Retinal Thinning as a Marker of Disease Progression in Patients With Wolfram Syndrome

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Wolfram syndrome (WFS), caused by recessive mutations in *WFS1*, is characterized by neurodegeneration due to apoptosis provoked by increased endothelial reticulum stress (1). Currently, it is incurable and leads to a premature death at an average age of 35 years (2). Despite initial success with spectroscopy-based studies (3), there is a lack of repeatable and robust markers for monitoring the clinical course of WFS. The aim of our study was to evaluate retinal parameters, measured with optical coherence tomography, as biomarkers of WFS progression. The Ethics Committee of the Medical University of Lodz approved the project (RNN/140/13/KE). Optical coherence tomography was performed after mydriasis using the Topcon 3D OCT-2000 system. Average retinal thickness and central thickness were measured using three-dimensional disc and macula scans covering a retinal area of 6 × 6 mm. The study was performed between August 2013 and April 2014. Two cohorts were enrolled: a pediatric/adolescent group and an adult one. The first consisted of patients with genetically confirmed WFS (median age 17.25 [interquartile range 14.00–18.90] years, duration of diabetes 10.70 [7.10–13.80] years, $n = 10$) recruited from the largest repository of WFS data (EURO-WABB) (4), patients with type 1 diabetes mellitus (T1DM) (median age 16.45 [12.20–17.51] years, duration of diabetes 1.48 [0.46–8.84] years, $n = 12$), and healthy control subjects (median age 16.45 [15.51–17.31] years, $n = 16$). The second cohort consisted of adult heterozygous carriers of *WFS1* mutations (median age 44.70 [40.50–46.00] years, $n = 10$) and healthy adults (median age 50.01 [49.09–60.88] years, $n = 13$). Details on the study group characteristics were presented in previous studies (5).

Average retinal thickness was significantly lower in pediatric/adolescent patients with WFS compared with both patients with T1DM (median 229 [25–75% interquartile range 221–232] vs. 273 [269–286] μm) and control subjects (229 [221–232] vs. 264 [262–276] μm, $P < 0.001$) (Fig. 1*A*). No differences were noted between children/adolescents with T1DM and control subjects ($P > 0.05$) or between adult *WFS1* mutation carriers and control subjects (273.85 [266.30–291.95] vs. 275.65 [266.60–277.80] μm, $P > 0.05$) (Fig. 1*A*). Adjustment for age at examination and duration of diabetes in the pediatric/adolescent cohort did not alter the results, confirming the impact of WFS on average retinal thickness. No differences of central thickness were observed between the three groups of the pediatric/adult cohort ($P > 0.05$). However, *WFS1* mutation carriers did show significantly lower central thickness than control subjects (199.75 [188.00–204.00] and 224.00 [203.00–244.00] μm, $P = 0.032$), although this difference was not significant after adjustment for age ($P = 0.138$).

For patients with WFS, we noted strong negative correlations between both age at examination ($r = -0.77$, $P = 0.009$) (Fig. 1*B*) and duration of diabetes and average retinal thickness ($r = -0.90$, $P < 0.001$). Age did not correlate with central thickness in WFS and T1DM groups, but a statistically significant correlation was noted between duration of diabetes and central thickness ($r = 0.68$, $P = 0.029$) among patients with WFS. No significant correlations of average retinal thickness or central thickness with either age or duration of diabetes were observed in patients with T1DM (both $P > 0.05$).

Despite a limited sample size caused by the extreme rarity of WFS, our results have shown retinal thinning to be a clinical feature of the syndrome and potential marker of disease progression in patients with WFS.

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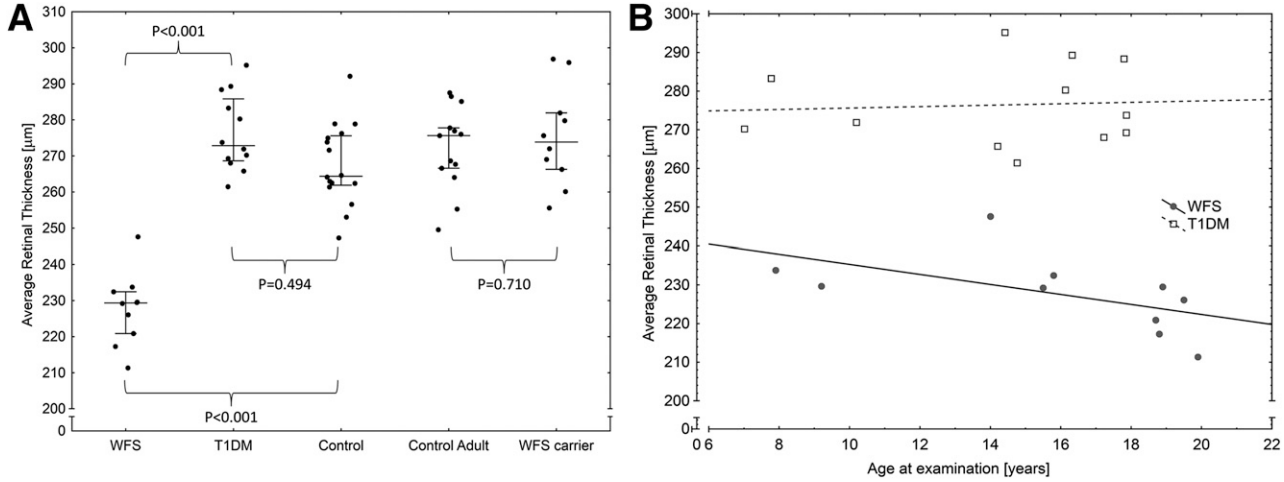

Figure 1—*A*: Comparison of retinal parameters in the pediatric cohort and adult cohort showed that children and adolescents with WFS had significantly lower average retinal thickness than healthy peers and children with T1DM ($P < 0.05$ in Kruskal-Wallis ANOVA with post hoc Dunn test). No such differences were noted in the adult group ($P > 0.05$ in Mann-Whitney *U* test). *B*: In pediatric/adolescent patients with WFS, there was a significant negative correlation of average retinal thickness with age (Spearman rank correlation coefficient $r = -0.90$, $P = 0.0003$); no such effects were noted in the T1DM group.

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