Absence of Antibodies to ICA512/IA-2 in NIDDM Patients With the Mitochondrial DNA bp 3243 Mutation

Diabetes with the mitochondrial DNA bp 3243 mutation is a new subtype of diabetes characterized by maternal inheritance and hearing disturbance (1). Although phenotype of diabetes is usually noninsulin-dependent, Oka et al. (2) detected the bp 3243 mutation in three islet cell antibody (ICA)$^+$ patients with slowly progressive IDDM; a finding that suggests the immune response to islet cells may be triggered by cell damage arising from mitochondrial dysfunction.

Recently, the major part of antigens for ICAs has been revealed to be the protein tyrosine phosphatase-like IA-2 (ICA512/IA-2) (3). We examined the antibodies to both ICA512/IA-2 and human GAD65 by sensitive radioligand-binding assays (4) in 14 diabetic patients with the bp 3243 mutation, including two patients with the syndrome of myoclonus, epilepsy, lactic acidosis, and stroke-like episode (MELAS). Although eight patients were taking insulin, fasting plasma C-peptide concentrations and urinary excretion of C-peptide revealed that these patients except one were noninsulin-dependent (Table 1). All 14 patients with the bp 3243 mutation were negative for both anti-ICA512/IA-2 and anti-GAD. This finding is consistent with previous reports in which neither of the ICAs nor the antibodies to bovine GAD were demonstrated in limited numbers of NIDDM patients (5,6) or in MELAS patients and their family members (7) with the bp 3243 mutation, but the finding contrasts with results of the recent report by Kobayashi et al. (8) in which 13 of 31 diabetic patients with the bp 3243 mutation were ICA$^+$ detected by a sensitive indirect immunofluorescence method. The difference may have been an artifact of patient selection. ICAs might be detected in NIDDM patients with mitochondrial mutation who also have a background of IDDM. Kobayashi et al. speculated that those who have IDDM-related human leukocyte antigen (HLA) react to islet cell antigen and produce antibodies to it when mitochondrial dysfunction occurs because ICA$^+$ patients tended to have IDDM-related HLA. In this study, eight patients had IDDM-related HLA (Table 1), indicating that HLA alone is not sufficient for the development of antibodies to ICA512/IA-2 or GAD in mitochondrial diabetes.

Another possibility is low specificity of antigens for ICAs assayed by indirect immunofluorescence. Although the principal islet antigens that react with ICAs are ICA512/IA-2 and GAD65, several other antigens have been proposed. In fact, among 11 patients with the bp 3243 mutation in this study in whom ICAs were sought, very low titers (10 Juvenile Diabetes Foundation [JDF] units in both) were detected in two (9). It is conceivable that antibodies to antigens other than ICA512/IA-2 or GAD65 exist in the patients with bp 3243 mutation. In the patients observed by Kobayashi et al., antibodies to GAD were detected only in two patients. In typical IDDM patients with recent onset, prevalence of ICA and antibodies to GAD is usually similar (10). Furthermore, ICA disappears shortly after the complete destruction of islet cells, while antibodies to GAD remain positive after absolute insulin dependency. The fact that most of the patients with mitochondrial bp 3243 mutation included in this study and in previous studies do not have antibodies to GAD suggests immunological background is somewhat different between ICA$^+$ mitochondrial diabetes and IDDM. In conclusion, the bp 3243 mutation in mitochondrial DNA is unlikely to be a trigger for production of antibodies to ICA512/IA-2 and GAD, and immune response to islet cell antigens in diabetes with mitochondrial mutation, if any, seems to be different from that in IDDM.

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Table 1—*Patients' profiles and results of the antibodies to ICA512/IA2 and GAD65*

Patient	Sex (M/F)	Age (years)	Onset (years)	Duration (years)	P-CPR (nmo/l)	U-CPR (mmg/day)	Treatment	Other characteristic	DQA1 0301	DR 4 or 9	ICA512/IA-2 antibodies	GAD antibodies
1	F	48	38	10	0.43	70	Insulin	—	pos	pos	neg	neg
2	F	35	31	4	0.20	25	Insulin	Onset with DKA	pos	pos	neg	neg
3	M	54	22	32	ND	ND	Insulin	Cardiomyopathy	neg	neg	neg	neg
4	M	37	34	3	0.23	94	Insulin	—	neg	neg	neg	neg
5	M	51	42	9	0.36	26	Insulin	—	pos	pos	neg	neg
6	F	64	53	11	0.50	68	Insulin	ICA$^+$†	pos	pos	neg	neg
7	F	71	58	13	0.56	110	Insulin	—	neg	neg	neg	neg
8	M	72	50	22	0.43	70	SU	—	pos	pos	neg	neg
9	M	61	57	4	0.83	97	Diet	ICA$^+$†	neg	neg	neg	neg
10	M	21	13	8	0.43	ND	Diet	—	neg	neg	neg	neg
11	M	40	39	1	0.36	47	Diet	—	pos	pos	neg	neg
12	F	64	—	—	ND	ND	IGT	Mother of Patient 2	pos	pos	neg	neg
13	M	21	18	3	ND	ND	Diet	MELAS	neg	neg	neg	neg
14	M	52	26	26	ND	ND	Insulin*	MELAS	pos	pos	neg	neg

pos, positive; neg, negative; ND, not done; SU, sulfonylurea; DKA, diabetic ketoacidosis; P-CPR, plasma C-peptide response; U-CPR, urine C-peptide response. *This patient was taking 8 U daily insulin, which indicates the absence of insulin dependency. †ICA was judged as positive with low titer in these patients by indirect immunofluorescence.

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Thrombolysis in Diabetic Patients With Myocardial Infarction

Hansen et al. (1) have confirmed our data (2) that diabetic patients with acute myocardial infarction (AMI) receive thrombolytic therapy less frequently than nondiabetic patients. However, in the Hansen et al. study the main reason was late presentation, while in our study there was no difference in the time between onset of AMI and presentation. The main reason for the difference in the frequency of use of thrombolytic therapy between diabetic and control subjects in our study was the presence of contraindications (especially proliferative retinopathy).

We agree with Hansen et al. and with Ward and Yudkin (3) that diabetic retinopathy should not be regarded as an absolute contraindication to thrombolytic therapy. However, the risk of retinal hemorrhage in patients with proliferative changes remains unknown. Although there has been only one case report of retinal hemorrhage in a diabetic subject after thrombolytic therapy (4), the condition may be underreported, especially if physicians regard it as a recognized complication. Furthermore, in a retrospective analysis of 507 diabetic patients with AMI, we found that of the 172 who received thrombolytic therapy, none had proliferative changes, and none of the 26 with proliferative retinopathy received thrombolytic therapy (5). It is therefore possible that retinal hemorrhage is uncommon only because thrombolytic therapy is often withheld in the more severe cases of diabetic retinopathy. This has to set against the undoubted benefit of thrombolytic therapy in diabetic patients with myocardial infarction. Until more precise data are available, it would seem best to regard proliferative retinopathy as a relative contraindication to thrombolytic therapy rather than an absolute one.

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Response to Fava and Azzopardi

Our study was designed to investigate why diabetic patients from the Department of Cardiology, Aalborg Hospital, Denmark, received thrombolytic therapy less frequently than nondiabetic patients. Diabetic retinopathy was not an absolute contraindication for thrombolytic therapy, but depended on severity. Only one patient was withheld from thrombolytic therapy in a 3-year period because of severe diabetic proliferative retinopathy (1). Because of the retrospective design of the study, we could not assess the number of diabetic patients with retinopathy being thrombolyzed.