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Increased Prevalence of NIDDM in Anterior Uveitis

Anterior uveitis refers to inflammation involving the anterior portions of the eye, namely, the iris and ciliary body. The exact etiology of this process is often not clear, with ~25–50% of all uveitis patients considered as idiopathic (1–3). However, it is well recognized that numerous infectious and autoimmune endogen diseases may be causally implicated. The latter category includes specific ocular syndromes and systemic diseases, such as sarcoidosis, rheumatic diseases, Behçet's disease, and even diabetes (3). The association of diabetes and anterior uveitis was first described more than 100 years ago (4). More recently, Rothova et al. (5), in a retrospective analysis of 340 cases of anterior uveitis, found a definitive association with IDDM. Moreover, up to 75% of 16 patients with idiopathic uveitis and IDDM suffered from severe diabetic complications, including angiopathy, nephropathy, and neuropathy (5). In the same way, studies performed with a series of diabetic patients confirmed this association and also found a high frequency of systemic complications in diabetic patients with anterior uveitis (6,7). Guy et al. (7) observed iritis in 30% of 47 patients with IDDM and severe autonomic neuropathy, compared with 0.7% of 143 control IDDM patients without neuropathy. In a prospective study on patients with clinical diagnosis of unknown etiology uveitis, we have found an unexpected high frequency of NIDDM associated with idiopathic anterior uveitis. The study included 111 consecutive patients who were referred to the uveitis unit of the "Virgen de las Nieves" University Hospital of Granada, Spain, with the diagnosis of unknown etiology uveitis. The first aim of the study was to establish the etiology of uveitis in patients without any potential previously diagnosed etiological disease. Patients with ocular disease caused by late microvascular complications of diabetes were therefore excluded. There were 51 males (46%) and 60 females (54%) with a mean age of 42.7 years, range 4–83. Location of uveitis was as follows: 78 anterior (70.3%), 7 intermediate (6.3%), 19 posterior (17.1%), and 7 panuveitis (6.3%). The study protocol included clinical history, physical examination, hematological and serum biochemical analysis, erythrocyte sedimentation rate (ESR), rheumatoid factor, antistreptolysin-O (ASLO), C-reactive protein, antinuclear antibody (ANA), serologic study for syphilis, toxoplasmosis and virus, mantoux, chest and sacroiliac X-ray and HLA B27 typing in case of anterior uveitis. Diabetes was defined according to criteria of the World Health Organization (8). After evaluation, 54 patients were declared to have an idiopathic uveitis (48.6%), and a specific diagnosis was confirmed in 57 patients. Of these, 11 (9.9%) had a specific ocular condition, and 41 (36.9%) had an underlying systemic disorder. The most frequently observed systemic diseases were HLA-B27–associated seronegative spondylarthropathies (12.6%) and Behçet's disease (4.5%). We used the χ^2 test and Fisher's exact test for statistical analysis. A P value of <0.05 was considered to indicate statistical significance. Diabetes was observed in five nonobese patients (two men and three women, mean age 64.8 years with an age range of 55–74 years), all of them with idiopathic and anterior uveitis. Only one patient had been previously diagnosed with diabetes about 2 years ago, which was managed with diet. Two patients had bilateral ocular involvement, two developed chronic or recurrent inflammation, and none had posterior synechiae, glaucoma, retinopathy, or iris neovascularization. The frequency of diabetes in patients idiopathic anterior uveitis was 14.3% (5 of 35 patients), compared with no case in the group of 43 anterior uveitis patients with an established diagnosis ($P = 0.01$). This percentage is significantly higher than the prevalence of diabetes in a normal Spanish population (5.6%) ($P < 0.001$) (9).

In conclusion, we found a definitive association between NIDDM and idiopathic anterior uveitis. Although such association has been previously observed in one third of 30 patients with anterior uveitis and diabetes, statistical significance was not achieved (5,6). The pathogenic significance of this association is unknown. Previous studies have postulated that microangiopathy produced by diabetes could induce ischemic processes in the anterior uvea with subsequent tissue reaction and clinical features of anterior uveitis (5,6), but such a mechanism is unlikely in newly diagnosed patients with NIDDM who have no clinical evidence of microvascular complications. However, iris fluorescein angiography could be useful to clarify whether uveitis is an ischemic phenomenon in these patients. On the other hand, the absence of retinopathy, recurrent episodes in some patients, and a usually good response to corticosteroid therapy suggest an inflammatory process (5). This is quite possible in those immunologically mediated diseases such as IDDM, but is difficult to understand in the case of NIDDM. Castagna et al. (6), in a recent study of peripheral lymphocyte subsets in patients with anterior uveitis and diabetes, found normal values in patients with NIDDM, while a significant increase in the $CD8^+$ subset together with a $CD4^+/CD8^+$ ratio decreased in all IDDM patients. Lastly, a careful monitoring of the ocular inflammatory processes presenting in diabetic patients, and probably a prospective more extensive study could help to elucidate whether anterior uveitis in NIDDM patients is a causal or a true relationship.

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The French Paradox and Diabetic Patients

The fact that dietary fat intake is similar to that in other countries, and yet the risk of death by ischemic heart disease in France is low, was first formulated as a "French Paradox" in the early 1980s (1). The age-standardized death rates from ischemic heart disease were 124 for 100,000 men in France, in comparison to 447 in England and Wales and to 318 in the U.S., for men aged between 40 and 74 years in 1990 (*International Classification of Diseases* codes 410–414 [2]). This low rate exists despite the fact that the major risk factors, high cholesterol, hypertension, and smoking, are known (based on the MONICA Study) to have frequencies that are not lower than in other countries (2). The main hypothesis as to why cardiovascular disease is less frequent in France is the higher consumption of alcohol in the French population (3–5).

French diabetic men are also protected against ischemic heart disease, in comparison with their English and American counterparts. We present data from three cohort studies of men who were followed for causes of death over ~15 years. These cohorts included men who were known to be diabetic or who were diagnosed at baseline as diabetic. In the Rancho Bernardo study (6), subjects were classified as diabetic by their personal history or if their fasting plasma glucose was ≥7.8 mmol/l, and as nondiabetic if they had no personal or family history of diabetes and a fasting plasma glucose <6.1 mmol/l. In the Whitehall Study (7), men were known as diabetic or classified as a newly diabetic patient based on the 2-h capillary glucose level >11 mmol/l after a 50-g glucose load, normoglycemic subjects were those in the lower 95% of the 2-h glucose distribution (<5.4 mmol/l), and the intermediate group was defined as glucose intolerant (Table 1). In the Paris Prospective Study (8), subjects were classified as follows: a known diabetic patient according to whether they had been treated pharmaceutically for diabetes, a new diabetic patient if their 2-h plasma glucose was >11.1 mmol/l after a 75-g oral glucose load, and impaired glucose tolerant (IGT) if nondiabetic with a 2-h glucose >7.8 mmol/l.

Table 1—*Absolute and relative risk of death by ischemic heart disease by glucose tolerance status*

Study	Age-group (years)	Glucose tolerance status	*n*	Death by ischemic heart disease (age-adjusted) Rate/1,000 person-years	Risk ratio (95% CI)
Rancho Bernardo (6)	40–79	Nondiabetic	893	7.1*	1
		Diabetic	207	12.1*	1.8 (1.2–2.7)
Whitehall (7)	40–64	Normoglycemic	17,051	4.7	1
		Glucose-intolerant	999	6.7	1.4 (1.2–1.8)
		New diabetic	56	28.1	3.9 (2.4–6.4)
		Known diabetic	121	10.5*	2.2*
Paris Prospective	44–55	Normal	6,156	2.3	1
		IGT	706	4.2	1.7 (1.2–2.5)
		New diabetic	160	5.6	2.4 (1.3–4.6)
		Known diabetic	132	6.0	2.6 (1.3–5.1)

*Calculated from data in paper—not age-adjusted.

As expected, the French men had lower absolute rates of death by ischemic heart disease in comparison to the English and American men, with death rates of 2.3, 4.7, and 7.1 per 1,000 person-years, respectively, in the normal glucose tolerant group (Table 1). For the Whitehall Study, the death rate was very high for the new diabetic subjects. These subjects were diagnosed following a low oral glucose load of 50 g; thus only the most severely glucose-intolerant subjects (0.3%) were classified as newly diabetic men; perhaps a lower limit would have been more appropriate. The Whitehall "glucose-intolerant" group may well include men who would be classified as diabetic in the Paris Prospective or the Rancho Bernardo Studies. The absolute death rates in the diabetic men were ~12 in Rancho Bernardo, 16 in Whitehall, and 6 in Paris.

The relative risks of death by ischemic heart disease of the diabetic subjects, in comparison with the baseline group of normal subjects, are of the same order in all three studies, being close to two. Other population studies including diabetic subjects give similar results (9).

Thus, the French Paradox would appear to apply also to NIDDM patients. If drinking alcohol is associated with a low ischemic heart disease death rate, the diabetic patient as well as nondiabetic subjects should not be completely discouraged from drinking in moderation, but it should be noted that an excessive alcohol consumption may lead to diabetes (8).

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