**Proliferative diabetic retinopathy: the role of heredity**

**Original article:**

**Summary and Comment:**
Georges Krzentowski, Charleroi, Belgium (georges.krzentowski@chu-charleroi.be)

**Key words:**
Diabetes, retinopathy, nephropathy, heredity, HbA1c, blood pressure

**Summary**

Diabetic nephropathy and retinopathy are severe microvascular complications of diabetes, especially in their most advanced form. Diabetic nephropathy clusters in families, which suggests that genetic factors play a role in its pathogenesis [1]. The question concerning a similar clustering for proliferative retinopathy has remained unanswered.

The aim of the investigation by the Finnish Diabetic Nephropathy (FinnDiane) study group was to elucidate whether there is a familial clustering of proliferative retinopathy in patients with longstanding type 1 diabetes and to estimate the degree of familiality by calculating the heritability (h²) of proliferative retinopathy.

The FinnDiane study recruited 4800 type 1 diabetic patients and aimed to identify genetic and environmental risk factors for diabetic complications in type 1 diabetes. In the cohort of 4800 patients, 188 families had at least two siblings with type 1 diabetes. Data relating to medication, cardiovascular status, diabetic complications, hypertension, cardiovascular diseases, height, weight, HbA1c and nephrology status (microalbuminuria, endstage renal disease, dialysis or renal transplantation), as well as ophthalmological records, were obtained for more than 90% of those patients. The Early Treatment of Diabetic Retinopathy grading scale was used for the classification of ophthalmology status, and the eye with the more severe retinopathy was used to define the severity of the retinopathy. For the statistical analysis, the oldest sibling was designated as the proband of each sibship.

To study familial aggregation of proliferative retinopathy (or any retinopathy) three complementary analyses were used:

1. The presence or absence of proliferative retinopathy or any retinopathy in the proband was estimated as a risk factor for the corresponding condition in the oldest sibling. The familial risks were estimated using logistic regression models, adjusted for conventional risk factors.
2. In the 29 sibships in which two siblings had proliferative retinopathy, the degree of concordance within sibships, the interclass correlation of duration of diabetes to the diagnosis of proliferative retinopathy was calculated.
3. The heritability of proliferative retinopathy was estimated by a liability threshold model with HbA1c, mean arterial pressure, sex and duration of diabetes as covariates.

Proliferative retinopathy was found in 115 of 369 subjects (31%). The mean duration from onset of diabetes to development of proliferative retinopathy was 20.9 ± 7.5 years. The familial risk of proliferative retinopathy was estimated in 168 of the 188 sibships. Proliferative retinopathy in the probands (48 of 168) was associated with a higher unadjusted risk (odds ratio 2.76, 95% CI 1.25–6.11; p = 0.01) of proliferative retinopathy in the siblings of probands (61 of 182), which remained significant after adjustment for duration of diabetes, HbA1c and mean arterial blood pressure (p < 0.01). The heritability of proliferative retinopathy was h²= 0.52 ± 0.31 (p < 0.05). The absence of any retinopathy was associated with a lower HbA1c (p < 0.04) and a shorter duration of diabetes (p < 0.001) but was not associated with blood pressure or sex, and the absence of any retinopathy in the probands was not associated with the absence of any retinopathy in the sibling.

**Familial clustering of proliferative retinopathy in type 1 diabetes suggests a genetic component in its pathogenesis**

The authors concluded that there is a familial clustering of proliferative retinopathy in patients with type 1 diabetes. As the phenomenon cannot be completely explained by conventional risk factors, they suggest a genetic component in the pathogenesis of proliferative retinopathy in type 1 diabetes.

**Comment**

After 20 years of diabetes almost all type 1 diabetic patients show signs of retinopathy.
The prevalence of proliferative retinopathy varies from 13% to 50% after 15–20 years of insulin-treated diabetes [2, 3]. If it is not treated, almost all patients presenting with proliferative retinopathy will become blind within 5–10 years [4].

Poor glycemic control and duration of diabetes (glucose exposure) increase the prevalence, incidence and progression of diabetic retinopathy [2, 3, 5, 6]. Diabetic retinopathy continues to progress even after improvement of glycemic control [5, 7]; and the more severe the retinopathy, the longer the delay before a beneficial effect of improved control is observed [5].

Clearly, glucose exposure is the major determinant of diabetic retinopathy, but other factors also play a role. In type 2 diabetes, high blood pressure increases the incidence of proliferative retinopathy [8]. In type 1 diabetes, other factors (BMI, age, sex, microalbuminuria) also have some influence [9, 10].

It is noteworthy that proliferative retinopathy is associated with diabetic nephropathy, a complication that is at least in part genetically determined [1, 2]. Such an association suggests that familial factors may also contribute to the development of proliferative retinopathy.

These findings may be consistent with an altered expression of one or multiple critical genes induced by hyperglycemia. Studies of families with type 2 and a mixture of type 1 and type 2 diabetes observed a familial clustering of non-proliferative retinopathy [11–13]. Associations with various biologically relevant candidate genes have been extraordinarily difficult to replicate [14], which is typical of multifactorial diseases. The genetic component of diabetic retinopathy is likely to be polygenic. Environmental factors (HbA1c, blood pressure) play an obvious role but also appear to be genetically determined, as has been demonstrated for HbA1c [15] and blood pressure [16].

Microalbuminuria is a well-known predictor of proliferative retinopathy in patients with type 1 diabetes [17]. There is controversy as to whether this association is due to hyperglycemia or whether nephropathy is truly an independent risk factor for proliferative retinopathy. The present study noted a strong positive association between the severity of retinopathy and the severity of nephropathy (p < 0.001), which supports the hypothesis that there are common predisposing factors behind these two microvascular complications, without excluding of course the role of conventional risk factors such as HbA1c and blood pressure.

This study shows an increased risk of proliferative retinopathy and familial clustering of proliferative retinopathy in patients with type 1 diabetes that cannot be accounted for by conventional risk factors alone. This suggests that there is a significant genetic component in the pathogenesis of proliferative retinopathy.

References