

# Autoimmune Type I Diabetes Mellitus in a Perinatally HIV Infected Patient with a Well-Preserved Immune System

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## ABSTRACT

**We report an 8 year-old girl with well-controlled perinatally acquired HIV infection who developed autoimmune type 1 diabetes mellitus (DM1A) confirmed by the presence of diabetes-related auto-antibodies. Although non-autoimmune insulin dependent diabetes mellitus (DM1B) and more frequently type 2 DM has been reported in patients affected with HIV, this is the first report of DM1A diagnosed in an HIV positive patient.**

## KEY WORDS

type 1 diabetes mellitus, HIV, autoimmunity, perinatal infection, antiretroviral therapy

## PATIENT REPORT

An 8 year-old Hispanic girl with well-controlled perinatally acquired HIV was found to have more than 1,000 mg/dl glucose on a routine urinalysis. Hyperglycemia was confirmed by random finger-stick of 475 mg/dl and venous glucose measurements of 349 mg/dl and 282 mg/dl a few hours later. At presentation, she was asymptomatic, without polyuria, polydipsia, polyphagia, abdominal pain, weight loss or fatigue. Her physical examination was unremarkable with appropriate growth, and she was prepubertal at Tanner stage I for pubic hair and breast development. Initial

electrolytes, CBC, liver function tests, and venous serum pH were within normal limits, and she did not have ketones in her urine. The three diabetes-related auto-antibodies (Esoterix laboratories, confirmed at ARUP laboratories), namely, anti-GAD65 antibody, anti-tyrosine phosphatase (IA-2) antibody and anti-insulin antibody, were all positive, confirming type 1 diabetes mellitus (DM1A) (results summarized in Table 1).

The patient's past medical history was significant for perinatally acquired HIV diagnosed at 2 months of age. Her mother, who was diagnosed with HIV during pregnancy, did not receive anti-retrovirals before or during delivery, and the child was not treated with AZT for perinatal prophylaxis. The patient was initially treated with zidovudine, didanosine and nevirapine, but due to the elevation of her viral load, the antiretroviral regimen was changed to stavudine, lamivudine and abacavir at 15 months of age. She has remained on the same therapy since then, with a consistently undetectable viral load and normal CD4 counts throughout. She has had no serious infections or hospitalizations, and her CDC classification is N-1. Her family history is negative for DM or any other autoimmune diseases.

Additional work-up for autoimmune markers was significant for positive anti-parietal cell antibody (done at ARUP laboratories), while thyroid peroxidase antibody, thyroglobulin antibody, 21-hydroxylase antibody, ANA, dsDNA antibody, tissue transglutaminase and gliadin antibodies were all negative. HLA typing revealed DRB1\*0401, 0405 which are both DR4 alleles and represent high risk for the development of DM1A. The patient was started on subcutaneous injections of insulin with a good response on her subsequent follow-ups.

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**TABLE 1**  
Laboratory findings

Test	Normal	Result
<b>Anti-Gad 65 antibody</b>	<0.5 U/ml	4.4 U/ml
<b>Anti-tyrosine phosphatase antibody (IA-2)</b>	<0.5 U/ml	18 U/ml
<b>Anti-insulin antibody</b>	<5 $\mu$ U/ml	9.8 $\mu$ U/ml
<b>HbA<sub>1c</sub></b>	<6%	7.5%
<b>C-peptide</b>	0.8-3.5 ng/ml	1.3 ng/ml

### DISCUSSION

The occurrence of type 2 DM, insulin resistance and the metabolic syndrome in HIV-infected patients, especially those treated with antiretrovirals, is well documented. Protease inhibitors which have contributed greatly to the increased survival of patients with HIV in the HAART era are particularly notorious for their role in the development of type 2 DM<sup>1</sup>. Pentamidine used for PCP prophylaxis has also been implicated in the development of DM<sup>2</sup>. Our patient has had well-controlled HIV since shortly after birth, and she has never been on a protease inhibitor or pentamidine. Although cases of antibody negative, insulin dependent DM have been reported<sup>3,4</sup>, to our knowledge there have not been any reports of an HIV positive pediatric or adult patient developing insulin dependent DM with positive antibodies.

DM1A is defined as an absolute insulin deficiency precipitated by autoimmune destruction of the pancreas evidenced by positive autoantibodies, as in our patient<sup>5</sup>. DM1A is a relatively common chronic illness in the US with a prevalence of approximately 0.76 cases per 1,000 youth, according to the recent SEARCH for Diabetes in Youth Study<sup>6</sup>. The prevalence of DM1A among Hispanic American youth is 0.44 cases per 1,000 children whereas it is most common among whites at 1.03 cases per 1,000 youth<sup>6</sup>. Our patient has no family history of autoimmune DM, but most cases of DM1A are sporadic<sup>7</sup>. Although our patient does not belong to an ethnic group with a high prevalence of DM1A, HLA genotyping revealed the presence of

the high-risk alleles for development of DM1. The lifetime risk of developing DM in a person with two DR4 alleles is 1/20<sup>7</sup>. More than 90% of patients with DM1A carry a high risk allele<sup>8</sup> and our patient certainly falls into that category.

DM1A results from the interaction of genetic, environmental and immune factors. The most widely accepted model of DM1A suggests that in genetically susceptible individuals immune mediated beta-cell destruction is induced following exposure to an environmental trigger such as a viral infection. The exact pathogenesis is, however, unknown although it is thought that the beta-cells of the pancreas are destroyed by autoreactive cytotoxic T-cells<sup>9</sup>. Autoantibodies are often positive but are not believed to play a major role in the pathogenesis of the illness, and are often referred to as 'smoke of the fire' in the pancreas.

It has long been noted that patients with HIV are at higher risk for developing autoimmune syndromes than the general population. The frequency of such phenomena among HIV patients is reported to be as much as 60%, and the list of reported diseases includes SLE, sarcoidosis, antiphospholipid syndrome, vasculitis, primary biliary cirrhosis, polymyositis, Graves' disease, Hashimoto's thyroiditis, psoriasis and Behcet's disease<sup>10,11</sup>. Autoimmune syndromes may occur at different stages of HIV disease, and the relationships between autoimmunity and HIV infection and its treatment remain to be fully elucidated. Some phenomena, such as HIV-related immune thrombocytopenic purpura, are associated with early infection and/or high viral load. The

mechanism is thought to be due to molecular mimicry, where immunogenic HIV epitopes induce an antibody response to human tissue<sup>12</sup>. Other diseases, such as SLE and Guillain-Barre syndrome, are associated with immune reconstitution, particularly in previously immunosuppressed patients. They usually present within a few months of starting antiretroviral therapy and may reflect preexisting autoreactive lymphocytes or a newly-potentiated inflammatory reaction to occult pathogens such as CMV or *Mycobacterium avium complex*<sup>13</sup>. In contrast, autoimmune thyroid disease tends to present 1-2 years after immune reconstitution has begun and may represent a chronic immune dysregulation of long-term controlled infection<sup>14</sup>.

HIV infection affects all parts of the immune system, causing a generalized immune activation and dysregulation of immune homeostasis. These defects present early in infection and have been shown to persist even in well-controlled patients on HAART, albeit to a lesser degree than in those who are untreated. T cells exhibit increased activation markers with respect to healthy controls months to years after effective antiretroviral therapy, particularly in patients who were severely immunosuppressed prior to treatment<sup>15,16</sup>. In addition, the function and distribution of important T cell subsets, notably CD4+CD25+ T-regulatory cells, have been shown to be altered by HIV infection and treatment<sup>17,18</sup>. Although the precise implications of these alterations are still under investigation, it is significant that T-regulatory cells play a critical role in regulating self-reactive T cells and preventing autoimmune disease<sup>19,20</sup>.

Similarly to other T-cell mediated autoimmune disorders, DM1A is caused by the loss of immune tolerance leading in the case of DM1A to the destruction of pancreatic islet beta-cells by auto-reactive dysregulated cytotoxic T-cells<sup>21-23</sup>. Despite the frequent findings of autoimmunity in HIV positive patients, this is the first report of DM1A in this population. Our patient has never been profoundly immunosuppressed and has never had a very low CD4 count. She may have been at an uncommonly high risk for development of DM1A because of her HLA type. A case like this has not been described before and it may be that such

illnesses will become more common as care for HIV infected individuals is improved and their immune systems remain 'normal' enough to develop autoimmune diseases such as DM1A.

The authors have no conflict of interest to disclose.

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