Two Fifth-Generation Fighter Pilots Discovered with Latent Autoimmune Diabetes

Joe X. Zhang; Jacob Berry; Nathan M. Kim; Justin J. Gray; Savannah Fotheringham; Tom J. Sauerwein

BACKGROUND: Fighter pilots undergo extensive medical screening but may still miss rare diseases like latent autoimmune diabetes in adults (LADA). LADA patients have circulating autoantibodies directed against pancreatic beta cell antigens and present with frank diabetes late in life which may elude conventional military flight screening.

CASE REPORT: Two fifth-generation fighter pilots, a 38-yr-old man (patient 1) and a 27-yr-old man (patient 2), with no significant past medical histories developed symptoms of fatigue, weight loss, episodic polyuria, and arthralgia. Patient 1's symptoms were initially thought to have been caused by COVID-19, but he subsequently tested negative for viral infection. Lab work instead showed elevated TSH, HgbA1C 11.4%, positive GAD-65, anti-TPO, and anti-islet cell antibodies. Patient 2 developed symptoms following a military deployment and a 72-h diarrheal illness. Due to flight status, patient 2 did not seek expert medical attention for several months, but lab work found HgbA1C of 10.4%, positive GAD-66, and ZnT8 antibodies. Both patients were started on insulin therapy. Patient 1 was also started on levothyroxine for hypothyroidism and retired from flying duties. Patient 2 eventually transitioned to metformin without insulin and returned to flying duties with an aeromedical waiver.

DISCUSSION: Our patients maintained peak physical fitness throughout their selection and aviation careers, which likely delayed their clinical presentation. Current USAF flight rules prohibit insulin use with flying fighter aircraft. Early antibody screening during pilot selection may be a cost-effective means of diagnosis as traditional screening techniques are unlikely to detect LADA.

KEYWORDS: fighter pilot, diabetes, latent autoimmune diabetes in adults, military, accession criteria.

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During first quarter 2020, we encountered two instances of latent autoimmune diabetes in adults (LADA) in the USAF fighter pilot population. The two unrelated individuals were both fully combat qualified fifth-generation fighter pilots. Neither pilot had significant family history nor other outward clinical signs prior to their diagnosis. One pilot has become fully dependent on insulin and is no longer flying, while the other has returned to single seat fighters after transitioning from insulin to metformin.

The pathogenesis of LADA lies with impaired insulin production though autoimmune damage of components in the normal insulin pathway. This process is generally slow and clinical diabetes presents later in life. Type 1 diabetes has a similar disease mechanism, with the symptoms typically occurring by adolescence.[7]

Both type 1 diabetes and LADA share the same spectrum of autoimmune antibodies responsible for destruction of pancreatic beta cells. Antibodies of clinical relevance include islet cell antibodies (ICA), antibodies to glutamic acid decarboxylase-65 (GADA, GAD-65, Anti-GAD), anti-insulin antibody (IAA), anti-islet cell antibody 2 (IA-2A, antibody for the tyrosine phosphatase like molecule),[6] and antibodies to zinc transporter (ZnT8).[7] While there are cases of idiopathic type 1 diabetes (approx. 5–10%) where no traceable autoimmune

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antibodies are found,[6] a diagnosis of LADA requires the presence of autoimmune antibodies and signs of diabetes.

LADA itself is a relatively rare diagnosis compromising around 2–12% of all diabetes cases. In some Northern European countries, approximately 40% of type 1 diabetes occur in people older than 30 yr of age and multiple country aggregate studies of type 2 diabetes patients suggests 4–14% of these patients may also be positive for type 1 associated autoantibodies.[5]

The Immunology of Diabetes Society (IDS) has proposed criteria to standardize the definition of LADA with the following requirements: age ≥ 30, positive any antibody type seen in type 1 diabetes patients, and not requiring insulin therapy within the first 6 mo after diagnosis. Some sources, however, have opted to remove the insulin free portion of the criteria as many patients have presented only after they have lost the majority of their insulin production capabilities.[3] Patients may also have relative insulin insufficiency for years and clinically resemble a type 2 diabetic patient.

CASE REPORT

The first patient is a 38-yr-old Caucasian male active-duty fifth-generation fighter pilot with over 10 yr of flying experience. He initially noticed a 25–30 lb weight loss over the course of a year. The patient was transitioning to a command position and was actively trying to lose weight by changing his diet and increasing exercise, so these symptoms did not alarm him. The patient was otherwise healthy without any previous medical history or aeromedical waivers. The patient had no recent travel nor deployments within the past 2 yr. He takes a daily multivitamin but no other medications. His family history was only significant for a maternal grandmother who developed diabetes in her late 60s. The patient's prior screening blood work from 4 yr ago showed a nonfasting blood glucose level of 103 $mg \cdot dL^{-1}$.

Toward the end of March 2020, the patient complained of fever (measured at 100.6°F), fatigue, nausea, and constipation. The symptoms were initially thought to have been a result of COVID-19, though the patient eventually tested negative for both SAR-CoV2 rapid PCR and Influenza A+B Ag. The patient was diagnosed with a nonspecific viral syndrome and his symptoms mostly self-resolved within a week, after which he returned to flying status.

During the following week, the patient continued to struggle with fatigue and documented a rapid weight loss of 10 lb (4.5 kg). After a training flight on 8 April 2020, he sought further medical evaluation. His physical exam was unremarkable and without evidence of neuropathy or retinopathy. At that time, his vital signs were within normal limits. His BMI was 24.4 $kg \cdot m^{-2}$. His metabolic panel showed a blood glucose level of 450 $mg \cdot dL^{-1}$ and an HgbA1C of 11.4%. Additional labs showed an elevated thyroid stimulating hormone (TSH) level of 8.660 $mIU \cdot mL^{-1}$ (Ref. 0.5–5.0 $mIU \cdot L^{-1}$) with low normal free T4 of 0.73 $ng \cdot dL^{-1}$ (Ref. 0.8–1.8 $ng \cdot dL^{-1}$). The patient was also found to have marked elevations of thyroglobulin antibody of 23.17 $IU \cdot mL^{-1}$ (Ref normal < 20 $IU \cdot mL^{-1}$) and thyroperoxidase Ab of 796.14 $IU \cdot mL^{-1}$ (Ref. normal < 35 $IU \cdot mL^{-1}$).

Further endocrinology evaluation discovered elevated GAD-65 > 250 $u \cdot mL^{-1}$ (Ref. < 5 $u \cdot mL^{-1}$) and elevated islet cell antibodies (IA-2) at 512 $nmol \cdot L^{-1}$ (Ref. < 0.02 $nmol \cdot L^{-1}$). C-peptide was 0.3 $ng \cdot mL^{-1}$ (Ref. 0.5–2.7 $ng \cdot mL^{-1}$). The patient was diagnosed with LADA and he was started on insulin glargine 10 units with insulin aspart correctional doses as initial treatment. He responded very well to insulin and had excellent blood glucose control within a week of insulin titration. The patient was also started on 50 mcg of levothyroxine which brought his TSH down to 4.02 $mIU \cdot mL^{-1}$ over the next 4 mo. His HgbA1C also decreased to 5.4%. The patient is no longer flying but remains on active duty. He has not had significant hypoglycemic events and his symptoms have resolved since beginning treatment.

The second patient is a 27-yr-old Caucasian male active-duty fifth-generation fighter pilot with 4 yr of flying experience. He presented to the flight medicine clinic with a 5-mo history of fatigue, irritability, unintentional 30–35 lb weight loss, episodic polyuria and nocturia, polydipsia, polyphagia, and arthralgia. He stated that his fatigue and mood changes began after he returned from deployment to southwest Asia 7 mo prior. During that deployment, the pilot flew 8-h sorties 2–3 times per week with inconsistent meals, but was asymptomatic.

Past medical history was unremarkable except for single resolved episode of rhabdomyolysis due to excessive exercise in 2016 and seasonal allergies status post subcutaneous immunotherapy well controlled on fexofenadine. The patient did not have any aeromedical waivers. The patient took no other medications regularly and had otherwise been healthy. At initial pilot selection evaluation 4 yr prior, his fasting blood glucose level was near the upper limit of normal at 98 $mg \cdot dL^{-1}$ (Ref. 70–100 $mg \cdot dL^{-1}$) without other abnormalities.

The patient experienced a 72-h episode of diarrhea and upset stomach after returning to the United States in November 2019. He began to have episodic increases in urination and thirst 2 mo later that he attributed to eating higher carbohydrate meals. These episodes occurred 1–2 times a month, but steadily increased to multiple times a week. His symptoms progressed to lightheadedness upon standing and complaints of feeling dehydrated even though he was drinking several liters of water a day.

After home glucometer testing revealed glucose > 400 $mg \cdot dl^{-1}$, he called his flight surgeon in late May 2020. At that time, his vital signs and physical exam were within normal limits with a BMI of 23 $kg \cdot m^{-2}$ and without evidence of neuropathy or retinopathy. The patient had a substantial family history of cardiovascular disease and atopy. Multiple family members also had autoimmune conditions including psoriasis, vitiligo, and rheumatoid arthritis. His initial diagnostic labs were significant for HgbA1C of 10.4%, serum glucose of 276 $mg \cdot dl^{-1}$, and urine glucose of 500 $mg \cdot dl^{-1}$ with greater than 80 ketones. He had normal blood chemistries, liver function tests, and TSH levels.

Further endocrinology evaluation in June 2020 showed elevated GAD-65 antibodies of greater than 250.0 IU · mL^{-1} (Ref. < 5 u · mL^{-1}), and elevated ZnT8 antibodies of 339.2 U · mL^{-1} (Ref. < 18 U · mL^{-1}). His C-Peptide was normal at 1.4 ng · mL^{-1} (Ref 0.5-2.7 ng · mL^{-1}). Insulin antibody, islet antigen-2 (IA-2 Ab) autoantibody, and islet cell cytoplasmic IgG antibody were all negative.

Due to complaints of clay colored stool shortly after beginning treatment with insulin, the patient was evaluated for additional hepatic and pancreatic disease. An abdominal ultrasound was performed that suggested a transient blockage of the bile ducts, but no other abnormalities were found. Stool color returned to normal spontaneously and no specific diagnosis was made.

The patient began treatment with insulin glargine at 10 units with insulin aspart correctional doses. He responded very well to insulin and had excellent blood glucose control within 3 wk of insulin titration. The patient was also prescribed a continuous glucose monitor to allow for better blood glucose trending when performing other ground-based flight duties. He did not have significant hypoglycemic events and his symptoms resolved over the subsequent month. His HgbA1C decreased to 5.7% over the next 4 mo.

Due to his wish to continue flying, as well as his low normal C-peptide levels suggesting that he still retained some insulin production, the patient underwent a trial of metformin and initiation of strict lifestyle management. The patient was successfully titrated off insulin by mid-October 2020 and after a period of observation for stability with excellent blood glucose control, a waiver to resume flight was approved in January 2021 with very close follow-up requirements. There is no predictive data for when the patient may ultimately require insulin and be forced to retire from flying fighters.

DISCUSSION

Late presentation of autoimmune mediated diabetes is a relatively rare diagnosis among diabetes patients. It is even more uncommon among a highly prescreened military pilot population. This rarity also lends to a relative paucity of information available in the literature, making diagnosis and management of LADA more challenging, especially in the setting of fighter aviation. A search of the U.S. Air Force aeromedical waiver database showed 65 total diabetes cases over the past 4 yr with no other reported LADA cases. Our discussion will lightly touch on the classification and nuances of these disease processes, but will be primarily focused on the aeromedical impacts for these members and costs for screening tests.

One such nuance involves concurrent autoimmune disease, such as thyroid disease in these patients. In 15–30% of type 1 diabetes adult patients, antithyroid antibodies are also found with gradual erosion of thyroid tissue and eventual loss of function. Patient one exemplified this. Other endocrine autoimmune diseases are also more frequently found in this population, such as adrenal insufficiency. This is more common in type 1 diabetic patients with frequent hypoglycemia episodes. A total of 10% of patients may also have celiac sprue (positive TTG IgA).[1]

For aeromedical considerations, it is important to discuss the current pilot selection criteria. U.S. Air Force pilot candidates require a bachelor's degree and they must be less than 30 yr old at the time of entrance to undergraduate flying training. The U.S. Navy or Marine Corps require applicants to be between the ages of 19 to 26 yr old, while the U.S. Army requires applicants to be under the age of 33 yr.

The various branches all have similar initial selection processes that require a comprehensive physical, mental, and laboratory exam for screening to ensure applicants are medically qualified. The U.S. Air Force model specifically requires laboratory testing that includes: hemoglobin and hematocrit, fasting blood sugar, HIV testing, urine drug screen, blood type and Rh factor, G6PD testing, sickle cell screening, blood alcohol level, lipid panel, urinalysis, syphilis testing, and a hepatitis screen.[10] There are service specific differences with regards to medical history and what medical diagnoses are allowed, but currently no genetic screening tests or antibody screening tests are involved for pilot candidate selection.

Patients who develop insulin dependent diabetes, as in our first case, are typically not granted a waiver to continue to operate single seat high performance military combat aircraft. In fact, only since November 2019 has the U.S. Federal Aviation Administration grant special commercial issuances to insulin dependent pilots provided that they fly with a second pilot. Other countries such as Canada and the UK have similar waiver policy. This practice has not shown significant adverse events with excellent safety records to date. No country, however, has yet granted waivers for insulin treated diabetic pilots to fly single seat commercial airliner operations. Due to lower risk to others, solo flying in private civil aviation has been allowed in most countries, including the United States, for these patients.

Single seat high performance military aircraft offer further physical demands that make it even more unlikely for a waiver to be granted. The potentially catastrophic consequences of a hypoglycemic episode midflight and hyperglycemic stressors on fluid balance in a combat environment increases the potential risk beyond the comfort levels of most regulators. These factors essentially force a fighter pilot on insulin to be medically removed from the force despite undergoing one of the most expensive training pipelines in existence.

It will be critical for policy makers to evaluate the costs and benefits of selecting these members for different flight roles due to the incredible expense of producing such an aviator. A recent Rand corporation study estimated that to train a basic qualified F-22 pilot cost $10.9M USD and $10.17M for a F-35 pilot in 2018.[9] These figures are likely to be significantly higher for pilots who further complete their full combat mission qualifications and other specialty qualification certifications. Discussions with the fifth-generation fighter pilot community suggests costs may be closer to $20M USD in 2020 to complete the training up to wingman ready status and even more to qualify for the flight lead position.

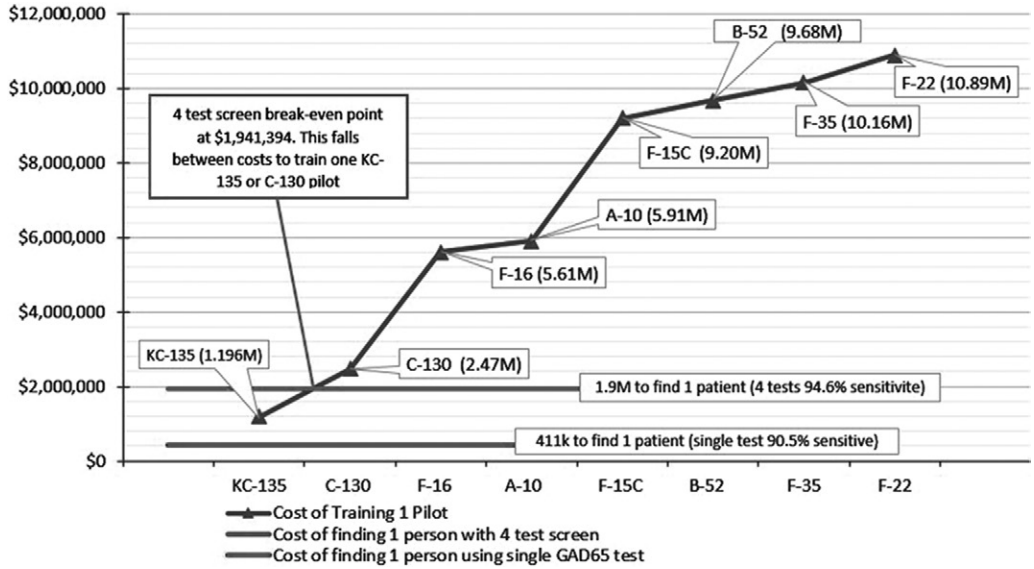

Fig. 1. Training cost to basic level vs. cost to find one LADA patient using 11.5 patients/100,000 estimate.[8]

In a cost benefit analysis, we analyzed various screening mechanisms that maybe implemented. The cheapest mechanism is to use a survey. Both family history of type 2 diabetes as well as type 1 diabetes were associated with increased risk of LADA. Type 2 diabetes risk, however, only seemed to have a direct relationship with family history of type 2 diabetes, not type 1 diabetes. LADA seems to have a greater genetic relationship with a family history of type 1 diabetes (odds ratio 5.8), but it is also slightly elevated with type 2 diabetes (odds ratio 1.9), which emphasizes the mixed linkage of LADA patients. These factors make surveys an unreliable basis for screening.[6] The second pilot was actually the first person in his family to develop any form of diabetes.

For objective laboratory screening, HgbA1C and fasting blood sugar levels may be normal in LADA patients at recruitment. Our case studies demonstrated this. C-peptide, a marker of beta cell insulin production, may also be normal or only marginally declined during early disease for LADA patients. C-peptide may also be low normal for type 1 patients prior to significant pancreatic islet cell destruction. In some cases, it may even be suppressed due to high glucotoxicity. All these factors make C-peptide difficult to use as a potential screening test.[12]

Alternatively, an antibody screen would offer more sensitivity and specificity to detect these diseases. The most commonly found antibodies for both type 1 diabetes and LADA would most likely include: GADA (90.5%) followed by IA-2A (2.3%), and then ZnT8A (1.8%). Of patients, 24.1% are found to have more than one type of autoimmune antibody.[5]

In the large European Nicotinamide Diabetes Intervention Trial (ENDIT), it was found that the 5-yr risk for developing diabetes was 17% for one antibody, 39% for two antibodies, and 70% for three antibodies.[2] It is generally accepted that while the antibody tests are highly sensitive and specific, they do not offer any ability to prevent the development of type 1 diabetes in the patient's lifetime. The time from diagnosis to insulin dependence is highly variable, making it difficult to predict if a particular pilot applicant would be able to successfully serve out a typical 10 yr flying contract incurred during accession.

To determine a cost benefit analysis of screening, we averaged the prices from the common reference laboratories under contract to the hospitals treating our two patients.

- IA-2A: $78.78
- GAD: $42.85
- ZnT8: $80
- Anti-insulin antibody: $21.63
- Total cost $223.26 USD per candidate screened

A total of 44,790 pilot candidates could be screened for the $10M cost of a single novice fifth-generation fighter pilot. The average national incidence rate of type 1 diabetes over the age of 15 yr old is 11–12 cases per 100,000.[8] Applying this ratio would result in uncovering 5.1 cases of LADA. The break-even point where the cost of one pilot is equal to the cost of discovering one occult disease is then $1,941,394.30 using a four-test screening battery. The higher the training costs, the more beneficial it becomes to spend funds to screen candidates (see **Fig. 1**).

Military accessions may also consider a single screening test of GAD-65 antibodies with follow-up testing if positive. This would still help identify up to 90.5% of potential cases at a much lower total cost. The estimate for discovering one individual using this screening method would be $411,722.32 when factoring in additional tests such as a four-test confirmation battery if the initial test was positive. When compared with the costs of training a single pilot in any of the available platforms, there is no intersection point (see Fig. 1). This means that until costs of training an individual falls below the $411,722.32 threshold, a plan to screen all candidates would still result in net savings. Individuals found can either be selected out of training,

be enrolled in high frequency monitoring programs under an aeromedical waiver, or offered training in military roles that permit the use of insulin.

Current NASA astronaut selection standards already perform a version of this using an antibody screen for quantitative immunoglobulins (IgG, IgA, and IgM).[4] A positive test suggests, but is insufficient by itself to diagnose, conditions such as immunodeficiency or chronic inflammatory diseases. This single test has a low initial overhead cost averaging $100 USD per test with a positive test triggering further evaluation.

Finally, consideration should be taken for the cost and benefit of retaining an otherwise excellent military asset. Even if disqualified from flight duties, these members have potential use in other ground-based jobs as subject matter experts, who are always in high demand. There has never been a study evaluating the relative cost effectiveness of this path, however, and it deserves future investigation. It will ultimately be up to each aeromedical service branch to weigh the risks of losing an expensive asset versus the cost to conduct additional screening tests at selection. Developments of autoimmune modulation treatments[11] and future flight standard updates will further influence the stakes in these decisions.

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REFERENCES

1. Barker JM. Type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. J Clin Endocrinol Metab. 2006; 91(4):1210–1217.
2. Bingley PJ. Clinical applications of diabetes antibody testing. J Clin Endocrinol Metab. 2010; 95(1):25–33.
3. Buzzetti R, Tuomni T, Mauricio D, Pietropaolo M, Zhou Z, et al. Management of latent autoimmune diabetes in adults: a consensus statement from an international expert panel. Diabetes. 2020; 69(10):2037–2047.
4. Dunbar B. Medical requirements integration documents. MR 089S: annual medical examinations. 3.5. Clinical laboratory testing. Houston (TX): NASA Johnson Space Center; 2004:4.
5. Hawa MI, Kolb H, Schloot N, Beyan H, Paschou SA, et al. Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: Action LADA 7. Diabetes Care. 2013; 36(4):908–913.
6. Hjort R, Alfredsson L, Andersson T, Carlsson PO, Grill V, et al. Family history of type 1 and type 2 diabetes and risk of latent autoimmune diabetes in adults (LADA). Diabetes Metab. 2017; 43(6):536–542.
7. Leslie RD, Williams R, Pozzilli P. Clinical review: type 1 diabetes and latent autoimmune diabetes in adults: one end of the rainbow. J Clin Endocrinol Metab. 2006; 91(5):1654–1659.
8. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. Endocrinol Metab Clin North Am. 2010; 39(3):481–497.
9. Mattock MG, Asch BJ, Hosek J, Boito M. The relative cost-effectiveness of retaining versus accessing Air Force pilots. Santa Monica (CA): Rand Corporation; 2019:12-16. Research Report RR-2415-AF.
10. Miller RI. Air Force instruction 48-123. Medical examinations and standards. Washington (DC): U.S. Air Force; 2020:14–16, 24–25, 30–59.
11. Piñero-Piloña A, Litonjua P, Aviles-Santa L, Raskin P. Idiopathic type 1 diabetes in Dallas, Texas: a 5-year experience. Diabetes Care. 2001; 24(6):1014–1018.
12. Pozzilli P, Pieralice S. Latent autoimmune diabetes in adults: current status and new horizons. Endocrinol Metab. 2018; 33(2):147–159.