

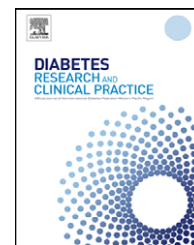


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Brief report

Drug-induced insulin autoimmune syndrome

Yasuko Uchigata^{*}, Yukimasa Hirata, Yasuhiko Iwamoto

Diabetes Center, Tokyo Women's Medical University School of Medicine, 8-1 Kawada-cho, Shinjuku, Tokyo 162-8666, Japan

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ABSTRACT

Although insulin autoimmune syndrome (IAS) was found to be strongly related with methimazole, rapidly increasing numbers of cases with alpha lipoic acid-induced IAS have been confirmed to be reported since 2003. As alpha lipoic acid has gained popularity as a supplement for dieting and anti-aging, a warning should be issued.

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The insulin autoimmune syndrome (IAS), or Hirata's disease, is characterized by the combination of fasting hypoglycemia, high concentration of total serum immunoreactive insulin, and presence of autoantibodies to native human insulin in serum [1]. In addition, IAS has a striking association with HLA-DR4 (mainly with DRB1*0406 and sometimes with DRB1*0403 and DRB1*0407) [2,3], which showed that glutamate at position 74 in the HLA-DR 1 molecules was presumed to be essential to the production of polyclonal insulin autoantibody in IAS [2]. Between 1970 [1] and September of 2007, the number of spontaneous hypoglycemia cases caused by IAS reported to us was up to 380.

Another characteristic has been observed in the medication at the onset of IAS as Hirata already mentioned a relationship between IAS and methimazole [4]. The drugs are listed in Table 1 which were given to cases at the onset of IAS at the end of September of 2007. All of the drugs are sulphydryl compounds which are also reducing compounds. There have

been reports of IAS outside Japan which were also associated with sulphydryl compounds: pyritinol for rheumatoid arthritis (Archambeaud-Mouverouz F. et al. 1988), Imipenem (beta-lactam antibiotic) for urosepsis (Lidar M. et al. 1999), and Penicilline G (beta-lactam antibiotic) for tonsillitis (Cavaco B. et al. 2001) except those listed in Table 1.

In 2003, a case with IAS which was possibly induced by an alpha lipoic acid was reported for the first time at the Kyushu local meeting of Japan Diabetes Society by Hashinaga T, et al. An increasing number of cases with alpha lipoic acid-induced IAS [5–7] have been recently remarkable. There are 56 IAS case reports in the database of Japan Centra Revuo Medicina between 2004 and September of 2007. Among 56 cases, methimazole for Graves' disease was prescribed for 11 cases, Tiopronin for one, Loxoprofen for one, and alpha lipoic acid for 17 cases. Also, garlic might have been given (containing S-allyl-mercapto-cystein which has s–s bond) to one case. Some of polyclonal insulin autoantibodies were served for Scatchard

^{*} Corresponding author. Tel.: +81 3 3353 8111; fax: +81 3358 1941.

E-mail address: uchigata@dmc.twmu.ac.jp (Y. Uchigata).

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Table 1 – Drugs exposure ahead of development of IAS and associated diseases from 1970 to September 2007 in Japan.

Drugs	Diseases	n
Methimazole*	Graves' disease	63
Alfa-mercapto-propionyl glycine (tiopronin)*	Chronic liver function/cataract/dermatitis/rheumatoid arthritis	45
Glutathione*	Urticaria	8
Gold thioglucose*	Bronchial asthma	1
Captopril*	Hypertension	1
Penicillamine*	Rheumatoid arthritis	1
Acegratone	Urinary bladder carcinoma	1
Steroid	Polymyositis	1
Interferon-alfa	Renal cell carcinoma	1
Loxoprofen sodium	Rheumatoid polymyositis/lumbar pain	2
Alfa lipoic acid*	Dieting/anti-aging supplement	17
Miscellaneous		48

* Contains sulphhydryl compounds itself or after decomposition.

plot analysis to investigate characteristics of them in our laboratory. They showed the same characteristics as those shown previously [2]. Molecular typing of the DRB1 gene studied in 12 among 17 patients with alpha lipoic acid-IAS revealed DRB1*0406 in 10, DRB1*0403 in two patients, whereas all 11 patients with methimazole-IAS possessed DRB1*0406. Rapidly increasing numbers of cases with alpha lipoic acid-induced IAS have been confirmed to be reported since 2003.

Generally in Japan, alpha lipoic acid has gained popularity as a supplement for dieting and anti-aging since 2004. Formerly, it was used as a remedy for diabetic neuropathy in the western countries while it was prescribed for the cases of subacute necrotizing encephalopathy, hearing impairment, and Reye's syndrome in Japan. Alpha lipoic acid is a coenzyme of an enzyme which activates oxidative decarboxylation against pyruvic acid and alpha-keto acid in mitochondria. When it is taken orally, it is reduced to dihydrolipoic acid with sulphhydryl compounds in the presence of NADH or NADPH, having a strong reducing ability to protect peripheral cells from oxidative stress.

We previously reported that Graves' disease patients who carry DRB1*0406 developed IAS when they took methimazole (Odds ratio, 2727; $p < 1 \times 10^{-10}$) [8]. Matsushita, et al. indicated that a reducing compound such as methimazole may cleave the disulfide bond in vivo and allow DRalpha-DRB1*0406 complex on antigen-presenting cells to bind much of the linear fragment of insulin A chain, which may lead to the activation of self-insulin-specific T-helper cells [9].

Although the development of IAS is convinced to be more frequent in Japanese than Caucasians with respect to the evolution of HLA-DR4 alleles [10], it is conceivable that those who carry DRB1*0403 or DRB1*0407 which are more frequent in Caucasians could develop IAS when they take drugs such as alpha lipoic acid even though DRB1*0406 (Odds ratio, 56.6) is stronger predisposition to risk of development of IAS than DRB1*0403 (Odds ratio, 1.6), and DRB1*0407 (Odds ratio, 1.1) [2].

Conflict of interest

There are no conflicts of interest.

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