

Adding IA2beta autoantibodies (aab) to a panel of defined islet aab improves type 1 diabetes (T1D) prediction.

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Abstract

The Washington State Diabetes Prediction Study (WSDPS) and the more recent Diabetes Evaluation in Washington State (DEW-it) were used to test the predictive value of multiple “defined” islet aab (MAab) (≥2 aab to GAD65, IA2 and insulin) alone and together with IA2-Beta aab. Children seropositive for MAab were followed to T1D. Aab were detected by radiobinding assays using protein A bound to microtiter plates.

In WSDPS, 12 children had MAab by age 14, 7 of these had IA2beta aab. After 16 years of follow-up, 8 of 12 MAab subjects developed T1D (67% positive predictive value (PPV) 95% CI (35-89%)), 6 of 7 subjects with IA2beta aab developed T1D (86% PPV, 95% CI (42-99%)). 6 of 8 subjects with T1D (75% of cases, 95% CI (36-96%)) had IA-2 beta aab. Survival analysis compared disease outcome for MAab subjects vs. those without IA2beta aab. IA2beta aab marked progression to T1D in 16 years (p=0.041).

In DEW-it, 29 children had MAab by age 9. 15 had IA2beta aab. After 3 years of follow-up, 6 of 29 MAab subjects developed T1D, 5 of 6 subjects also had IA2beta aab. In this shorter follow-up, MAab had 21% PPV (95%CI (9-40%)). In the MAab positive subjects, IA2beta aab had 33% PPV (95% CI (13-61%)) and included 83% of cases (95%CI (37-99%)). In this short follow up, the additional IA2beta aab did not yet mark significantly increased probability to develop T1D (p=0.140). Follow-up of this cohort continues.

We conclude that in long-term follow-up, MAab successfully identified children who would develop T1D. Having IA2beta aab significantly increased PPV if the follow-up period was sufficiently long. IA2beta aab along with the more established islet aab tests could be especially useful for pre-diabetes intervention studies requiring high positive predictive value.

Background

> T1D is an autoimmune disease attacking islets. It affects 1/400 U.S. children, with incidence increasing. Nearly 90% of new cases have no close T1D relative.

> Predictive testing appears to lessen morbidity at diagnosis and may lead to better metabolic function in the early period after diagnosis (1) and enable early intervention therapy, when available.

> Three serum-based islet autoantibodies (GAD, IA2 and insulin) have proven to be highly sensitive and specific for T1D. Having ≥ 2 of 3 islet aab carries a future T1D risk of > 50% in the general population (2). However, this may not be great enough for intervention therapies that carry side effects or risks.

Objectives

The predictive value of multiple “defined” islet aab (to GAD65, IA2 and insulin) (MAab) alone and together with IA2beta aab was evaluated in two long-term prospective T1D prediction studies: the Washington State Diabetes Prediction Study (WSDPS) and the more recent Diabetes Evaluation in Washington Study (DEW-IT).

Methods

Children seropositive for multiple “defined” islet aab in the WSDPS and DEW-IT studies were followed prospectively for the development of T1D. Aabs were detected by established radiobinding assays using protein A bound to microtiter plates (3).

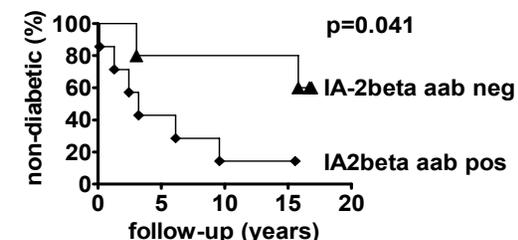
Results

Table 1: islet Aabs in WSDPS and DEW-it studies

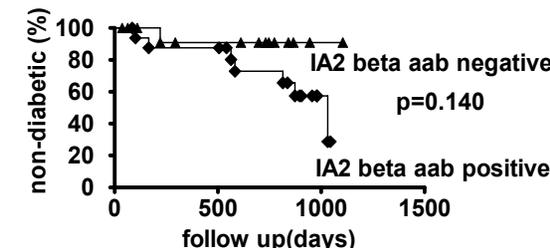
	WSDPS	DEW-it
Follow up (yrs)	16	3
Total MAab (n)	12	29
MAab developed T1D	8 (67% PPV, 95%CI 35-89%)	6 (21% PPV, 95%CI 9-40%)
IA2beta+ in MAab	7	15
IA-2beta+ in MAab developed T1D	6 (86% PPV, 95%CI 42-99%)	5 (33% PPV, 95%CI 13-61%)
IA-2beta+ in T1D group	6 (75% cases, 95%CI 36-96%)	5 (83% cases, 95%CI 37-99%)

Results

WSDPS: Survival analysis by IA-2beta aab presence in MAab positive subjects



DEW-it: Survival analysis by IA2-beta Aab presence in MAab positive subjects



Conclusions

In long-term prospective follow up, MAab successfully identified children who would develop T1D and the additional IA2beta aab significantly increased PPV, but only if the follow-up was sufficiently long. Including IA2beta aab testing with the more established islet aab tests could be especially useful for pre-diabetes intervention studies requiring high PPV.

References

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2. LaGasse J, et al. *Diabetes Care* 25:505-511, 2002
3. Woo W, et al. *J. Imm. Methods* 244:91-103, 2000