Fever of unknown origin in a Swiss-born child: don't miss tuberculosis!

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Abstract

Tuberculosis incidence is low in Switzerland. We report here on a Swiss-born toddler. Tuberculosis manifested with a fever of unknown origin, mimicking an inflammatory or autoimmune disorder triggering a high dose of corticosteroid treatment. The disease went unrecognized for several weeks until development of a miliary tuberculosis with advanced central nervous system involvement. This case highlights the difficulties encountered in diagnosing tuberculosis and in identifying the origin of this case. It reminds us that this disease must never be forgotten when facing a child with persistent fever who must be screened for, before starting immunosuppressive therapy.

Case Report

This boy was in excellent general condition until 23 months of age when he started presenting daily bouts of fever without localizing signs. The fever subsided with no antimicrobial therapy after 10 days. The spontaneous clinical resolution precluded further investigations despite elevated inflammation parameters (CRP 60 mg/L, ESR 40 mm/h, hemoglobin 10^9 g/L, leukocyte count 11.8 G/L). The fever bouts recurred twice in the following three months. The third recurrence did not resolve spontaneously. Recurrences came along with some fatigability and a history of transient limp while rising up in the morning suggesting arthritis, as well as a transient ill-defined skin rash concomitant with a fever peak. Investigations performed at this time (chest X-ray, imaging study of the hip and abdomen, serology screening) turned out normal except the chest x-ray showing a diffuse micro-nodular infiltrate consistent with a viral bronchial infection (Figure 1). No other significant signs were reported over the entire period, in particular no weight loss, no cough and no alteration of his general condition. Inflammation parameters were still elevated (CRP 43 mg/L, ESR 40 mm/h, hemoglobin 97 G/L with microcytosis, leukocyte count 14.5 G/L with 63% neutrophils).

Taking into account the long history of recurrent daily bouts of fever, the history of limp and transient skin rash temporally related to a fever peak, and the ongoing inflammatory process, a systemic type of juvenile idiopathic arthritis was suspected and a steroid therapy started then (600 mg/m^2 methylprednisolone for 3 days by the IV route, then prednisone 2 mg/kg/day orally). However, the fever did not abate at all and, on the 10th day of therapy, the steroid drug was stopped and the child was admitted for investigation in our institution. Early results suggested a miliary form of tuberculosis (mediastinal adenopathies and extensive pulmonary micronodular infiltrate (Figure 2) on the thoraco-abdominal computed tomography-scan; enhanced captation of the left knee capsule (vascular phase) of the distal part of the left femur and captation of the proximal end of the left tibia and humerus (tissular and late phase) on the bone scintigraphy; acid-fast bacilli on a bone marrow sample). An antituberculous treatment was started with a combination of four antimicrobial drugs (isoniazide 5 mg/kg/d, rifampin 10 mg/kg/d, ethambutol 15 mg/kg/d and pyrazinamide 25 mg/kg/d). Along with the beginning of the treatment, the child's condition deteriorated on the 2nd hospital day as he developed a right-sided hemiparesis and showed a decreased level of consciousness. The cerebral imagery showed additional signs consistent with miliary tuberculosis (communicating hydrocephalus, multiple granulomas and multiple ischemic lesions (Figure 3). The cerebrospinal fluid (CSF) pressure was high (50 mmHg) on lumbar tapping and the fluid analysis revealed numerous acid-fast bacilli, an elevated protein (858 mg/L) and lactate (6.2 mmol/L) content, a low glucose content (1.2 mmol/L), and a high white blood cell count (13/mm^3, 57% granulocytes). The *Mycobacterium tuberculosis* complex PCR performed on the CSF sample was positive (10'000 copies/ml), as well as the CSF culture and the T-spot TB® test (133 SFU/mio cells) in a later stage. Eventually, *Mycobacterium tuberculosis* was proven to be sensitive (absence of mutations within the rifampin–resistance determining region of the *rpo*B gene and satisfactory response in regular susceptibility tests to all antimicrobial used). Initially, considering that the child had no major alteration of consciousness in spite of the cerebral edema, a ventricular derivation device did not seem necessary and a steroid treatment (4 mg/kg/d) was started instead. However, on the 3rd hospital day, the child developed seizures requiring an anticonvulsive therapy as well as decreased consciousness. Concomitantly, the cerebral imagery evidenced increased hydrocephalus and a ventricular derivation device was inserted to drain CSF and monitor the intracranial pressure. In addition to the above-mentioned neurological signs, the child presented a left Horner's syndrome and an extensive bilateral chorioretinitis with macular involvement in the left eye. The external ventricular derivation device was withdrawn on the 9th hospital day and the child progressively recovered from his neurological impairments while on rehabilitation therapy. He still showed residual signs of hemiparesis and a moderate aphasia at the time of discharge and some degree of permanent visual impairment was anticipated in the left eye owing to the persistent macular lesion.

Discussion

This case raises quite a few of issues, and leaves some of them unanswered.

First, the risk of tuberculosis was underestimated. Data from the Swiss public health office indicate that the incidence of new cases of tuberculosis is around 7/100,000 population with more than 80% of cases observed in young migrant adults and the remainder in elderly Swiss-born individuals reactivating an ancient infection. Based on these observations, the common opinion is that children born into non-migrant families residing in Switzerland are essentially unconcerned by the risk of tuberculosis unless exposure is

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Key words: fever, Swiss, tuberculosis.

Contributions: MC, BV, contributed equally to this work.

Acknowledgments: the authors would like to thank Dr J. Cotting, Dr S. Lebon and Dr C. Pollo for kind support and advices.

Received for publication: 15 December 2011.
Revision received: 7 February 2012.
Accepted for publication: 9 February 2012.

Clinics and Practice 2012; 2:e36
doi:10.4081/cp.2012.e36

clearly identified. In the present case, the chest X-ray obtained rather early in the fever period is suggestive of a miliary tuberculosis but initially not interpreted as such. The moderately elevated ESR was probably not sufficiently taken in account. However, ESR has been proven to be of little value in diagnosing tuberculosis; the range of value of ESR is wide and its elevation has little significant value in tuberculosis in children.[1] Even though the possibility of tuberculosis is indeed thought of as a differential diagnosis, it is not seriously considered given: i) the child's Swiss household conditions; ii) the absence of recognized exposure to tuberculosis; iii) and the regional epidemiological conditions in fall and winter characterized by plenty of benign respiratory viral infections rather than tuberculosis.

Second, this case highlights the difficulties in identifying the source of tuberculosis transmission. Children are known to be *sentinels* of recent adult infection. A pediatric case of tuberculosis, such as ours, indicates a failure in the prevention and control of tuberculosis in the population. Household exposure to a source case is a frequent and high risk factor of transmission to children, particularly to those younger than 2 years of age.[2] Consequently, when a pediatric case is identified, searching for a source case within the household is of paramount importance in order to protect other children living in the same environment. In our country, individuals at high risk of developing tuberculosis are the migrant population and comprise adults who recently arrived from a high endemic area (regardless of their legal status) and children born to such adults or in contact with them. The latter also applies to children having a parent from a high endemic area. Contact with individuals from these countries is indeed a risk of tuberculosis transmission, particularly in children less than 6 years of age.[3] In Switzerland, it is recommended that a detailed history, a complete physical examination, and a tuberculosis-screening test (tuberculin skin test or interferon-α releasing assay in BCG vaccinated children) be performed in individuals belonging to the at-risk population or having a history of contact with tuberculosis. In addition, a chest X-ray is indicated whenever the person is symptomatic, or has a definite contact history, or shows a positive tuberculosis-screening test. The search for *Mycobacterium tuberculosis* in respiratory secretions or gastric fluid is recommended on individuals showing clinical signs compatible with tuberculosis or an abnormal chest-X ray. In the present case, health authorities ordered a contact enquiry aimed at all pediatric and adult contacts of the sick child (children attending the same day care center, family members, acquaintances, day care center personal). None of the contacts was found to have an active and contagious tuberculosis disease. A young adult, undocumented migrant from South America, announced himself spontaneously to health authorities as he was a neighbor of the family and was coughing for many months. Active pulmonary tuberculosis was diagnosed. Another possible source of contamination might be a 4-weeks travel of the family across Argentina one year earlier. However, the child's parents have no recollection of dealing with someone they would suspect of having tuberculosis. Molecular typing of both isolates seemed to be different.[4,5] In conclusion, we have at this stage no idea of where, when and how this child got infected while living in a low endemic area and seemingly away from at-risk populations.

Third, control of tuberculosis is a challenge in undocumented migrants. In the present case, the concerned undocumented migrant can be exonerated from being the source case of tuberculosis since his isolate of *Mycobacterium tuberculosis* and that of the

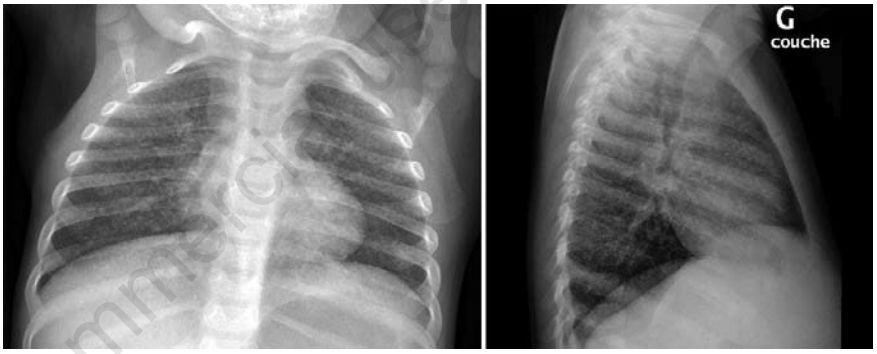

Figure 1. Full-face chest X-ray: bilateral micronodular parenchymal lesions. Profile: diffuse micronodular opacity including anterior mediastinum.

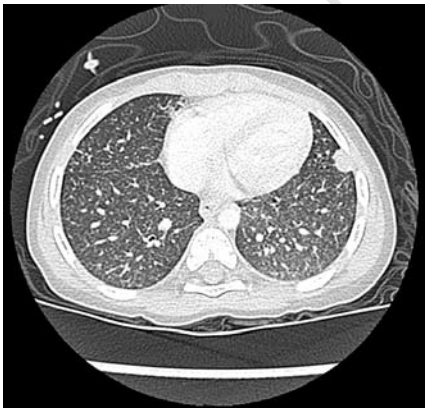

Figure 2. Thoracic computed tomography-scan: diffuse bilateral micronodular infiltrate; one nodular lesion (diameter: 1 cm).

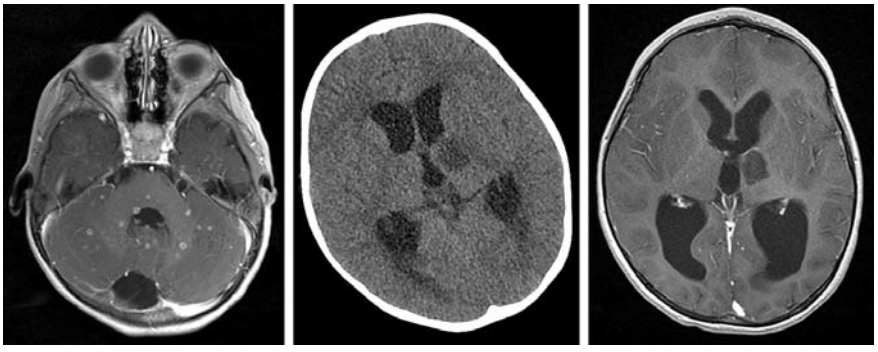

Figure 3. Left Panel) multiple contrast-enhanced nodular lesions of the whole encephalus on T1 sequence cerebral magnetic resonance imaging (MRI). Central Panel) Cerebral computed tomography-scan demonstrating enhancing hydrocephalus and hypodense lesion of left thalamic region two days later. Right Panel) Evolution after 7 weeks of antituberculous and steroids therapy: disappearance of nodular lesions, persistence of hydrocephalus and thalamic ischemic lesion on T1-weighted + gadolinium MRI.

child are genetically different. However, tuberculosis control is obviously quite a challenge in this population. First of all, because of their illegal status, undocumented migrants escape the tuberculosis screening set up for legal migrants. Then, for socioeconomic reasons, they tend to have a restricted access to medical care because of lack of health insurance coverage. In Switzerland, illegal migrants represent a significant proportion of the resident population (1-2% of the total population) and most of them come from high endemic countries. They represent a potential source of uncontrolled disease transmission and efforts must be continued to adequately control tuberculosis in such a vulnerable population.[6]

Forth, steroid therapy was inappropriate. This child was given a steroid therapy for a presumed juvenile idiopathic arthritis while developing a tuberculosis disease. As immunosuppressive drugs are known to be risk factors for tuberculosis disease extension,[2] the steroid therapy is very likely to have accelerated and/or amplified the process. However, it might be argued that the rapid clinical deterioration secondary to prednisone therapy prompted diagnostic procedures within a short time frame allowing identification of the disease and the starting of an adequate antimicrobial treatment possibly earlier than if the natural course was sole at play. It can be argued whether the inadvertent steroid drug had a downmodulating effect on the growing cerebral edema accompanying the miliary infection in the brain. The close temporal relation is striking between the cessation of the prednisone therapy and the onset of clinical manifestations of increased intracranial pressure.

Fifth, the delay in diagnosis leads to serious neurological consequences. Tuberculosis is associated with serious acute manifestations and long-term sequelae in case of central nervous system involvement. In addition, according to US and British guidelines, a cerebral involvement implies a much longer duration of antimicrobial therapy. Mortality rate of tuberculous meningitis is high (20-50%); poor outcome predictors are young age, stage of disease at presentation and specific pattern of distribution of ischemic lesions.[7] Hydrocephalus is a common complication (70%) and 4 out of 5 cases present with a communicating type.[8] Medical and/or surgical treatments are well recognized to improve the clinical outcome but the most effective therapy of hydrocephalus is not determined yet. There are reports that early surgery should be reserved for those with obstructive hydrocephalus whereas medical therapy should be tried initially in those with a communicating form of hydrocephalus.[9] However, a ventricular derivation device should be inserted promptly in the face of decreasing consciousness or increasing hydrocephalus on imagery. According to the latest Cochrane review, mortality and long term sequelae are decreased in HIV negative children when steroid therapy is used.[10] In the present case, cerebral lesions had almost disappeared after 7 weeks of anti-tuberculous and steroids treatment (Figure 3). After 6 months of evolution, the child recovered most of his hemiparesis but still had features of behavioral disturbances and aggressiveness, which may be attributed to cerebral lesions. Close neurological follow-up is needed to determine cognitive and neurological development.

Pulmonary tuberculosis is quite rare in the Swiss-born pediatric population and miliary tuberculosis even more so. The present case is indeed the only one recorded over recent decades in our institution. However, it is proof that tuberculosis can be transmitted to Swiss-born children without known contact with an at-risk population. That reminds us that the suspicion of tuberculosis must not be rejected without further ado in a Swiss-born child on ground that Switzerland is a low incidence country. Tuberculosis should be systematically considered in children with fever of unknown origin and screening performed with a tuberculin skin test or an interferon-α-releasing assay. Tuberculosis should also be systematically screened for in all children about to start an immunosuppressive therapy since immune suppression and young age are well recognized risk factors for the rapid development of disease in children with a latent tuberculosis infection,[2] particularly so among children less than 2-3 years old.

Conclusions

Tuberculosis remains a major public health problem worldwide, and HIV infection or multiple drug resistant tuberculosis present major challenges for the control of this disease.[11,12] Paradoxically, in low incidence areas such as Switzerland, the risk of childhood tuberculosis tends to be overlooked with delays in diagnosis and adequate therapy. This case report reminds us how important it is to consider tuberculosis whenever facing a young child with fever and unspecific signs or symptoms.

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