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Patterns of lacrimal dysfunction in primary biliary cirrhosis

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SUMMARY The lacrimal function has been evaluated in 23 patients suffering from primary biliary cirrhosis by rose bengal test, the Schirmer test 1, and the tear breakup time. Ocular dryness was present in 78% of cases studied. No difference was found with respect to the length or severity of the hepatic involvement between patients with and without lacrimal dysfunction, but in patients with signs of hypolacrimation the changes in the lacrimal tests increased with the duration and histological progression of liver disease.

Primary biliary cirrhosis (PBC) is a chronic cholestatic disease. It is characterised by granulomatous infiltration of portal tracts with destruction of intrahepatic bile ducts.¹ It is associated with a variety of immunological abnormalities. Among them are a close association with M2-antimitochondrial antibodies,² found in nearly 90% of cases, alterations of cell mediated immune functions, and increased serum IgM immunoglobulins.³ Recently an aberrant expression of HLA-DR antigens on bile duct epithelium has been demonstrated.⁴ Besides the biliary ducts the lacrimal, salivary, and pancreatic ducts may also be involved, thus presenting the picture of a 'dry gland syndrome'.⁵ PBC should therefore be regarded as a systemic disease rather than a disorder confined to the liver. The involvement of different organs may induce a variety of clinical pictures, whose common denominator is the presence of chronic liver disease.

The frequent occurrence of ocular dryness⁶⁻⁹ has led us to study the presence of possible correlation between lacrimal dysfunction and the histopathological stage, serological parameters, and duration of liver disease.

Material and methods

Twenty-three patients (21 females) ranging in age from 42 to 75 years were studied. The disease

duration varied from 1 to 15 years. The patients showed typical biochemical changes (Table 1); all of them were positive for antimitochondrial antibodies (AMA) and had a liver histology (biopsy and/or laparoscopy) supporting the diagnosis of PBC.

The patients had no significant eye disorders other than eye dryness, and on the basis of the American Rheumatism Association criteria none of them had osteoarticular symptoms or signs suggesting the diagnosis of rheumatoid arthritis.

The liver biopsy findings were classified in four stages according to accepted criteria.¹⁰

The ophthalmological investigations included the following,

(1) A history with particular emphasis on conjunctival-lacrimal symptoms.

(2) Biomicroscopic analysis of the anterior and posterior segments.

(3) Tear breakup time (BUT): values lower than 10 seconds are generally considered suggestive of an early rupture of the precorneal film.¹¹

(4) Rose bengal test. We referred to Van Bijsterveld's classification¹² to assess the severity of the corneoconjunctival epitheliopathy (four stages with increasing severity: degree 0=no impregnation, degree 1=low impregnation, degree 2=medium impregnation, degree 3=high impregnation) and to indicate the site (arabic numerals 1, 2, and 3) for temporal bulbar conjunctival, nasal bulbar conjunctival, and corneal, respectively. The rose bengal test was considered positive when a degree 1 epitheliopathy was present in at least two corneocon-

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Patterns of lacrimal dysfunction in primary biliary cirrhosis

Table 1 Biochemical parameters of 23 PBC patients

Case	TB	AP	Chol	Alb	Glob	IgG	IgA	IgM	AMA titre
1	0.25	82	270	3.6	1.7	1436	205	557	1:320
2	0.4	75	268	4.2	1.9	1735	511	560	1:320
3	5	330	281	4.00	2.6	2166	493	1079	1:320
4	0.4	210	175	3.7	1.3	1200	250	160	1:320
5	1.4	163	467	4.1	1.5	1007	160	452	1:40
6	0.6	75	269	4.00	1.1	640	212	562	1:320
7	0.5	58	150	4.5	1.3	1058	398	680	1:80
8	1.5	90	220	2.8	1.9	1500	215	160	1:80
9	1.2	70	183	4.35	2.2	2350	780	380	1:320
10	19.8	120	128	2.4	2.8	1970	1180	544	1:160
11	1.4	175	233	4.1	1.8	1644	402	586	1:320
12	6.5	40	180	2.4	1.8	1740	500	560	1:80
13	2.6	115	154	2.5	3.4	2750	775	1940	1:320
14	0.5	13	214	4.4	1.0	1220	79	410	1:80
15	1.0	112	307	4.2	2.4	3200	812	680	1:320
16	1.6	27	158	2.7	3.2	2640	729	520	1:80
17	1.6	27	158	2.7	3.2	2644	729	520	1:80
18	0.85	177	210	2.6	2.9	2800	450	230	1:80
19	0.35	106	240	3.2	2.3	1365	440	1486	1:160
20	0.45	115	270	4.00	1.4	1250	100	440	1:10
21	0.5	89	200	4.2	1.6	1224	232	764	1:320
22	8.1	185	289	4.5	1.1	1270	560	335	1:320
23	0.6	35	249	4.5	1.7	1330	274	1248	1:20

TB=total bilirubin (normal 1 mg/dl). AP=alkaline phosphatase (normal 12–30 mU/ml). Chol=cholesterol (normal 150–250 mg/dl).

Alb=albumin (normal 3.6–4.3 g/dl). Glob=gammaglobulins (normal 1.1–1.4 g/dl). IgG normal range=420–1450 mg/dl.

IgA normal range=60–480 mg/dl. IgM normal range=50–390 mg/dl.

SI conversion. TB mg/dl \times 17.1= μ mol/l. Chol mg/dl \times 0.0259=mol/l. Alb and Glob g/dl \times 10=g/l. Ig mg/dl \times mg/l.

junctional zones. The data reported in Table 2 represent the mean value of the two eyes.

Tests 3 and 4 are not affected by the age of the patients.

(5) Schirmer's tests 1. Each patient was tested by using blotting paper strips 5 mm wide and 55 mm long (blue Carlo Erba litmus paper) inserted 5 mm down from the temporal side of the inferior fornix. The test

Table 2 Relation between clinical data and lacrimal function in 23 PBC patients

Case	Age	Sex	Stage	Duration (years)	Eye symptoms	Rose bengal	Schirmer I (normal \geq 10 mm)	BUT (normal \geq 10 s)
1	63	M	I–II	1	–	1 ₁ 2 ₁ 3 ₀	9–11	25–30
2	54	F	I	2	+	1 ₁ 2 ₁ 3 ₀	11–12	10–10
3	48	F	I	3	–	1 ₁ 2 ₁ 3 ₀	9–9	10–11
4	60	M	I	3	+	1 ₁ 2 ₁ 3 ₀	6–10	20–20
5	47	F	II	3	–	1 ₁ 2 ₁ 3 ₁	9–9	12–12
6	52	F	II	3	+	1 ₁ 2 ₁ 3 ₀	5–5	11–12
7	69	F	I–II	6	+	1 ₁ 2 ₀ 3 ₀	9–10	5–8
8	51	F	III	3	+	1 ₁ 2 ₂ 3 ₁	16–15	6–8
9	66	F	III	7	+	1 ₁ 2 ₁ 3 ₀	9–11	16–16
10	55	F	IV	8	+	1 ₀ 2 ₂ 3 ₁	12–6	8–7
11	47	F	III–IV	9	–	1 ₁ 2 ₁ 3 ₁	2–2	7–8
12	52	F	IV	10	+	1 ₁ 2 ₂ 3 ₀	3–6	9–8
13	63	F	IV	12	+	1 ₂ 2 ₂ 3 ₁	1–2	5–6
14	59	F	III–IV	8	+	1 ₂ 2 ₂ 3 ₂	3–3	5–6
15	75	F	IV	13	+	1 ₂ 2 ₂ 3 ₂	1–3	7–8
16	68	F	IV	13	–	1 ₁ 2 ₁ 3 ₁	7–7	9–9
17	71	F	IV	14	–	1 ₁ 2 ₂ 3 ₁	9–9	9–7
18	42	F	IV	15	+	1 ₂ 2 ₂ 3 ₃	6–9	7–7
19	50	F	I	2	–	1 ₁ 2 ₀ 3 ₀	15–17	20–20
20	49	F	I	4	–	1 ₀ 2 ₀ 3 ₀	10–16	15–15
21	57	F	III–IV	3	–	1 ₀ 2 ₀ 3 ₀	10–16	14–20
22	72	F	III–IV	4	–	1 ₀ 2 ₀ 3 ₀	15–16	20–20
23	58	F	IV	7	–	1 ₀ 2 ₀ 3 ₀	15–20	12–13

was performed with open lids, with the patients' eyes turned upwards. As Schirmer's test 1 is affected by age¹³⁻¹⁵ in subjects under 60 years, only values lower than 10 mm after 5 minutes were regarded as suggestive of hypolacrimation.

Results

The results in each patient are reported in Table 2, as well as age, histological stage, duration (in years) of the disease, and the presence of ocular symptoms suggestive of eye dryness.

Twelve patients (52%) had symptoms of ocular dryness, all of them lacrimal dysfunction. Functional changes without symptoms were observed in a further six patients. Thus 18 patients (78%) gave abnormal results in the lacrimal tests. In particular the rose bengal test was positive in 17 cases (74%), the Schirmer's test in 12 (52%), and the BUT was reduced in 11 (48%). The results of the Schirmer's test 1 in cases 1, 7, 9, 17, were not regarded as positive because of the age of the patients (63, 69, 66, 71 years respectively).

As to the relation between the results of lacrimal tests and liver histology, Table 2 shows that simultaneous positive results of the three lacrimal tests were never found in 9 patients with stages I and II PBC, and two early cases had a normal lacrimal function. Simultaneous positive results of the three tests were found in eight out of 14 patients with stages III-IV PBC, while three patients showed no eye disorder at all.

No correlation between AMA titre, serum IgM levels, and the presence or degree of ocular dryness was found.

The relation between lacrimal function tests and the duration of disease in the 15 patients with altered lacrimal function is shown in Table 2. The rose bengal test was clearly the first to be altered, followed by Schirmer's test 1 and the BUT test. In eight of the nine stage III-IV PBC patients with a duration of disease of 8-15 years all the tests were simultaneously altered.

Discussion

As was expected, lacrimal function tests are more sensitive than ocular symptoms in the detection of lacrimal dryness. From the above data it appears that patients suffering from PBC can be divided in two groups: the first comprises a small number of patients with different stages of the disease who do not show any lacrimal disorder; the second group, which is larger (78%), comprises patients with a progressive increase of lacrimal dysfunction; the positivity of the rose bengal test appears first, and it is followed by the

Schirmer's test 1 and the BUT test. The number of tests positive in the individual patient and the number of patients positive for all three tests progressively increases in relation to the duration of the disease.

The prevalence of lacrimal changes observed in our patients (78%) is in agreement with the data of Golding *et al.* (72%),⁷ McFarlane *et al.* (69%),⁸ and Alarcon-Segovia *et al.* (71%).⁹ Alarcon-Segovia and colleagues reported in detail the results obtained in 14 patients with PBC. In the cases with keratoconjunctivitis sicca (71%) they found no relation either with the histological stage or with the duration of the liver disease, which was shorter than that of the present series (1-6 years compared with 1-15 years). In their study the lacrimal function was examined by the rose bengal test and the Schirmer's test 1, which was considered positive if moistening of the strip was less than 5 mm; the BUT test was not performed.

The interpretation of the results obtained by the Schirmer's test 1 is still debated because various factors can considerably affect tear formation. In a recent study performed on 100 normal subjects an average tear production of 19 mm¹³ was found; men older than 55 years and women older than 60 years have a lower tear production, so that at ages between 70 and 80 years values lower than 5 mm were commonly observed in subjects without eye disorders.^{14,15} Consequently one may question the interpretation of the negative findings (Schirmer's test 1 values less than 5 mm) given by Alarcon-Segovia *et al.*⁹ for three patients with ages between 45 and 62 years who had been suffering from liver disease for 5-6 years. If on the contrary the limiting value of this test is fixed at 10 mm, these observations could be interpreted as confirmatory of our results.

In conclusion, most PBC patients seem to acquire the sicca syndrome. No clear-cut differences in duration or severity of liver disease are seen between patients with and without lacrimal disorders. Since the subgroup of PBC without ocular-lacrimal involvement comprises patients with a long disease duration and an advanced histological stage, it is conceivable that they will never have eye disorders. On the contrary, most patients develop lacrimal dysfunction in the early stages of the disease, starting with slight positivity of the rose bengal test and followed by progressively positive results from the other tests.

It is now known that the primary and secondary sicca syndromes (as observed in PBC) are distinct diseases, since they are associated with different immunological markers.¹⁶ While primary sicca syndrome is linked to HLA-B8,DR3 haplotypes, no such relation has been found in secondary sicca syndrome.¹⁷

Whether lacrimal dysfunction in PBC is related to

Patterns of lacrimal dysfunction in primary biliary cirrhosis

the same immunological mechanism responsible for biliary destruction remains to be clarified.

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