



No Sign of Proliferative Retinopathy in 15 Patients With Permanent Neonatal Diabetes With a Median Diabetes Duration of 24 Years

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The knowledge about the long-term consequences of diabetes with onset in the neonatal period is scanty. We investigated the impact of long-standing diabetes (>15 years) on the retina of 10 patients with permanent neonatal diabetes mellitus (PNDM) (diabetes diagnosis within 6 months of birth) associated with mutations of *GCK*, *KCNJ11*, *INS*, or *ABCC8* genes and of two parents carrying an *INS* gene mutation diagnosed with diabetes in their childhood (1,2) (Table 1, patients 1–12). Eye complications were also evaluated in three patients with diabetes onset within 1 year of age and negative for type 1A diabetes autoantibodies (2) (Table 1, patients 13–15).

The mean age at diagnosis of diabetes of patients with PNDM was 7 weeks (patients 1–9 and 12), and median duration of diabetes of the entire group was 24 years (\pm 10.2 SD; range 16–47 years). Six patients had diabetes for more than 30 years.

Fundus photography, performed according to EURODIAB recommendations

(3), was available for 12 patients and read independently by two experts (M.P., A.d.B.) who did not have access to clinical data. For the remaining three patients, reports of fundus oculi or fluorescein angiography were evaluated. Because the patients are transferred to adult diabetes clinic when they reach the age of 18 years, information on recent HbA_{1c} was obtained in some occasions directly from the patient and not from medical records.

The results obtained were compared with those published by our study group (4) describing 105 patients with diabetes duration of 20 years, 53 of which had diabetes onset before puberty.

Proliferative retinopathy was reported in none of the patients. Eight individuals (53%) with diabetes duration between 16 and 24 years had no sign of diabetic retinopathy (DR), five were judged to have mild DR, one had moderate DR with possible initial signs of diabetic macular edema (DME), and one had DME. All

patients with mild or moderate DR had diabetes for more than 30 years, but one. No difference was observed between the five patients with *INS* mutations (on insulin therapy) or the six patients with K_{ATP} channel (*KCNJ11/ABCC8*) mutations (four patients were weaned from insulin as adults and were currently on glyburide therapy) (Table 1).

These results compare well with those of our previous work (4), in which we observed that in patients with prepubertal onset of type 1A diabetes, 60% showed no DR after a mean duration of diabetes of 20 years. This subgroup had a better outcome than patients with pubertal or peripubertal onset of type 1A diabetes, who showed only 29% of cases free of DR and a significant number of cases with severe DR.

This low prevalence of severe DR in patients with PNDM of long duration is in contrast with that reported in other forms of monogenic diabetes with onset at puberty and beyond, such as *HNF1A*-maturity-

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Table 1—Clinical and genetic features of PNDM patients with a median diabetes duration of 24 years

| Patient no. | Mutation | Age (years)/sex | Diabetes duration (years) | Therapy | HbA _{1c} % (mmol/mol) on INS | HbA _{1c} % (mmol/mol) on SU | DR |
|-------------|----------------------------|-----------------|---------------------------|---------------|---------------------------------------|--------------------------------------|---------------------------|
| 1 | <i>INS</i> -R89C | 18/F | 18 | INS | 8.4 (68) | — | No |
| 2 | <i>INS</i> -LB39Y40delinsH | 19/F | 19 | INS | 7.3 (56) | — | No |
| 3 | <i>INS</i> -Y108X | 20/F | 20 | INS | 7.9 (63) | — | No |
| 4 | <i>ABCC8</i> -V324M/W688R | 20/F | 20 | SU since 2010 | 7.1 (54) | 6.4 (46) | No |
| 5 | <i>KCNJ11</i> -K170N | 20/F | 20 | SU since 2008 | 8.3 (67) | 6.0 (42) | No |
| 6 | <i>GCK</i> -T228M | 22/F | 22 | INS | 8.0 (64) | — | No |
| 7 | <i>ABCC8</i> -A355T | 24/M | 24 | INS | 9.2 (77) | — | No |
| 8 | <i>KCNJ11</i> -R201C | 33/M | 33 | INS | 8.9 (74) | — | Moderate, initial DME (?) |
| 9 | <i>KCNJ11</i> -G53D | 33/F | 33 | SU since 2006 | 8.0 (64) | 6.4 (46) | Mild |
| 10 | <i>INS</i> -R89C | 39/M | 35 | INS | 7.2 (55) | — | DME (initial) |
| 11 | <i>INS</i> -R89C | 48/F | 47 | INS | 10 (86) | — | Mild |
| 12 | <i>ABCC8</i> -L213P | 48/M | 48 | SU since 2011 | 8.4 (68) | 6.5 (48) | Mild |
| 13 | Unknown | 17/M | 16 | INS | 9.1 (76) | — | Mild |
| 14 | Unknown | 25/M | 24 | INS | 8 (64) | — | No |
| 15 | Unknown | 44/M | 43 | INS | 7.2 (55) | — | Mild |

The interval (years) in which HbA_{1c} values were available for calculation of the mean(s) in the table are listed below; those patients with an observation period equal or longer than 10 years are in bold. **Patient 1 = 2000–2013; Patient 2 = 1994–2013; Patient 3 = 1994–2014;** Patient 4 INS = 2006–2009, SU = 2010–2013; Patient 5 INS = 2005–2007, SU = 2008–2013; Patient 6 = 2006–2013; **Patient 7 = 1990–2014; Patient 8 = 1990–2014; Patient 9 INS = 2004–2005, SU = 2006–2013;** Patient 10 = 2011–2012; **Patient 11 = 2000–2013; Patient 12 INS = 2004–2010, SU = 2011–2013;** Patient 13 = 2010–2012; Patient 14 = 2010–2012; Patient 15 = 2010–2012. INS, insulin; F, female; M, male; SU, sulfonylurea.

onset diabetes of the young 3, where the percentage of patients with proliferative DR is as high as in type 2 diabetes (5).

We acknowledge that a limitation of our study is the small group of patients considered. Nevertheless, these results support the notion that onset of diabetes before puberty has a lesser impact on DR than in patients with other monogenic forms of the disease.

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F.C., and M.P. researched data. F.B. wrote the manuscript. F.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

- Colombo C, Porzio O, Liu M, et al.; Early Onset Diabetes Study Group of the Italian Society of Pediatric Endocrinology and Diabetes (ISPED). Seven mutations in the human insulin gene linked to permanent neonatal/infancy-onset diabetes mellitus. *J Clin Invest* 2008;118:2148–2156
- Russo L, lafusco D, Brescianini S, et al.; ISPED Early Diabetes Study Group. Permanent

diabetes during the first year of life: multiple gene screening in 54 patients. *Diabetologia* 2011;54:1693–1701

3. Aldington SJ, Kohner EM, Meuer S, Klein R, Sjølie AK. Methodology for retinal photography and assessment of diabetic retinopathy: the EURODIAB IDDM complications study. *Diabetologia* 1995;38:437–444

4. Salardi S, Porta M, Maltoni G, et al.; Diabetes Study Group of the Italian Society of Paediatric Endocrinology and Diabetology. Infant and toddler type 1 diabetes: complications after 20 years' duration. *Diabetes Care* 2012;35:829–833

5. Isomaa B, Henricsson M, Lehto M, et al. Chronic diabetic complications in patients with MODY3 diabetes. *Diabetologia* 1998;41:467–473