Latentna tuberkulozna infekcija u osobe sa šećernom bolesti – prikaz bolesnika

Latent tuberculosis infection in a subject with diabetes mellitus – a case report

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Sažetak

Uvod: Bolesnici sa šećernom bolesti tipa 1 često imaju narušenu staničnu imunost i podložni su zaraznim bolestima. Cilj je ovog rada prikazati slučaj latentne tuberkulozne infekcije (LTBI) u 46-godišnje zdravstvene djelatnice (medicinske sestre na odjelu za tuberkulozu male djece) koja 20 godina boluje od šećerne bolesti tipa 1.

Materijali i metode: Tuberkulinski kožni test učinjen je s 2 tuberkulinske jedinice (Tuberkulin RT-23, Statens Serum Institute, Kopenhagen, Danska). Krv za ispitivanje oslobađanja interferona gama, IFN-γ, (engl. *Interferon Gamma Releasing Assay*, IGRA) uzorkovana je u epruvete koje sadrže specifične antigene mikobakterija tuberkuloze (ESAT-6, CFP10 i TB7.7). Nakon inkubacije (22 sata) na 37ºC u plazmi je određena koncentracija IFN-γ metodom ELISA (QuantiFERON-TB Gold In Tube – Cellestis Ltd., Victoria, Australia). Pozitivna kontrola bila je krv uzorkovana s mitogenom fitohemaglutininom, a negativna kontrola krv uzorkovana s heparinom.

Rezultati: Tuberkulinski kožni test bio je negativan (induracija 6 mm), a nalaz otpuštanja IFN-γ iz aktiviranih limfocita (≥ 0,35 kIU/L) pozitivan. Normalna stanična imunost potvrđena je pozitivnom kontrolom. Ispitanica nema znakova aktivne tuberkuloze.

Zaključak: U medicinske sestre koja boluje od šećerne bolesti tipa 1, a godinama radi s tuberkuloznim bolesnicima LTBI je dokazana testom oslobađanja IFN-γ, ali ne i tuberkulinskim kožnim testom. Unatoč dugogodišnje šećerne bolesti tipa 1, reakcija oslobađanja IFN-γ prema specifičnim tuberkuloznim antigenima je očuvana, a aktivna se tuberkuloza nije razvila.

Ključne riječi: Latentna tuberkulozna infekcija; šećerna bolest; šećerna bolest tipa 1; IFN-gama

Abstract

Introduction: Patients suffering from diabetes mellitus type 1 often have impaired cell-mediated immunity and are prone to infectious diseases. The aim of this paper is to present a case study on latent tuberculosis infection (LTBI) in a 46 year-old female health care worker (a nurse at the department for tuberculosis in young children) who has been having type 1 diabetes for 20 years.

Materials and methods: Tuberculin skin test was performed using 2 tuberculin units (Tuberkulin RT-23, Statens Serum Institute, Copenhagen, Denmark). Blood for interferon gamma (IFN-γ) release assay, (IGRA) was sampled in test tubes containing specific antigens of mycobacterium tuberculosis (ESAT-6, CFP10 and TB7.7). After incubation (22 hours) at 37°C, IFN-γ concentration in plasma was determined by ELISA assay (QuantiFERON-TB Gold In Tube - Cellestis Ltd., Victoria, Australia). For positive control, blood was sampled by mitogene phytohemagglutinin and for negative control by heparin.

Results: Tuberculin skin test was negative (induration 6 mm) and test result of IFN- γ release from activated lymphocytes (≥ 0.35 kIU/L) positive. Normal cellular immunity was confirmed by positive control sample. The subject showed no signs of active tuberculosis.

Conclusion: In a nurse suffering from type 1 diabetes who has worked for years with tuberculosis patients, LTBI was detected by IFN-γ release assay rather than by tuberculin skin test. In spite of the long lasting diabetes, reaction of IFN-γ release toward specific tuberculosis antigens has been preserved and active tuberculosis has not developed.

Key words: Latent tuberculosis infection; diabetes mellitus; diabetes mellitus type 1; IFN-gamma

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Uvod

Oko 2 milijarde ljudi ima latentnu infekciju mikobakterijem tuberkuloze (engl. *latent tuberculosis infection*, LTBI) (1). Učestalost LTBI kod zdravstvenih djelatnika (engl. *health care workers*, HCW) u srednje i slabo razvijenim zemljama kreće se između 33 i 79% (2), a u visoko razvijenim zemljama nije veća od 55% (3). Zbog profesionalne izloženosti tuberkuloznim bolesnicima, zdravstveni djelatnici imaju povećani rizik za tuberkuloznu infekciju.

Dijagnoza LTBI stotinjak se godina provodi metodom *in vivo*, tuberkulinskim kožnim testom (engl. *tuberculin skin test*, TST). TST se temelji na mjerenju reakcije odgođene preosjetljivosti nakon potkožne primjene slabo definirane smjese mikobakterijskih antigena (engl. *purified protein derivative*, PPD). Njime se određuje kumulativan učinak profesionalne i neprofesionalne izloženosti bacilu tuberkuloze, a na ishod reakcije utječu i čimbenici poput BCG-cijepljenja (Calmette-Guerin Bacillus) i prethodne izloženosti ne-tuberkuloznim mikobakterijama (4,5). Heterogenost sadržaja PPD-pripravaka, subjektivnost pri očitavanju reakcije te različite granične vrijednosti za određivanje pozitivnog TST smanjuju njegovu specifičnost. Kako se u testu ne koristi pozitivna kontrola, mogući su i lažno negativni rezultati kao posljedica imunosupresivnih stanja (6). U zemljama kao što je Hrvatska, gdje se BCG cijepljenje redovito provodi, TST može dati lažno pozitivne rezultate.

Novi pristup otkrivanju LTBI temelji se na *ex vivo* testovima iz pune krvi kojima se određuje IFN-γ oslobođen iz limfocita T nakon što su kroz dulje vrijeme bili u kontaktu s antigenima specifičnim za *M. tuberculosis*. Po tim se antigenima *M. tuberculosis* razlikuje od većine preostalih mikobakterija (7). Upravo ta činjenica pridonosi većoj specifičnosti ovoga testa u odnosu na TST. Upotrebom testa oslobađanja IFN-γ (IGRA) mogu se isključiti osobe koje su BCG-cijepljene, što kod TST-a nije slučaj.

Bolesnici sa šećernom bolesti tipa 1 često imaju narušenu staničnu imunost i podložni su zaraznim bolestima (8). Cilj je ovog rada prikazati slučaj LTBI u 46-godišnje zdravstvene djelatnice (medicinske sestre na odjelu za tuberkulozu male djece) koja boluje od šećerne bolesti tipa 1. Prema našem znanju, ovo je prvi prikaz primjene IGRA u otkrivanju LTBI u osobe koja je profesionalno izložena mikobakteriju tuberkuloze, a boluje od IDDM.

Prikaz bolesnika

Prikazana je 46-godišnja zdravstvena djelatnica (medicinska sestra) koja 26 godina radi na odjelu za tuberkulozu male djece. Zadnjih 20 godina boluje od šećerne bolesti tipa 1. Zbog bliskog kontakta s tuberkuloznim bolesnicima podvrgnuta je uobičajenom pregledu za probiranje tuberkulozne infekcije.

Introduction

Around 2 billion people suffer from latent mycobacterium tuberculosis infection (LTBI) (1). Prevalence of LTBI in health care workers (HCW) in middle and low-income countries ranges between 33 and 79% (2) and in high-income countries it is not higher than 55% (3). Due to professional exposure to tuberculosis patients, health care workers are at increased risk of tuberculosis infection.

LTBI diagnosis has been made for over last hundred years by *in vivo* method, tuberculin skin test (TST). TST is based on measuring reaction of postponed oversensitivity after a mixture of non-specified mycobacterium antigens (PPD, purified protein derivative) has been injected into the inner surface of the forearm. PPD is used to determine total effect of professional and non-professional exposure to tuberculosis bacillus and the result of reaction is influenced by factors like BCG vaccination (Calmette-Guerin Bacillus) and previous exposure to non-tuberculosis mycobacteria (4,5). Heterogeneity of PPD-solution, subjectivity at reaction reading and different cut-off values for determination of positive TST diminish its specificity. No positive control samples were used in the test and therefore false negative results were possible as consequence of immunosuppressive conditions (6). In countries like Croatia, where BCG vaccination is conducted regularly, TST can give false results.

A new approach to LTBI detection is based on whole human blood *ex vivo* assays which determine IFN-γ released from T-lymphocytes after their prolonged exposure to *M. tuberculosis* specific antigens. These antigens distinguish M. tuberculosis from the majority of other mycobacteria (7). This fact specifically contributes to higher specificity of this assay compared to TST. By using IFN-γ releasing assay (IGRA, interferon-gamma release assay) BCG-vaccinated individuals can be excluded, which is not the case with TST. Patients suffering from diabetes mellitus type 1 often have impaired cell immunity and are prone to contagious diseases (8). The aim of this study is to show a LTBI case in a 46 year-old female health care worker (a nurse at the department for tuberculosis in young children) suffering from diabetes mellitus type 1. Up to our knowledge, this is the first report of IGRA application in revealing LTBI in an individual who is professionally exposed to mycobacterium tuberculosis and at the same time suffers from type 1 diabetes mellitus.

Case report

A 46 year old female health care worker (a nurse) has been working for 26 years at the department for tuberculosis in young children. During the last 20 years she has been suffering from diabetes mellitus type 1. Because of the close contact with tuberculosis patients, she underwent a routine screening for tuberculosis infection.

Bolesnica je cijepljena s BCG te ima ožiljak (engl. *BCG scar*). Trenutno nije akutno bolesna, afebrilna je, eupnoična, auskultacijski nad plućima ima normalan šum disanja. TST je bio negativan (promjer induracije 6 mm; očitanje nakon 72 sata; 2 tuberkulinske jedinice tuberkulina RT-23, Statens Serum Institute, Kopenhagen, Danska). Nalaz *ex vivo* određivanja IFN-γ bio je pozitivan (≥ 0,35 kIU/L), a pozitivna mitogenska kontrola uredna (≥ 0,50 kIU/L). Ispitanica je imala povećanu koncentraciju glukoze, IgA, hsCRP, te povećane vrijednosti sedimentacije eritrocita (Tablica 1).

The subject was BCG vaccinated and has a BCG scar. At admission she was not acutely ill, she had normal body temperature, was eupneic and lung auscultation showed normal breathing. TST was negative (induration diameter 6 mm; reading after 72 hours; 2 tuberculin RT-23 units, Statens Serum Institute, Copenhagen, Denmark). *Ex vivo* IFN-γ test result was positive (≥ 0.35 kIU/L) and positive mitogen control was normal (≥ 0.50 kIU/L). The subject had elevated concentrations of glucose, IgA and hsCRP and elevated erythrocyte sedimentation rate (Table 1).

Tablica 1. Rezultati laboratorijskih pretraga

Table 1. Results of laboratory analyses

	Result	Reference values
IFN-γ	4.72 kIU/L	≤ 0.35
Mitogen	15.01 kIU/L	≥ 0.50
Glucose	15.2 mmol/L	4.2–6.1
IgG	13.2 g/L	7.0–16.0
IgA	4.93 g/L	0.7–4.0
IgM	0.55 g/L	0.4–2.8
hsCRP	3.29 mg/L	< 0.1
ESR	32	4–24

IFN-γ – interferon gama; hsCRP – high sensitive C-reactive protein; ESR - erythrocyte sedimentation rate

Načelo određivanja interferona gama nakon aktivacije s tuberkuloznim antigenima

Uzorkovanje venske krvi provodi se prije izvođenja TST. Postupak određivanja odvija se u dvije faze:

- aktivacija limfocita iz pune krvi ispitanika sa specifičnim antigenima mikobakterija tuberkuloze (epruveta sadrži tri antigena – ESAT-6, CFP10 i TB7.7). Istodobno se uzorkuju krvi za pozitivnu kontrolu (epruveta s fitohemaglutininom) i negativnu kontrolu (epruveta s heparinom). Sva tri uzorka inkubiraju se preko noći (22 sata) na 37 °C, nakon čega se odvaja plazma te pohranjuje na +4°C do analize (najdulje 7 dana).
- određivanje koncentracije IFN-γ metodom ELISA s pomoću komercijalnog testa QuantiFERON-TB Gold In Tube (Cellestis Ltd., Victoria, Australija). Nalaz se izražava kao pozitivan ako je koncentracija IFN-γ veća od granične vrijednosti 0,35 kIU/L.

Principle of interferon gamma determination after activation with tuberculosis antigens

Venous blood is sampled before TST. Determination procedure is carried out in two phases:

- Activation of patient's whole blood lymphocytes with specific mycobacterium tuberculosis antigens (test tube contains three antigens - ESAT-6, CFP10 and TB7.7). At the same time blood is sampled for positive (test tube with phytohemagglutinin) and negative control (test tube with heparin). All three samples are incubated over night (22 hours) at 37°C, and plasma is thereafter separated and stored at 4°C until analysis (for max 7 days).
- IFN-γ concentration determination by ELISA assay with QuantiFERON-TB Gold In Tube (Cellestis Ltd., Victoria, Australia) commercial assay. Test result is displayed as positive if IFN-γ concentration is higher than the cut-off value of 0.35 kIU/L.

Rasprava

Samo je test oslobađanja IFN-γ (IGRA) ukazao na postojanje LTBI kod medicinske sestre koja je godinama u kontaktu s tuberkuloznim bolesnicima, a nalaz TST bio je lažno negativan. Unatoč dugogodišnjoj šećernoj bolesti, aktivna se tuberkuloza nije razvila. Od ostalih nalaza treba ukazati na povećanu koncentraciju glukoze kao pokazatelja loše kontrolirane bolesti, te na povećane upalne biljege. Povećana koncentracija IgA može se naći u serumu oko 23% bolesnika sa šećernom bolesti, osobito ako se bolesti liječi dulje od 10 godina (9), što je slučaj kod naše ispitanice, odnosno ako se razvije dijabetička nefropatija (10). Povećana koncentracija hsCRP ukazuje na latentnu upalu koja je svojstvena bolesnicima sa šećernom bolesti (11), odnosno ukazuje na rizik pojave kardiovaskularne bolesti (12).

Ovaj prikaz slučaja otvara dvije teme za raspravu: vrijednost *in vivo* i *ex vitro* testova za otkrivanje tuberkulozne infekcije u osoba profesionalno izloženih uzročniku, te odnos između tuberkulozne infekcije i šećerne bolesti.

Britanske preporuke za dijagnozu i liječenje tuberkuloze predlažu početno pretraživanje pomoću TST te potvrđivanje pozitivnih rezultata nekim od IGRA testova (13). Prema američkim preporukama novija inačica IGRA (QuantiFERON-TB Gold) može u potpunosti zamijeniti TST te nije potrebno oba testa izvoditi istodobno (14). Međutim, treba imati u vidu dijagnostičku vrijednost tih testova. Dijagnostička vrijednost TST ovisi o određivanju granične vrijednosti koja razlikuje pozitivne od negativnih rezultata (15), o prethodnoj izloženosti ne-tuberkuloznim mikobakterijama (4), a za oba testa važna je procijepljenost populacije (16-18). BCG-cijepljenje utječe na rezultate TST, osobito u osoba < 40 godina u zemljama s malom incidencijom tuberkuloze (19). BCG-irane osobe koje imaju TST > 11 mm mogu se smatrati inficiranima (20). Pozitivan rezultat TST nakon zaraze bakterijom *M. tuberculosis* često ostaje trajno pozitivan („jednom pozitivan, nikad više koristan") (21,22). Određivanje koncentracije IFN-γ bolji je indikator u cijepljenih osoba (18) i u osoba koje su u dugotrajnijem kontaktu s *M. tuberculosis* (23) nego TST jer ukazuju na akutnu izloženost specifičnim tuberkuloznim antigenima. Rezultat IGRA kod osoba s LTBI pokazao je osjetljivost od 90% i specifičnost 98% (24). Dodatak više antigena specifičnih za *M. Tuberculosis* u epruvetu, povećava specifičnost IGRA. Rezultate testova jednostavno je tumačiti kad su njihovi rezultati sukladni. U većini istraživanja podudarnost između rezultata TST i IGRA može varirati između 60–90% (25). U slučajevima gdje je rezultat TST pozitivan, a IGRA negativan, to bi se razilaženje moglo pripisati prethodnom cijepljenju BCG (25). Obrnuta nepodudarnost (TST negativan; IGRA pozitivan) također je zabilježena među zdravstvenim djelatnicima (26). Podudarnost rezultata IFN testova nove generacije (Quantiferon-TB Gold,

Discussion

Only IFN-γ releasing assay (IGRA) indicated the LTBI presence in the nurse who has been for years exposed to tuberculosis patients, while TST result was false negative. Despite diabetes mellitus over many years, active tuberculosis has not developed. From other test results, attention should be drawn to elevated glucose concentration as an indicator of poor diabetes control, and to elevated concentration of inflammatory markers. Elevated IgA concentration can be found in serum in approximately 23% of diabetes mellitus patients, especially if disease has been treated longer than 10 years (9), which is the case with our female health care worker, or if diabetic nephropathy develops (10). Elevated hsCRP concentration points to latent inflammation which is characteristic for diabetes mellitus patients (11) or to a cardiovascular risk (12).

This case report opens two discussion topics: *in vivo* and *ex vivo* test result values for detecting tuberculosis infection in individuals professionally exposed to infectious agent, and relation between tuberculosis infection and diabetes mellitus.

British guidelines for tuberculosis diagnosis and treatment suggest initial screening by TST and positive result confirmation by some of IGRA assays (13). According to US guidelines, the newer IGRA version (QuantiFERON-TB Gold) can completely replace TST assay and it is not necessary to perform both assays simultaneously (14). However, one should bear in mind the diagnostic value of these assays. TST diagnostic value depends on the cut-off value determination that distinguishes positive from negative results (15), and on previous exposure to non-tuberculosis mycobacteria (4). For both assays, population vaccination is very important (16-18). BCG vaccination influences TST test results especially in individuals < 40 years old in countries with low tuberculosis incidence (19). BCG-vaccinated individuals with TST > 11 mm can be considered infected (20). A positive TST result after infection with *M. tuberculosis* often remains permanently positive ("once positive, no longer useful") (21,22). IFN-γ concentration determination is a better indicator in vaccinated individuals (18) and in individuals longer exposed to *M. tuberculosis* (23) than TST because it points to acute exposure to specific tuberculosis antigens. Result of the IGRA in people with LTBI showed sensitivity of 90% and specificity of 98% (24). Specificity of IGRA is enhanced by introducing more mycobacterial antigens in the test tube. Test results are simple to interpret when they are comparable. In most studies, concordance between TST and IGRA results could vary between 60-90% (25). In the cases where TST is positive but IGRA is negative, discrepancy could be assigned to prior BCG vaccination (25). Reverse discrepancy (TST negative; IGRA positive) has also been documented in health care workers (26). Agreement of the new genera-

korišten u ovom istraživanju) s TST je 79–94% (27). Međutim, u osoba koje imaju smanjenu staničnu imunost (bolesnici s malignim bolestima, šećernom bolesti, kroničnim bubrežnim oštećenjem, HIV, imunosupresivnom terapijom) rezultati tih testova ne moraju biti sukladni (28). Kobashi i sur. su pokazali da imunokompromitirani bolesnici imaju negativan kožni test, a pozitivan nalaz IGRA (23), što je slučaj i kod naše ispitanice. Dakle, u osoba s narušenom imunošću testovi *in vivo* i *ex vivo* nemaju jednaku dijagnostičku vrijednost kao u zdravih osoba. Tome u prilog ide i ovaj prikaz slučaja koji je pokazao lažno negativan rezultat kožnog testa, a pozitivan nalaz IGRA. Taj je nalaz potvrdio da je unatoč dugogodišnjoj šećernoj bolesti reakcija oslobađanja IFN-γ prema specifičnim tuberkuloznim antigenima još uvijek očuvana. Istodobno, ispitivanjem stanične imunosti određivanjem IFN-γ nakon aktivacije limfocita fitohemaglutininom izbjegnut je mogući lažno negativan rezultat. Veza između tuberkuloze i šećerne bolesti poznata je već 2000 godina (29). Već je u V. stoljeću tuberkuloza opisana kao komplikacija šećerne bolesti. Bolesnici sa šećernom bolesti podložni su infekcijama (8), pa tako i infekciji s mikobakterijem tuberkuloze. Iako nema dovoljno spoznaja o tome kako šećerna bolest oštećuje obrambeni sustav, čini se da se smanjena obrambena sposobnost može pripisati hiperglikemiji (30). Na tu je uzročno-posljedičnu svezu ukazalo i ispitivanje na dijabetičnim miševima zaraženima s *M. tuberculosis* (31) i ispitivanje uloge IFN-γ u osoba sa šećernom bolesti (32). Dijabetični miševi imali su upalne promjene u plućima te istodobno smanjeno stvaranje IFN-γ (31), a osobe sa šećernom bolesti bile su podložne obolijevanju od tuberkuloze upravo zbog pomanjkanja IFN-γ koji je potreban za inhibiciju početnog rasta *M. tuberculosis* (32). Iz toga slijedi da bi, u svrhu otkrivanja smanjenog stvaranja IFN-γ i posljedične podložnosti razvoju aktivne tuberkuloze, *ex vivo* određivanje IFN-γ bilo potrebno uključiti u redovitu godišnju obradu naše ispitanice.

tion of IFN tests (Quantiferon-TB Gold, used in the present study) with TST is 79-94 % (27). However, in individuals with impaired cell immunity (patients suffering from malignant diseases, diabetes mellitus, chronic kidney disorder, HIV or on immunosuppressive therapy), results of these assays do not have to be comparable (28). Kobashi et al. showed that immunocompromised patients had negative skin test and positive IGRA test result (23), which is also the case in our study. Therefore, in individuals with impaired immunity, *in vivo* and *ex vivo* assays do not have the same diagnostic value as in healthy individuals. This case report confirms the foregoing statement. It showed false negative skin test result and positive IGRA test result. Such outcome confirmed that, in spite of type 1 diabetes over many years, the IFN-γ releasing reaction toward specific tuberculosis antigens is still preserved. At the same time, by examining cell immunity by IFN-γ determination after phytohemagglutinin-mediated lymphocyte activation, we avoided a possible false negative result. Connection between tuberculosis and diabetes mellitus is a fact known for over 2000 years (29). Already in the 5th century, tuberculosis was described as a complication of diabetes mellitus. Diabetic patients are prone to infections (8) and therefore also to *mycobacterium tuberculosis* infection. Although there is not sufficient knowledge about the way diabetes impairs the immune system, it seems that this weak immune ability can be attributed to hyperglycemia (30). A study conducted on diabetic mice infected with *M. tuberculosis* (31) and investigation of the IFN-γ role in individuals suffering from diabetes mellitus also pointed to this causal connection (32). Diabetic mice had inflammatory changes in lungs and at the same time lowered IFN-γ production (31), and individuals with diabetes mellitus were prone to tuberculosis because of IFN-γ deficiency needed for initial growth inhibition of *M. tuberculosis* (32). Hence we can conclude that, in order to detect low IFN-γ production and consequent susceptibility to active tuberculosis, *ex vivo* IFN-γ assay should be included in the annual check-up of our subject.

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