# Comparison of Juvenile Diabetics with Positive and Negative Organ Specific Antibody Titers

## Evidence for Genetic Heterogeneity

*S. Peter Nissley, M.D., Allan L. Drash, M.D., Robert M. Blizzard, M.D., Mark Sperling, M.D., and Barton Childs, M.D., Baltimore and Pittsburgh*

SUMMARY

**Juvenile diabetics with significant thyroid, gastric or adrenal antibody titers were compared with juvenile diabetics with negative antibody titers on the basis of various parameters of clinical and family history. Parents and siblings of juvenile diabetics with positive antibody titers have a significantly higher frequency of positive antibody titers than do parents and siblings of juvenile diabetics with negative antibody titers. This finding provides evidence for genetic heterogeneity among juvenile diabetics.** DIABETES *22*:63-65, January, 1973.

Although there is an increased frequency of diabetes among relatives of diabetics, the pattern of genetic transmission is not clear.[1] One hypothesis is that there is more than one genetically transmitted cause of diabetes (genetic heterogeneity).[2,3] However, there has been little objective evidence for genetic heterogeneity among diabetics. Since there is direct evidence that some cases of juvenile diabetes are associated with chronic lymphocytic thyroiditis,[4] a disease believed to be of autoimmune origin, the authors compared a group of juvenile diabetics who had positive thyroid, adrenal, or gastric antibody titers versus a group without antibodies. A significantly higher frequency of positive antibody titers was found among parents and siblings of juvenile diabetics with positive titers than among relatives of juvenile diabetics with negative titers. These findings support the hypothesis of genetic heterogeneity among juvenile diabetics.

From the Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, and the Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

Address reprint requests to: Barton Childs, M.D., Department of Pediatrics, Johns Hopkins Hospital, Baltimore, Maryland 21205.

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### METHODS

*Patients*

The juvenile diabetics (less than twenty years of age) studied were seen either at the Pittsburgh Children's Hospital or the Children's Medical and Surgical Center, Johns Hopkins Hospital. The data were obtained from a questionnaire mailed to and completed by the patients' parents. Information on the completed questionnaire that concerned clinical history, such as hospital admissions, growth, and insulin dosage, was verified by examination of the hospital record.

*Antibody measurement*

On a routine visit to the clinic, a blood sample was drawn and the serum stored at —20° until measurement. Sera were titrated for antibodies to human thyroid epithelium, adrenal cortex, and parietal cells of the gastric mucosa by the indirect method of Coon with fluorescein tagged antihuman gamma globulin.[5] Antibodies to thyroglobulin were also titered with the use of tanned, thyroglobulin coated sheep erythrocytes.[6] Thyroglobulin, cytoplasmic thyroid and parietal cell antibody titers were considered significant if present in 1:4 dilutions of sera, and adrenal antibodies were considered significant if present in serum at 1:2 dilution.

### RESULTS

The antibodies among the eighteen juvenile diabetics with significant titers were distributed as follows: versus thyroglobulin—12, versus thyroid follicle cells—5, versus parietal cells of the gastric mucosa—6, and versus adrenal cortex—2.

In table 1 the results in juvenile diabetics with posi-

TABLE 1

Comparison of juvenile diabetics with positive and negative antibody titers

| | Positive antibody titer | | Negative antibody titer | |
|---|---|---|---|---|
| | n | Mean±S.D. | n | Mean±S.D. |
| Birth weight (kg.) | 15 | 3.4 ± 0.5 | 67 | 3.4 ± 0.4 |
| Days in newborn nursery | 17 | 5.4 ± 1.9 | 67 | 5.7 ± 1.8 |
| Milestones (mo.): | | | | |
| Sat alone | 16 | 6.3 ± 1.4 | 63 | 6.0 ± 1.3 |
| Walked alone | 17 | 12.8 ± 3.6 | 71 | 11.4 ± 2.3 |
| Talked | 13 | 25.1 ± 16.1 | 57 | 22.9 ± 7.0 |
| Age when diabetes was diagnosed (yr.) | 28 | 7.3 ± 3.5 | 72 | 6.3 ± 3.5 |
| Duration of polyuria and polydipsia before diagnosis (wk.) | 16 | 2.9 ± 1.9 | 65 | 6.1 ± 9.1 |
| Hospital days/year since diagnosis | 18 | 3.0 ± 2.5 | 66 | 4.2 ± 7.8 |
| Present insulin dose (U./kg.) | 17 | 1.08 ± 0.41 | 68 | 1.01 ± 0.33 |
| Paternal age at birth (yr.) | 18 | 31.2 ± 7.0 | 71 | 31.2 ± 6.3 |
| Maternal age at birth (yr.) | 18 | 28.2 ± 6.0 | 72 | 28.2 ± 6.2 |
| Father's weight (kg.) | 18 | 78.9 ± 8.9 | 72 | 82.2 ± 9.1 |
| Mother's weight (kg.) | 18 | 66.6 ± 15.9 | 71 | 64.8 ± 12.7 |

tive and negative antibody titers for several parameters of clinical history and family history are compared. The data were not significantly different for the patients with negative and positive titers at the 90 per cent confidence level (Student's *t*-test). In addition, the two populations did not differ with respect to growth—the mean for height and weight for both populations was slightly less than the 50th percentile.

In table 2 the frequency of diabetes (juvenile and adult onset) among parents, siblings, and grandparents of the juvenile diabetics with positive and negative antibody titers is compared. The frequency among relatives of the two populations was not significantly different ($X^2 = 0.0187$, $0.8 > P < 0.9$).

TABLE 2

Incidence of diabetes among relatives of patients with positive and negative antibody titers

| | Diabetic | | | Nondiabetic | | |
|---|---|---|---|---|---|---|
| Patients | Parents | Siblings | Grandparents | Parents | Siblings | Grandparents |
| Positive antibody titer (n = 18) | 1 | 1 | 6 | 35 | 31 | 66 |
| Negative antibody titer (n = 72) | 3 | 5 | 33 | 141 | 190 | 255 |

The frequency of positive antibody titers among siblings and parents of juvenile diabetics with positive and negative antibody titers is shown in table 3. The difference in frequency of positive antibody titers among parents and siblings in the two groups is highly significant ($X^2 = 13.40$, $P < 0.0005$).

TABLE 3

Antibody titers among relatives of patients with positive and negative antibody titers

| | Positive antibody titer | | Negative antibody titer | |
|---|---|---|---|---|
| Patients | Parents | Siblings | Parents | Siblings |
| Positive antibody titers | 7 | 4 | 10 | 5 |
| Negative antibody titers | 5 | 1 | 32 | 35 |

## DISCUSSION

The finding of a significantly higher frequency of positive antibody titers among siblings and parents of juvenile diabetics with positive titers than among siblings and parents of diabetics with negative antibody titers suggests that there are at least two different genetically determined causes of juvenile diabetes, possibly one of autoimmune etiology. This argument for genetic heterogeneity among juvenile diabetics depends upon the assumption that autoimmune phenomena can be implicated in a causal way in some cases of juvenile diabetes. The case for autoimmune phenomena possibly playing a causal role in juvenile diabetes rests upon the following indirect evidence: (1) Goldstein et al.[4] reported that the frequency of significant thyroid, gastric or adrenal antibody titers among 155 juvenile diabetics was 14 per cent compared to 0.5 per cent among 203 controls. Landing and coworkers[7] also reported an increased frequency of thyroid antibodies among juvenile diabetics. (2) Lymphocytic infiltration of the pancreatic islets has been noted at autopsy in some juvenile diabetics.[8] (3) There is an increased frequency of autoimmune disorders among juvenile diabetics. Ungar et al. reported that 4 per cent of a large diabetic population had latent pernicious anemia, as determined by the Schilling test performed on diabetics with antibodies to intrinsic factor and/or low serum vitamin $B_{12}$ levels.[9] There is also an increased frequency of Hashimoto's thyroiditis among juvenile diabetics,[10] and diabetes mellitus is often associated with Schmidt's syndrome (thyroid and adrenal insufficiency of autoimmune origin).

An alternative, although we believe less likely, explanation of the finding of an increased frequency of positive antibody titers among parents and siblings of juvenile diabetics with positive titers would be that a portion of the population has a propensity to have thyroid, adrenal, or gastric antibody titers; this propensity is transmitted genetically; and juvenile diabetes somehow causes this propensity for antibody formation to be expressed. If this explanation were true, then the finding of an increased frequency of positive thyroid, gastric, or adrenal antibody titers among parents and siblings of juvenile diabetics with positive titers could not be used as evidence for genetic heterogeneity among juvenile diabetics. However, thyroid or adrenal insufficiency frequently precedes the diabetes mellitus observed in patients who have these entities, and makes this possibility unlikely.

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