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The validity of CCCRC test in patients with nasal polyposis

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SUMMARY

Both the Connecticut Chemosensory Clinical Research Center (CCCRC) test and Cross Cultural Smell Identification Test (CC-SIT) are used to assess the sense of smell in patients all over the world. Our aim is to know whether the CCCRC test is a valid olfactory test in comparison with CC-SIT. Therefore, we have done a prospective study in 60 adult patients with nasal polyposis to compare the validity of CCCRC with UPSIT. We used the CCCRC olfactory test made up of a threshold and suprathreshold test while CC-SIT relies solely upon suprathreshold measurement. We determined the specificity, sensitivity, positive predictive value and negative predictive value for patients suffering nasal polyposis with the CCCRC test. The validity index was 95% and accuracy rate was 8%. We determined unit cost and the reliability of the CCCRC test. For patients with nasal polyposis: the sensitivity was 86%; the specificity was 94%; the positive predictive value was 93% and the negative predictive value was 88%. The reliability was 92%. The unit cost of the CCCRC was € 5.60. The CCCRC test is a valid test in comparison with CC-SIT. CCCRC is cheap and can be used in routine clinical settings.

Key words: olfaction, anosmia, hyposmia, olfactory disorders

INTRODUCTION

There is a lack of public awareness regarding olfactory impairment, despite the relatively high prevalence [1,2]. There are several methods for characterizing the type and degree of olfactory loss. One of these tests is the test of UPSIT (University of Pennsylvania Smell Identification Test). The UPSIT relies solely upon suprathreshold measurement but with 40 odors rather than 10. Each odor is presented in a microencapsulated "Scratch and Sniff" booklet. UPSIT has been administered to many individuals and data exists for normosmic, hyposmic and anosmic individuals. The score is based on the number of correct answers to 40 questions. This test has two advantages: first, there are normal data for men and women separately where the relationship between the function sense of smell, age and sex can be appreciated; second, it does not require trained personnel to perform it (the patient can do it by himself at home). When the patient returns to the office, any medical professional can interpret. This test is not applicable to situations in which olfactory function must be assessed in less than 5 minutes. Furthermore, a number of the odors of this test are not universally known. For these reasons, the same authors developed a 12-item self-administered odor identification test, analogous to the UPSIT. This test, termed the CC-SIT (Cross Cultural Smell Identification Test) [3] incorporates multicultural odorant items selected from the UPSIT. Another sense of smell test that is more frequently used, is the CCCRC (Connecticut Chemosensory Clinical Research Center). The CCCRC test is portable, inexpensive to create, and can be administered uni- or bilaterally. Nevertheless, problems with this test include the length of execution and the administration requires trained personnel. Although the results of the UPSIT and CCCRC tests can vary, some studies show a high correlation between both smell tests [4] (r=0.88-0.92).

The aim of this report is to determine if the CCCRC is a valid test when it is compared with the CC-SIT test. We chose CC-SIT because it is comparable in countries outside the USA, CC-SIT is cheaper that UPSIT and finally such a comparison has never been done.

MATERIAL AND METHODS

Patients

Testing was performed on 60 patients with nasal polyposis recruited in Alcorcón (Madrid). Participants were given thorough ear, nose and throat examinations, including nasal endo-

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scopy. We determined the polyposis endoscopic extension according to the Lund classification [5]. There were 29 males and 31 females. Mean age was 52.2 (SD 13.9, CI 48.6-55.8). There were 34 patients over 50 years and 26 under 50 years. Informed consent was obtained from all subjects before study participation. In all cases, the study fulfilled the principles outlined in the Declaration of Helsinki.

Odour tests

We used the Connecticut Chemosensorial Clinical Research Centre test (CCCRC). This test was manufactured in our institution with the collaboration of the Pharmacy Department following the guidelines of the original article of Cain [6], who was the first to describe this olfactory test. This test was made up of two parts: the butanol threshold test and identification test. The *threshold test* employed aqueous dilutions of 1-butanol where successive dilutions differed by a factor of three. The highest aqueous concentration equalled 4%. The number of dilution steps ranged from 0 to 8 depending on testing circumstances. The test solutions were presented for smelling in 250 ml capacity polyethylene bottles containing 60 ml of solution. The bottle closure had a pop-up spout that fitted to both nostrils. To sample a bottle, the person placed the spout into both nostrils and then sniffed simultaneously. Testing began with the lowest concentration. The test participant received the bottle with this concentration along with a blank and had to decide which one smelled stronger. If incorrect, the participant received another blank paired with the next higher concentration. Errors triggered increments in concentration, whereas correct choices led to another presentation of the same concentration (in another bottle) and a blank. Four correct choices in a row led to an end of the testing. The concentration at which this occurred marked the threshold.

The participant received the *identification* test after the threshold test. A kit was composed of ten 180 ml opaque plastic jars containing 5 g of the substance in sachet-like packets of stimuli. Based on the performance of anosmic patients, we can say that seven stimuli appealed exclusively, or almost so, to the sense of smell (baby powder, chocolate, cinnamon, coffee, mothballs, peanut butter and bar soap) and one appealed to the common chemical sense as well (Vicks). The eight items were presented in the same order for both nostrils. When presented with an item, the participant chose from a 20-item list. The list contained the names of the eight test items and of thirteen distractors. In addition to the names on the list, responses of "no sensation" and "do not know" were permitted. The examiner gave corrective feedback whenever the participant made an error. If the participant exhibited some evidence of function, but nevertheless made mistakes, the examiner presented missed items a second time. A correct answer upon second presentation cancelled a previous error. This allowed a participant to rectify mistakes and thereby decreased the possibility of cognitive errors. In such cases, the first trial with an item served as training. This corrective feedback was as well given for CC-SIT to make the comparison valid. The score for the test comprised the number of olfactory items out of seven correctly identified and a notation regarding ability to perceive trigeminal stimulation. In order to control the rapidly fluctuating olfaction in patients with nasal polyposis, we administered CC-SIT immediately after the CCCRC test to compare both tests in the same period of time with the same olfactory sensation.

The outcome of the threshold and identification test was combined into a *composite score*, an average of the two tests.

According to normative data for males and females published by Doty [3], the results were considered negative or positive. We showed with which odors the patients had failed in the CC-SIT test. The same way, according to normative data for males and females published by Toledano [7], the results were considered negative or positive. We took into account the gender, the age and the polyposis grade of the patients.

Statistics

We studied the sensibility, the specificity, the negative and positive predictive value and the global value of the CCCRC compared with CC-SIT. We were hoping that 95% of the patients would be diagnosed. We wanted to estimate the number of patients with a good 8% accuracy and a 95% confidence rate. With this requirement, the sample size should be 60 patients: 30 patients for the sensibility study and 30 patients for the specificity study. We chose patients who suffer nasal polyposis because this disease is the most frequent cause of olfactory impairment in our office. We compared the CCCRC with CC-SIT that is a modified test of UPSIT. We applied the following formula: $N= Z^2$ alfa/2*p*(1-p)//I^2 where Z mean alpha = 1.96 is the value for z with a 95% confidence rate. P is the proportion of the expected validity index that in this case is 95%.

We studied how much money the CCCRC costs. For this reason, we added the costs of all products to make the test to the personnel expenses spent performing the CCCRC. Besides, we added the variable costs that depended on the number of tests we performed in the office. We used euros as monetary unit. Besides, we studied the time spent to administer each test in our office.

Finally, we did a reliability analysis of the CCCRC in 30 patients with nasal polyposis. We performed the test and repeated it 3 weeks later. We determined the intragroup correlation quotients with its confident intervals for every single test: butanol, supraliminar and composite score (test-retest reliability).

RESULTS

According to the results of CC-SIT, abnormal olfactory function was present in 29 (48.3%) patients compared with 27 patients (45%) with CCCRC. On the other side, 31 patients (51.7%) were normal with CC-SIT and 33 patients (55%) with CCCRC.

There was an agreement between the subjective sense of smell and CC-SIT in 90% of the patients and the Kappa value was 0,76. The agreement between the subjective sense of smell and

Table 1. Comparative CC-SIT against CCCRC. N: number of a patient; CC-SIT: whether the test was failed (+) or not (-). CCCRC: whether the test was failed (+) or not (-). Gender: 0 is female and 1 is male.

No.	CC-SIT	Failures (CC-SIT)	CCCRC	CCCRC score	Subjective smell	Age	Gender	Poliposis grade
1	-	0	+	1,8,4.5	Good	60	0	3
2	+	Smoke, lemon, pineapple	+	2,6,4	Bad	45	0	2
3	+	Cinnamon, pepper, lemon, smoke, chocolate, roses, banana, pineapple, soap, onion	+	0,2,1	Bad	52	1	4
4	-	0	-	7,8,7.5	Good	41	0	2
5	-	0	-	4,8,6	Good	40	1	2
6	+	Lemon, pineapple, banana	+	2,6,4	Bad	56	0	3
7	-	0	-	5,7,6	Good	52	1	2
8	+	Cinnamon, pepper, lemon, smoke, chocolate, roses, banana, pineapple, soap, onion	+	0,3,1.5	Bad	49	1	4
9	+	Lemon, roses, smoke	+	3,7,5	Good	71	0	2
10	+	Cinnamon, pepper, lemon, smoke, chocolate, roses, banana, pineapple, petrol, soap, onion	+	0,2,1	Bad	48	0	3
11	+	Cinnamon, pepper, lemon, smoke, chocolate, roses, banana, pineapple, petrol, soap, onion	+	1,2,1.5	Bad	41	0	4
12	-	0	-	5,8,6.5	Good	52	0	2
13	-	0	-	5,7,6	Good	64	1	2
14	+	Cinnamon, pepper, lemon, smoke, roses, banana, pineapple, soap, onion	+	0,2,1	Bad	56	0	3
15	+	Pepper, lemon, roses, banana, pineapple, soap	+	2,7,4.5	Bad	85	0	2
16	+	Pepper, lemon, smoke, roses, banana	+	5,3,4	Bad	17	0	2
17	+	Cinnamon, pepper, lemon, smoke, chocolate, roses, paint, banana, pineapple, petrol, onion	+	0,0,0	Bad	56	1	4
18	-	0	-	5,8,6.5	Good	53	1	2
19	+	Cinnamon, pepper, lemon, smoke, chocolate, roses, paint, banana, pineapple, onion	+	0,0,0	Bad	62	1	3
20	+	Cinnamon, pepper, lemon, smoke, chocolate, roses, paint, banana, pineapple, petrol, soap, onion	+	1,0,0.5	Bad	69	0	3
21	+	Cinnamon, pepper, lemon, smoke, chocolate, roses, banana, pineapple, soap, onion	+	0,2,1	Bad	77	1	3
22	-	0	-	4,8,6	Good	48	0	2
23	-	0	-	6,7,6.5	Good	40	1	2
24	+	Cinnamon, lemon, chocolate, pineapple, onion	-	4,7,5.5	Good	46	0	2
25	-	0	-	5,8,6.5	Good	34	1	2
26	-	0	-	5,8,6.5	Good	49	1	2
27	+	Cinnamon, pepper, lemon, smoke, chocolate, roses, paint, banana, pineapple, petrol, soap, onion	+	1,3,2	Bad	68	1	3
28	+	Smoke, roses, banana, pineapple, soap	-	4,7,5.5	Good	57	1	2
29	+	Smoke, roses, banana, pineapple, soap	-	4,7,5.5	Good	33	0	3
30	-	0	-	7,7,7	Good	34	0	2
31	-	0	-	5,8,6.5	Good	65	0	2
32	+	Cinnamon, pepper, lemon, smoke, chocolate, roses, paint, banana, pineapple, petrol, soap, onion	+	0,1,0.5	Bad	25	1	3
33	-	0	-	4,7,5.5	Good	56	1	2
34	+	Chocolate, smoke, roses	+	3,7,5	Bad	62	0	2
35	+	Lemon, smoke, soap	+	1,7,4	Bad	42	0	3
36	-	0	-	5,6,5.5	Good	64	0	2
37	+	Cinnamon, pepper, lemon, smoke, chocolate, roses, paint, banana, pineapple, petrol, soap, onion	+	0,0,0	Bad	71	1	3
38	-	0	-	5,7,6	Good	54	1	2
39	-	0	-	5,8,6.5	Good	50	1	2
40	-	0	-	,4,8,6	Good	54	0	2
41	+	Cinnamon, pepper, lemon, smoke, chocolate, roses, paint, banana, pineapple, petrol, soap, onion	+	1,0,0.5	Bad	67	1	3
42	+	Cinnamon, pepper, lemon, smoke, chocolate, roses, paint, banana, pineapple, petrol, soap, onion	+	0,2,1	Bad	77	0	3
43	-	0	-	4,8,6	Good	48	1	2
44	-	0	-	6,7,6.5	Good	40	0	2
45	+	Smoke, roses, banana, pineapple, soap, onion	-	4,7,5.5	Good	46	1	2
46	-	0	-	5,8,6.5	Good	34	1	2
47	-	0	-	5,8,6.5	Good	49	1	2
48	-	0	+	1,7,4	Bad	68	1	3
49	-	0	-	4,7,5.5	Good	57	1	2
50	-	0	-	4,7,5.5	Good	33	0	2
51	-	0	-	7,7,7	Good	34	0	2
52	-	0	-	5,8,6.5	Good	65	0	2
53	+	Cinnamon, pepper, lemon, smoke, chocolate, roses, paint, banana, pineapple, petrol, soap, onion	+	0,1,0.5	Bad	25	1	3
54	-	0	-	4,7,5.5	Good	56	1	2
55	+	Pepper, roses, banana, pineapple, soap	+	3,7,5	Bad	58	1	2
56	+	Lemon, roses, smoke	+	1,7,4	Bad	42	0	3
57	-	0	-	5,6,5.5	Good	62	1	2
58	+	Cinnamon, pepper, lemon, smoke, chocolate, roses, paint, banana, pineapple, petrol, soap, onion	+	0,0,0	Bad	71	0	3
59	-	0	-	5,7,6	Good	54	1	2
60	-	0	-	5,8,6.5	Good	52	0	2

CCCRC was 96% of the patients and the Kappa value was 0,93. When we compared CCCRC with CC-SIT, the sensitivity of the CCCRC was 86% (CI: 67-95%) and the specificity was 94% (CI: 78-98%). The positive predictive value was 93% (CI: 74-98%) and the negative predictive value was 88% (CI: 71-96%). The global value was 90% (Table 1). There were no differences, neither between male and female patients (Table 2) nor between patients over 50 or under 50 years (Table 3).

The cost of the first production was € 445.56, whereas the cost for subsequent times was € 64.85 per test. This difference was

Table 2. Validity of the test: over **(>50)** and under **(<50)** 50 years old. Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value; GV: global value. The figures between parenteses are confident intervals.

	Sens	Spec	PPV	NPV	GV
<50	0,75	1	1	0,82	0,88
	(0,99-0,5)			(1-0,64)	(1-0,76)
>50	0,93	0,83	0,83	0,93	0,88
	(1,05-0,82)	(1-0,66)	(1-0,66)	(1-0,66)	(0,99-0,77)

Table 3. Validity of the test: females **(F)** and males **(M)**. Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value; GV: global value. The figures between parentheses are confident intervals.

	Sens	Spec	PPV	NPV	GV
F	0,87	0,92	0,93	0,86	0,89
	(1,04-0,71)	(1,07-0,78)	(1,06-0,8)	(1,04-0,67)	(1-0,78)
M	0,83	0,89	0,83	0,89	0,87
	(1,04-0,62)	(1,03-0,75)	(1,04-0,62)	(1,03-0,75)	(0,99-0,75)

because the authors needed some time (seeking articles, coordinating differents departments) and some materials (odorants, bottles) to design the test for the first time. The time spent to perform the test in the office was 8.5 minutes. Therefore, the ENT cost to perform one test in the office was € 4.40. We have done 368 tests in the office uuntil the time of writing. The unit cost of the CCCRC was obtained by dividing the production cost by the number of tests administered. Therefore, the unit cost of the CCCRC was € 5.61 when this test was made for the first time and € 4.57 when the test was subsequently administered (Table 4).

We studied the reliability of the CCCRC. We found that the intraclass correlated quotient in the threshold test and identification test was 0.92 for both tests. The confidence intervals were 0.77-0.97 for the threshold test and 0.77-0.98 for the identification test (Table 5). Neither the CC-SIT nor CCCRC are time-consuming tests (Table 6).

Table 4. Comparative cost of the CC-SIT and CCCRC smell test. Cost are shown in euros and converted to dollars (exchange rate of 2004).

SUPRALIMINAR TEST	**COST**
Cost of the all products used for the test	4.53
Pharmaceutical cost for the first manufacturing	17.25
Nurse cost for the first manufacturing	20.92
Total cost for the first manufacturing	**42.70**
Cost of the all products	4.53
Pharmaceutical cost for the following manufacturing	3.49
Nurse cost for the first manufacturing	18.30
Total cost for the following manufacturing	**26.32**
THRESHOLD TEST	
Cost of the all products used for the test (8 bottles)	2.98
Pharmaceutical cost for the first manufacturing	201.07
Nurse cost for the first manufacturing	20.92
Total cost for the first manufacturing	**224.97**
Cost of the all products (8 bottles)	2.98
Pharmaceutical cost for the following manufacturing	17.25
Nurse cost for the first manufacturing	18.30
Total cost for the following manufacturing	**38.53**
ENT COST	
ENT cost to plan the test	177.89
ENT cost for performing one test	4.40
TOTAL COSTS	
MEAN TIME TO PERFORME THE CCCRC (minutes)	8,50
ENT COST (depending on the time spent by ENT)	4.40
1^0 PRODUCTION COST	445,56
2^0 PRODUCTION COST	64,85
TEST DONE UNTIL NOW	368,00
UNITARY COST 1^0 PRODUCTION	**445.56/368+4.4**
UNITARY COST 2^0 PRODUCTION	**64.85/368+4.4**
	€4.57 x 1.16 = $ 5.3
UNITARY COST CC-SIT (2004)	**$ 12,95**

Table 5. Reliability of CCCRC smell test. CI: confidence interval.

N=30	Intragroup correlation quotient	CI	F	p
Threshold	0,92	0,77-0,97	27,2	0,00
Identification	0,92	0,77-0,98	27,3	0,00
Composite	0,98	0,94-0,99	114,1	0,00

Table 6. Time-consumed by CCCRC and CC-SIT test.

N=60	Mean (minutes)	Typical deviation	Cl	t	p
CCCRC	8,50	1,42	11,2-5,7	4,4	*0,00*
CC-SIT	12,53	5,36	23.0-1,8		

DISCUSSION

Throughout history, many smell tests have been used [8,9,10,11]. Nevertheless, at present, smell tests of greater use are the UPSIT (University of Pennsylvania Smell Identification Test) and the CCCRC (Connecticut Chemosensory Clinical Research Centre). They both have their advantages and disadvantages. The UPSIT and the CCCRC test are easy to use and it is this ease of administration that makes both tests attractive for routine clinical use. The advantage of the UPSIT test is that it displays data standardized for males and females in different age groups; in addition, it is a test very easy to perform, and it does not need healthcare personnel to perform the test. The main disadvantage of the test is its high cost. The CCCRC test is less expensive test but its storage is more complex and a nurse is needed to perform it. In any case, the results of the CCCRC correlate well with the UPSIT and other smell tests [12].

There was a relationship between the subjective sense of smell and the CC-SIT of 90% less than CCCRC that was 96.6%. We think that was why the CC-SIT did not assess the olfactory threshold. We can see in Table 1 how those patients who failed the relation (9,24,25,29,45,49) were due to failing the threshold olfactory score.

Both the sensibility and specificity were high. The positive and negative predictive values were high as well. Therefore, we concluded that the test is valid in order to rule out olfactory impairment. When the test is positive, the patient has 93% possibility of abnormal olfactory function. Until now, we did not find any studies comparing CC-SIT with CCCRC in terms of validity. At the moment, we are comparing the CCCRC to the objective test to determine olfactory evoked potentials.

If we compare the cost of CCCRC with the cost of CC-SIT, we see the CCCRC ($6.5) is less expensive than CC-SIT ($12.95). It should be remembered that the CC-SIT does not need an ENT to perform the test and it can be done by the patient at home. In spite of that fact, the CCCRC is still less expensive than the CC-SIT, despite the higher cost by the ENT cost to perform a test in the office. At the moment, we are working on a screening test that would reduce both price and time even more [13].

The reliability of the CC-SIT was 71% [3]. However, the authors concluded that the reliability of the CC-SIT when compared to the UPSIT is 92%. The test described by Hummel [14] had a reliability of 78%. In our study, we find the reliability of the CCCRC to be greater than the CC-SIT.

CONCLUSION

CCCRC is as valid as CC-SIT to be administered in patients with nasal polyposis in clinical routine. More studies must be done to probe the usefulness of the CCCRC test in others types of olfactory impairments.

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