

### Serum Nerve Growth Factor in Type 1 Diabetic Patients, before and after Subclinical Peripheral Neuropathy

G. d'Annunzio<sup>a</sup>, M.A. Avanzini<sup>a</sup>, M. Marconi<sup>a</sup>, A. Moglia<sup>c</sup>, M. Martinetti<sup>b</sup>, M. Rallo<sup>a</sup>, G. Rossi<sup>a</sup>, R. Lorini<sup>d</sup>

<sup>a</sup>Department of Pediatric Sciences, and <sup>b</sup>HLA Laboratory, Immunohematology and Transfusion Center, IRCCS Policlinico San Matteo; <sup>c</sup>Department of Neurology, IRCCS C. Mondino Institute, Pavia; <sup>d</sup>Institute of Pediatric Clinic, G. Gaslini Institute, Genova, Italy

It has been hypothesized that diabetic neuropathy results from impaired neurotrophic tone, which could reflect diminished synthesis, secretion or responsiveness of neurotrophic factors, such as nerve growth factor (NGF). We aimed to measure NGF in 21 type 1 diabetic patients (13 males and 8 females), evaluated when peroneal motor nerve conduction velocity (PMNCV) was normal and thereafter when PMNCV was  $<-2$  SD than controls, compatible with subclinical diabetic neuropathy (SPN). All patients underwent HLA typing and HLA-DQ molecular analysis. As controls, 53 age- and sex-matched healthy subjects were considered. NGF levels were determined by ELISA at the same time in serum samples, stored at  $-30^{\circ}\text{C}$ , obtained from each patient before and after SPN. Before SPN patients' age was 8.2–19.3 years and disease duration 1 month to 8.7 years; serum NGF levels were higher in patients [median, 63 pg/ml (25th–75th centile, 19–137 pg/ml)] than in controls [25 (7.5–94)], but not significantly. At the time of SPN, patients' age was 10–22 years and disease duration 3.6–11.7 years; serum NGF levels were lower than previously found [63 pg/ml (19–137 pg/ml)] but not significantly, and similar to controls. No correlation was found between NGF levels and chronologic age, duration of disease, PMNCV values, HbA<sub>1c</sub> mean levels. No association was found between NGF and both HLA typing or DQ heterodimers. The decrease of NGF observed in our patients with SPN, even if not significant, suggests a possible role of this factor in diabetic neuropathy.

### Transient Diabetes Microvascular Complications in Prepubertal Children

K. Donaghue, A. Chan, J. Fairchild, S. Hing, M. Crocker, N.J. Howard, M. Silink

Ray Williams Institute of Paediatric Endocrinology, Royal Alexandra Hospital for Children, Westmead, University of Sydney, Australia

In our baseline assessment, we found that 11 of 68 prepubertal children had either retinopathy or abnormal albumin excretion (AER) [J Pediatr Endocr Metab 1997;10:579–585]. Presented here are the interim results of subsequent screening over a median of 16 (range: 2–35) months in the 64 children still enrolled in our prospective study. Forty are now pubertal and 24 are still prepubertal. At baseline, the median age and duration were 9.8 [9.0–10.2] and 3.6 [1.5–5.8] years, respectively. Two to eight 6-monthly retinal assessments were performed prior to the onset of puberty in each child.

Ungradable photos occurred in 4 of 225 visits. Retinopathy was defined as any microaneurysm or hemorrhage assessed by stereoscopic fundus photography of seven standard fields. AER was assessed every 3 months. Abnormal AER was defined as a mean greater than 7.5  $\mu\text{g}/\text{min}$  ( $\text{AER} > 7.5$ ) from 3 timed overnight urine collections. In 7 of 9 children with abnormalities at baseline, these were not present at reexamination 6 months later. In one boy retinopathy was still present 6 months later but had resolved 12 months after baseline and in a girl it recurred 12 months after baseline. In one boy  $\text{AER} > 7.5$  persisted over 6 timepoints (maximum 25  $\mu\text{g}/\text{min}$ ).  $\text{AER} > 7.5$  were present intermittently in 2 girls. In total, 21 of 64 had abnormalities on at least one occasion. No child had persistent retinopathy but one child had persistent elevation in AER. Transient microvascular complications were relatively common in this sample of prepubertal children.

### Diabetes Duration and Complications: Are All Ages at Equal Risk?

K. Donaghue, A. Chan, J. Fairchild, S. Hing, N.J. Howard, M. Silink

Ray Williams Institute of Paediatric Endocrinology, Royal Alexandra Hospital for Children, Westmead, Sydney University, Sydney, Australia

Younger children may be more protected from the effect of diabetes duration on the development of diabetes complications. Using logistic regression, the risk of diabetes duration for complications was investigated during three chronological periods: duration before age 5 years, between ages 5 and 10 years and after age 10 years. The study group was 937 children and adolescents aged 6–20 years in whom retinopathy and albumin excretion rate (AER) were assessed from 1990 to 1997. Retinopathy was present in 27%: defined as at least one microaneurysm or hemorrhage detected by stereoscopic fundus photography. Abnormal AER was present in 24%: defined as a mean greater than 7.5  $\mu\text{g}/\text{min}$  ( $\text{AER} > 7.5$ ) from 3 timed overnight urine collections. For each individual a mean HbA<sub>1c</sub> over the previous 36 months was calculated. A 1% increase in HbA<sub>1c</sub> conferred a 31% increased risk for retinopathy but was not significant for  $\text{AER} > 7.5$ . HbA<sub>1c</sub> and pubertal staging were allowed for by logistic regression. Diabetes duration before age 5 years was not a significant risk factor for either complication. Each year of diabetes duration between 5 and 10 years of age increased the risk for retinopathy by 31% and for  $\text{AER} > 7.5$  by 17%. Each year of diabetes duration after 10 years of age increased the risk for retinopathy by 36% and for  $\text{AER} > 7.5$  by 24%. Diabetes duration after 10 years of age may confer a greater risk for complications than duration between ages 5 and 10 years. Duration in a child less than 5 years does not significantly affect complications.

### Discordant Diabetic Retinopathy in Homozygous Twins: The Importance of Good Metabolic Control

H. Dorchy<sup>a</sup>, C. Veroustraete<sup>b</sup>, J. Libert<sup>b</sup>

<sup>a</sup>Diabetology Clinic, Hôpital Universitaire des Enfants Reine Fabiola, <sup>b</sup>Ophthalmology Clinic, Centres Hospitaliers Universitaires Brugmann et Saint-Pierre, Université Libre de Bruxelles, Brussels, Belgium

**Purpose:** The authors report a very exemplative illustration of the major role of metabolic control in diabetic retinopathy.

**Methods:** Description of clinical history, examination, metabolic control and fluorescein angiography in two homozygous diabetic twins, with a follow-up of 27 years.

**Results:** Two type 1 homozygous diabetic twins became diabetic at age 8. They share the HLA DQ genotype which gives the highest risk of type 1 diabetes in Belgium, i.e. A1\*0301-B1\*0302/A1\*0501-B1\*0201. Their way of life and their personal medical history was very similar, except that one brother had always been very compliant, which resulted in a good metabolic control of his diabetes, while his brother was undisciplined and had chronically shown a poor metabolic control. The twin with poor metabolic control had his first signs of retinopathy 3 years before his brother, and had a higher level of severity of retinopathy than his brother all through the follow-up. He developed a major proliferative retinopathy, with bilateral rubeosis after 24 years of diabetes, while at the same time his brother only showed moderate background retinopathy.

**Conclusion:** Suppressing the differential genetic influence on diabetic retinopathy evolution, and reducing to a minimum the external and personal differences, this homozygous diabetic twins study points out the major importance of metabolic control on the development of diabetic retinopathy.

### Assessment of Well-Being in a Population of 100 Diabetic Adolescents and Young Adults in Relationship to Their Metabolic Control

H. Dorchy, S. Olinger

Diabetology Clinic, University Children's Hospital Queen Fabiola, Brussels, Belgium

The principal aim of therapeutic management of the child, adolescent and adult with type 1 diabetes is to avoid severe hypoglycemia and long-term complications, by maintaining blood glucose concentrations – and thus glycated hemoglobin levels (HbA1c) – close to the normal range. However, the therapeutic constraints should not decrease the quality of life and well-being of patients. Therefore, the purpose of the present study was to evaluate by a questionnaire the well-being of our autonomous diabetic adolescents and young adults in relationship with their HbA1c levels and other characteristics. A total of 100 unselected subjects (73 men and 44 women), with a mean of age of 21 years (14–38) and a mean diabetes duration of 12 years (0–26), were included in the study over a 3-month period. Mean age at onset of diabetes was 10 years. Twenty-five percent of the patients

were of Moroccan origin. All the patients were autonomous for self-management and treatment. Their socioeconomic status was not different from that of the normal population. The mean annual HbA1c level in the 100 diabetic patients was 7.3% (4.7–11.7). Well-being was measured using a questionnaire developed by a working group of the World Health Organization, International Diabetes Federation and St Vincent Declaration. The questionnaire included 4 subscales labelled depression, anxiety, energy and positive well-being. The measurement of all 4 subscales involved 22 items and allowed an estimation of general well-being. General well-being in women was not as good as in men due to a greater tendency toward depression. Well-being was better in patients with a professional activity than in the others. Patients age, duration of diabetes, number of insulin injections, frequency of home blood glucose monitoring, presence of 1 or 2 subclinical complications, had no effect on well-being. On the other hand, well-being was negatively correlated with the HbA1c levels: higher the HbA1c, higher the anxiety and the depression, and lower the energy and the positive well-being.

In conclusion, well-being was mainly associated with HbA1c levels; it improved with better glycemic control.

### Clinical Manifestations and Laboratory Data at Onset of Type 1 Diabetes in Children, Adolescents and Young Adults

H. Dorchy<sup>a</sup>, F. Gorus<sup>b</sup>, C. Vandewalle<sup>b</sup>, I. Weets<sup>b</sup>,

K. Decochez<sup>b</sup>, K. Verelst<sup>b</sup>, M.-P. Roggemans<sup>a</sup>, and the Belgian Diabetes Registry

<sup>a</sup>Diabetology Clinic of the Hôpital Universitaire des Enfants Reine Fabiola, Brussels; <sup>b</sup>Department of Metabolism and Endocrinology, Diabetes Research Center, VUB, Brussels, Belgium

Since 1989, newly diagnosed type 1 diabetic patients and their first-degree relatives, aged <40 years, are enrolled in the Belgian Diabetes Registry. It allows analysis of clinical and laboratory features gathered at diagnosis in 581 diabetic children aged <15 years. In Belgium, the annual incidence rate of type 1 diabetes is 11.8 per 10<sup>5</sup> in the age group 0–14 years, and 8.9 per 10<sup>5</sup> in the age group 15–39 years. In the younger group, there is no sex difference, but in the older group, the male/female ratio reaches 1.7. The median duration of early clinical manifestations before diagnosis (polyuria, polydipsia, weight loss, fatigue) is 3 weeks before the age of 15 years, and 8 years afterwards. Weight loss, fatigue, ketonuria, and exhaustion of beta cells (measured by C-peptide) are more marked in the younger group. Moreover, when good metabolic control is obtained, the mean daily insulin dose per kilogram body weight is 0.75 units under 15 years of age, and only 0.44 in the age group 15–39 years. The subgroup of children aged <8 years, in comparison with the age group 8–14 years, differs only by lower HbA1c and C-peptide levels. In conclusion, these data show that type 1 diabetes is more 'aggressive' in diabetic children and adolescents than in adults and that insulin deficiency is more severe in the younger age group at the time of diagnosis.

## Childhood Vaccines and the Aetiology of Type 1 Diabetes

R.B. Elliott, N.K. Bibby, M. McGregor, C.C. Pilcher  
Department of Paediatrics, School of Medicine, Auckland,  
New Zealand

Some commonly given childhood vaccines have been accused of initiating islet autoimmunity, but on the other hand some have been described as having a preventive effect. Epidemiological studies in humans do not support either view. We have analysed the incidence of childhood type 1 diabetes in the Auckland area (total population  $1 \times 10^6$ ) over a 20-year period, during which time there has been a marked increase in incidence. The year-by-year incidence has been examined in relation to the introduction, alteration or abandonment of vaccination programs including BCG, hepatitis B, *Haemophilus influenzae* B, diphtheria/tetanus/pertussis (DTP), rubella, mumps and measles. No change in vaccination program involving any one vaccine could be associated with a change in diabetes incidence although the total number of vaccines used could. In the NOD mouse, DTP vaccine or its individual components given in a schedule starting at day 7 slowed the onset of diabetes but did not affect overall incidence 240 days later. Similar results were obtained using DPT + Hib vaccine. In a schedule starting at 60 days DTP prevented diabetes over a 190-day period. The addition of insulin A or B chain to DTP enhanced diabetes protection and the same was found with DTP + Hib only when the Hib component was coupled to tetanus toxin, but not diphtheria toxin. Clearly, the nature of the admixed vaccine determines the protective effect of the insulin chains. Great caution should be exerted in extrapolating results from the NOD mouse to humans, as the time scales for effective prevention are so different.

## Three-Year Experience in the Treatment of Diabetic Adolescents with Humalog

P. Fichna  
Department of Pediatric Endocrinology and Diabetes, Institute of Pediatrics, University of Medical Sciences in Poznań, Poland

The group of 40 diabetic adolescents started flexible intensive insulin therapy (3 shots of Humalog and 2 shots of NPH insulin per day) 3 years ago. They were successively joined by another 20 patients: 12 for intensive treatment and 8 for Humalog supplementation before lunch and/or dinner only. The aim of the observations was to evaluate the long-term effectiveness of rapidly acting insulin analogue in IDDM therapy. Diabetes control parameters (HbA1c, hypoglycemic episodes, insulin requirement, complications), Humalog usefulness in additional disease and patients opinions were taken into consideration. HbA1c has decreased from  $8.32 \pm 0.31$  to  $7.35 \pm 0.12\%$  after the first 9 months in the intensively treated patients and further progress was depending on individual circumstances. The hypoglycemic episodes were less frequent in adolescents with irregular and very active life styles who had this problem before introducing Humalog (8 patients). Daily insulin dose was diminished after 1–3

months from  $1.3 \pm 0.1$  to  $0.9 \pm 0.2$  IU/kg in patients with intensive treatment with Humalog. The patients who started Humalog treatment 3 years ago were free of diabetic complications and no new complications were found. In the group which joined later, there were 3 cases of incipient retinopathy and 1 positive microalbuminuria at the beginning and no further progress was observed. Diabetic adolescents on intensive Humalog therapy were controlled well during additional diseases due to NPH insulin increase and rapidly acting analogue dose changes. Humalog has appeared to be useful as the additional insulin shots supplementing occasionally or regularly the conventional insulin therapy before lunch and/or dinner. Young diabetics have declared a good acceptance of intensive therapy with Humalog and didn't want to change it. Two girls have been successful in their overweight reduction. Well motivated and cooperative patients can reach long-term satisfactory effects with Humalog treatment.

## Strategies for the Delivery of Care and Their Acceptance by Teenagers with Type 1 Diabetes: Micro- and Macrocultural Influences

A. Greene<sup>a</sup>, A. Morris<sup>b</sup>, R. Newton<sup>b</sup>, S. Greene<sup>c</sup>  
Departments of <sup>a</sup>Social Anthropology, University of St Andrews, St Andrews, and <sup>b</sup>Medicine and <sup>c</sup>Child Health, Ninewells Hospital and Medical School, Dundee, Scotland

Adherence to insulin regimens in type 1 diabetes is poorest during adolescence resulting in a marked deterioration in glycaemic control. Attention has focussed previously on individual behaviour patterns in relation to the acceptance of diabetes therapy and scant attention has been given to the broader cultural determinants that affect adherence to this chronic disorder. Information from 50 young adults (age 13 to 25 years) was obtained using the standard qualitative anthropological methodology of participant observation and semi-structured interview. The subjects were assessed on at least two occasions both at their diabetes consultation with health carers and individually out of the clinic environment. Health-care professionals (physicians, paediatricians, nurse specialists, dietitians and psychologists) were interviewed from 15 clinical centres. Research concentrated specifically on various micro-cultural influences (reciprocity, health goals and communication). A variety of interpretations were obtained from the observations. Diabetes creates unique facilities and strategies for care and the prediction of a good health outcome requires active rather than passive patient participation. Medical expertise is limited unless the patients' motivation is secured, requiring interdependence between patients and their carers, with the medical initiatives proceeding beyond the standard medical approach. The standard care package in Scotland appeared to limit the positive benefits expected from reciprocity, joint goal setting and effective communication, despite strenuous efforts from the health care professionals. Consideration of these factors is necessary for a change in the pattern of acceptance and adherence with management regimens.