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 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/m² 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 capture of the left knee capsule (vascular phase) of the distal part of the left femur and capture 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), a low glucose content (1.2 mmol/L) and a high white blood cell count (15/mm³, 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® 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 rpoB gene and facto- r 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 anti-convulsive 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
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-\(\alpha\) 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 \textit{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 \textit{Mycobacterium tuberculosis} and that of the

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**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, tuberculo-
sis 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 cover-
age. In Switzerland, illegal migrants represent
a significant proportion of the resident popula-
tion (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 con-
tinued to adequately control tuberculosis in
such a vulnerable population.  \(^6\)

Forth, steroid therapy was inappropriate.
This child was given a steroid therapy for a pre-
sumed juvenile idiopathic arthritis while devel-
oping a tuberculosis disease. As immunosup-
pressive 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 sec-
ondary to prednisone therapy prompted diag-
nostic procedures within a short time frame
allowing identification of the disease and the
starting of an adequate antimicrobial treat-
ment 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 accompa-
nying 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 nerv-
ous system involvement. In addition, according
to US and British guidelines, a cerebral
involvement implies a much longer duration of
antimicrobial therapy. Mortality rate of tuberc-
ulous meningitis is high (20-50%); poor out-
come predictors are young age, stage of dis-
ease at presentation and specific pattern of
distribution of ischemic lesions.  \(^7\) Hydroce-
phalus 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 out-
come but the most effective therapy of hydro-
cephalus is not determined yet. There are
reports that early surgery should be reserved
for those with obstructive hydrocephalus
whereas medical therapy should be tried ini-
tially in those with a communicating form of
hydrocephalus. \(^9\) However, a ventricular deriva-
tion device should be inserted promptly in the
face of decreasing consciousness or increas-
ing hydrocephalus on imaging. 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 disap-
peared 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 behav-
ioral 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 tuber-
culin skin test or an interferon-\(\gamma\)-releasing
assay. Tuberculosis should also be systemati-
cally 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 dis-
ease 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 multi-
ple 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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