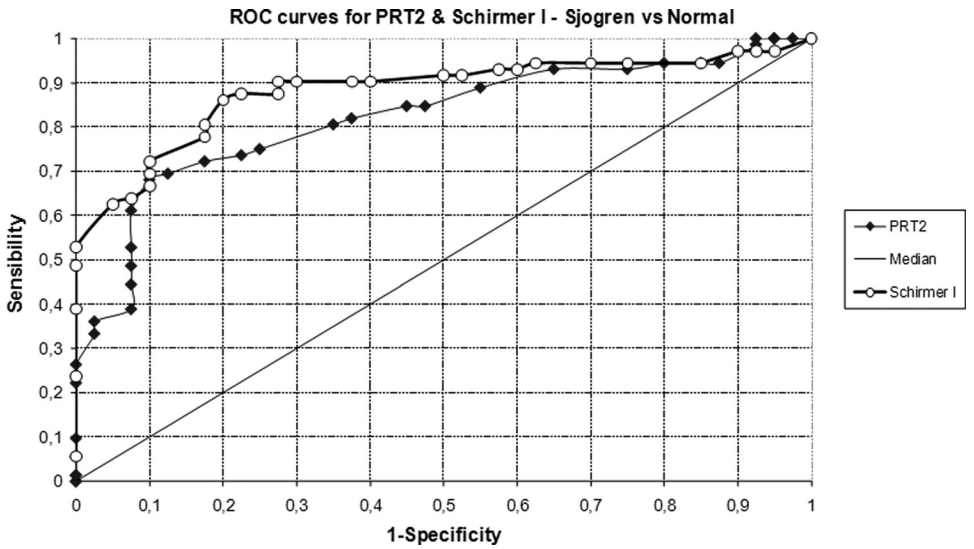

FIGURE 4. Comparison of receiver operating characteristic (ROC) curves for Schirmer I and PRT2 tests (Sjögren's syndrome vs. control patients), showing no difference in the effectiveness to distinguish Sjögren's syndrome from normal patients (no hinge point more obviously distinguishable in one of the two curves, and no significant difference between area under curves; $P = 0.82$).

TABLE 3. Sensitivity and Specificity Indexes of the Schirmer I, Phenol Red Thread Test When Performed after Schirmer I Test, and ΔPRT in Each of the Three Groups of Patients

Test	SS vs. Control	SS vs. SAPS	SAPS vs. Control
Schirmer I ≤10 mm	Sensitivity 77.8%, specificity 82.5%	Sensitivity 78.0%, specificity 46.5%	Sensitivity 54.0%, specificity 83.0%
PRT2 ≤15 mm	Sensitivity 68.0%, specificity 90.0%	Sensitivity 52.8%, specificity 67.6%	Sensitivity 38.0%, specificity 78.0%
ΔPRT ≤0	Sensitivity 61.0%, specificity 75.0%	Sensitivity 61.0%, specificity 69.0%	Sensitivity 31.0%, specificity 75.0%

ΔPRT is defined as the difference between phenol red thread test performed before and after Schirmer I test. PRT, phenol red thread test; SAPS, sicca asthenia polyalgia syndrome; SS, Sjögren's syndrome.

scribed earlier.[13,18,24] As reported by Patel et al.,[14] between dry eye and control patients, we found lower results in SS patients compared to SAPS patients ($P = 0.09$ for PRT1 and $P = 0.003$ for PRT2), and in SAPS compared to control subjects ($P = 0.001$ for PRT1 and $P < 10^{-5}$ for PRT2).

Despite such differences between the three groups of patients, the PRT per se did not appear as the ultimate test to screen dry eye from normal patients, because specificity and sensitivity indexes appeared at most equal to those of Schirmer I tests in our study population, even when the best cutoff value was chosen according to the ROC procedure. Indeed, when PRT was performed on a nonstimulated eye (i.e., PRT1, which was performed before the Schirmer I test in our study), no cutoff value was efficient to provide good sensitivity or specificity indexes, as shown by the lack of obvious hinge point in the ROC curve (Fig. 2), and when PRT was performed on a stimulated eye (i.e., PRT2, which was performed after the Schirmer I test), the best combination between sensitivity and specificity indexes (obtained with a threshold of 15 mm) was similar to those obtained with the Schirmer I test alone, using a threshold of 10 mm (68% and 90% vs. 77.8% and 82.5%).

However, we observed that PRT1 value was lower than PRT2 in 75% of control patients and in 69% of SAPS patients, but only in 39% of SS patients. This suggested that the triggering effect of the Schirmer I test on tear production persisted during several minutes in control patients, explaining the higher PRT2 value compared to PRT1. In contrast, dry eye patients were more frequently characterized by a PRT2 value equal or lower than PRT1, as a possible consequence of some drying up of the lachrymal secretion. We therefore studied an additional variable called ΔPRT, defined as PRT2 – PRT1. A positive value indicated persistent tearing after the Schirmer I test and was more expected in non–dry eye patients, as shown by the significant difference between PRT1 and PRT2 in these normal subjects (Table 2).

To make the difference between SS and control patient, this new variable provided sensitivity and specificity indexes that were similar to those of Schirmer I or PRT2 (61% and 75%, respectively; Table 3). Interestingly, some SS or SAPS patients with an unexpected Shirmer I test above 10 mm had a low PRT2 value (below 15 mm) and/or a negative ΔPRT value. This

TABLE 4. Comparison of Sensitivity and Specificity Indexes to Distinguish between Sjögren's Syndrome Patients and Control Subjects for Different Types of Combinations between Results of Schirmer I, PRT2, and ΔPRT

Different Types of Test Combinations	SS Patients vs. Control Subjects
Schirmer I test ≤10 mm AND PRT2 ≤15 mm	Sensitivity 61.1%, specificity 95.0%
Schirmer I test ≤10 mm AND ΔPRT ≤0	Sensitivity 48.6%, specificity 92.5%
(Schirmer I test ≤10 mm AND PRT2 ≤15 mm) AND ΔPRT ≤0	Sensitivity 45.8%, specificity 97.5%
(Schirmer I test ≤10 mm OR PRT2 ≤15 mm) AND ΔPRT ≤0	Sensitivity 54.1%, specificity 92.5%
(Schirmer I test ≤10 mm OR PRT2 ≤15 mm) OR ΔPRT ≤0	Sensitivity 91.7%, specificity 60.0%

Comparison of sensitivity and specificity indexes to distinguish between Sjögren's syndrome patients and control subjects, for different types of combinations between results of the Schirmer I and PRT2 tests (phenol red thread test performed after Schirmer I test) and ΔPRT (defined as the difference between phenol red thread test performed before and after Schirmer I test). PRT, phenol red thread test.

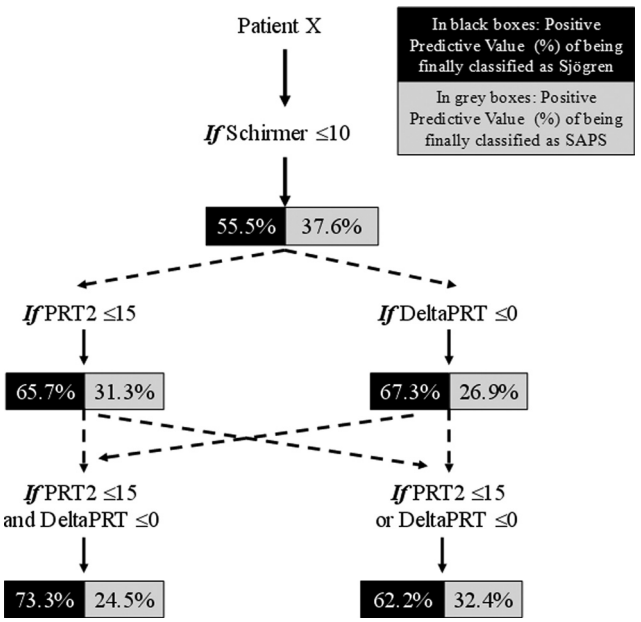

FIGURE 5. Positive predictive value (PPV; i.e., probability of being ill if the test is positive) of several combinations between the Schirmer I, PRT2, and ΔPRT tests. This diagram shows how the PPV increases with the combination of positive tests when patients are tested. For example, given a single patient of unknown status (so-called "X"), if only the Schirmer I is considered and is found inferior or equal to 10 mm (threshold selected as explained in Fig. 1), the probability of being finally classified as having Sjögren's syndrome or sicca asthenia polyalgia syndrome (SAPS) are indicated in the box below (55.5% and 37.6%, respectively). If concomitantly the PRT2 value is ≤15 mm, then the PPVs are 65.7% and 31.3%, respectively, and if ΔPRT is also ≤ 0, then the global PPVs of being finally classified as having Sjögren's syndrome or SAPS are 73.3% and 24.5%. Finally, combinations between positive tests not only increase the rate of being finally considered as a tear-deficient patients, but also increase the probability of finally classified as a Sjögren's syndrome patient, according to international criteria.

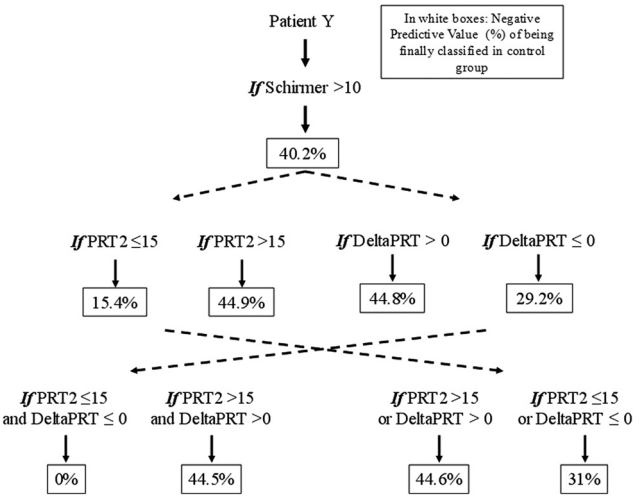

FIGURE 6. Negative predictive value (NPV; i.e., probability of being healthy if result is negative) of several combinations between Schirmer I, PRT2, and ΔPRT tests. This diagram shows how PRT2 and ΔPRT may be used as a rescue strategy to detect potential Sjögren's or sicca asthenia polyalgia syndrome patients. For example, given a single patient of unknown status (so-called "Y"), if only the Schirmer I test is considered and is found superior to 10 mm, the probability of being finally classified as normal is 40.2%. If concomitantly the PRT2 value is ≤15 mm, then global NPV decreases to 15.4%, and if ΔPRT is also ≤0, the putative final NPV is null.

suggested that PRT2 and ΔPRT could be used as rescue markers for the final diagnosis of tear secretion insufficiency.

We assessed several combinations of Schirmer I, PRT2, and ΔPRT, with the aim of helping the physician to predict if the patient would be finally classified as either SS or SAPS. We found that the combination of a positive Schirmer I test (≤10 mm) and a negative value of ΔPRT improved the specificity (92.5%) for screening SS patients from control subjects, as was the combination between a positive Schirmer I test (≤10 mm) and a positive PRT2 (≤15 mm). Interestingly, if only one of the Schimer I or PRT2 tests was positive, a negative value of ΔPRT raised the combination to an excellent specificity (92.5%) without no dramatic decrease of sensitivity (54.1%; Table 4).

The advantage of combining tests was also shown when analyzing the PPVs and NPVs by initiating the analysis with the current reference test of lachrymal production (i.e., the Schirmer I test)[6] (Figs. 5, 6).

For example, the PPV for being finally classified as having SS rose from 55.5% when only the positive Schirmer I test was taken into account to 73.3% when Schirmer I, PRT2, and ΔPRT were all conclusive (Fig. 5). The interest was even more striking for the NPVs of combined procedures. A patient with a normal Schirmer I test (>10 mm) had a 40% probability to finally be classified as normal, which decreased to 15.4% if PRT2 was positive (<15 mm) and even 0% even if both PRT2 and ΔPRT were below the threshold. Therefore, combining PRT2 and ΔPRT could play the role of a rescue strategy for optimizing the screening of potential sicca syndrome diagnostic strategy. For the physician in the daily clinical practice, at least one positive test among PRT2 (≤15 mm) or ΔPRT (<0) tests appears as a good indicator of the legitimacy to practice more invasive or expensive diagnostic procedures, because the probability that the patient is really affected by sicca syndrome is more important than if only the Schirmer I test had been taken into account.

To validate this idea in the real life, we analyzed the data of 71 additional patients referred to our department between April 2009 and April 2010 (i.e., different from those included in the main study) for a suspicion of sicca syndrome. The blinded analysis (by ML) of the tear production tests found 33 patients with a negative Schirmer I test (i.e., >10 mm), while the final analysis of the whole clinical files (XM and CM) had concluded that five patients could be classified as SS patients and 28 as SAPS patients.[6,17] Interestingly, the PRT2 and/or ΔPRT were positive (below the thresholds defined in our study) in 80% of SS patients but only in 25% of SAPS patients, confirming that the combined testing procedure improves the predictive value or tear production assessment for screening SS patients.

Despite several studies and clinical research programs, debates are still ongoing on the most accurate and/or reproducible diagnostic procedure to screen dry eye patients. This is likely related to the lack between signs and symptoms in these patients and with the poor repeatability of tests, including questionnaires on subjective signs.[3,5,9,28] In that respect, the Schirmer I test is commonly considered as poorly reproducible during the same, or between visits, while PRT has been advocated to be more reliable.[9,16,18,25] Our study suggests that their combination could improve the global effectiveness of tear production assessment in severe dry eye patients.

Interestingly, a recent study comparing 231 patients with primary SS with 89 dry eye patients showed that a rose Bengal staining in the temporal conjunctiva may also be a good marker to identify the dry eye disease in the eye care office.[29] Based on specificity and sensitivity indexes at 56.2%and 96.1%, respectively, this study suggested that a careful analysis of the eyes by the ophthalmologist is a valuable tool for the work-up of suspected SS patients. However, rose Bengal eye drops are not available in many countries, and most physicians have reduced their use in daily clinical practice because their instillation is very painful. Indeed, the use of rose Bengal needs to be preceded by topical anesthetics, which in turn are often toxic to the corneal epithelium, especially in dry eyes. The measurement of tear osmolarity also has been shown to be a very accurate test for the assessment of dry eye disease severity.[30] This new technology is rather expensive at present and risks to remain so as long as the volume of machines and devices of measure distributed in the world are limited. Because PRT is a painless and inexpensive test, with no side effects on the ocular surface,[10,31] we believe that it could represent a valuable alternative.

In conclusion, the combination of Schirmer I and PRT tests significantly improves the diagnostic procedure of ocular dryness, with optimized PPV and NPV values compared to the Schirmer I test alone. This combined procedure could be included in the general work-up of patients presenting with dry eye subjective symptoms, particularly in those suspected of SS, allowing for the better selection of patients that should benefit from more invasive and expensive tests, such as blood analysis for anti-SSA and anti-SSB antibodies or salivary gland biopsy.

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