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TEACHING FILES (GRAND ROUNDS)

POSITIVE INTERFERON-GAMMA RELEASE ASSAY RESULT IN A CHILD LESS THAN TWO YEARS OF AGE: HOW TO INTERPRET?

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Clinical Problem:
A 6-month-old boy presented in July 2024 with a right knee swelling and an inability to extend the right knee for 2.5 months. The swelling developed 10 days after receiving the Pentavalent vaccine in the right thigh. There was no history of fever, weight loss or loss of appetite. There is no history of tuberculosis (TB) contact. The patient had taken one month of oral cefaclor prior to presentation and did not report any improvement in the swelling size. On presentation, his weight was 7.2 kg (between 15th and 25th percentile according to the World Health Organisation (WHO) growth charts). On examination, a right knee fixed flexion deformity of 20 degrees was found. The range of knee flexion beyond 20 degrees was full and was painful up to 140 degrees of motion. The range of motion of both hips was normal. Magnetic resonance imaging (MRI) of the right knee showed mild effusion, moderate synovial thickening, irregularity of the articular surface of the unossified lateral femoral condyle and enlarged popliteal lymph nodes (7 x 6 mm). Ultrasound of both hips was normal. Other investigations are shown in Table 1. Ocular examination was normal. Synovial biopsy was advised but was not done. The patient was advised naproxen syrup and asked to follow-up after 4 weeks. At the 4-week follow-up, there was a decrease in the size of the swelling clinically and ultrasound showed a mild effusion with internal echoes and extension into the suprapatellar recess. The 3-tube Interferon-gamma release assay (IGRA) sent in August 2024 at an outside centre was positive with a titre of 1.39 IU/ml. Chest X-ray was normal. Naproxen was stopped and the patient was advised a repeat right knee ultrasound after 2 weeks. After 2 weeks, the right knee ultrasound showed no evidence of synovial effusion or thickening. The patient was not started on antitubercular treatment and was instead asked to follow-up after 2 months with a right knee ultrasound and IGRA testing. The follow-up ultrasound showed no joint effusion or thickening. IGRA was not done. The patient was advised to follow-up every three months with a right knee ultrasound.

How to interpret IGRA results in a child less than 2 years of age?

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Discussion:
There are two tests which can be used to diagnose latent tuberculosis (LTB), namely, IGRA and tuberculin skin test (TST) or Mantoux test.[1] TST is the historical standard, however, IGRA has been shown to have comparable sensitivity to TST in both adults and children. In regards to specificity, IGRA outperforms TST in both adults and children. This is due to the cross-reactivity of tuberculin antigen in patients sensitized by Bacillus Calmette-Guerin (BCG) and in patients with nontuberculous mycobacterial infections, particularly with Mycobacterium avium complex in the Mantoux test.[2] However, IGRA use in children less than 5 years of age and especially in children less than 2 years of age, has not been studied in detail. Current WHO guidelines recommend using either IGRA or TST for testing in children, however, they do not make any distinction in their recommendation based on the age of the child.[3] Current consolidated American Thoracic Society, Infectious Disease Society of America and Centre for Disease Control and Prevention guidelines recommend IGRA testing over TST in all children 5 years or older who are likely to be infected with *M. tuberculosis* (MTB), require testing for LTB, have a low-intermediate risk of progression of disease, and have undergone BCG vaccination or are not unlikely to return to have their TST interpreted. TST may be performed instead depending on the availability and affordability of IGRA.[1] However, in children less than 5 years of age in whom LTB is likely to progress to active TB, the guidelines recommend performing a TST rather than IGRA.[1] Even in situations where IGRA may be preferred as the diagnostic test by clinicians, current guidelines do not recommend using the test in children less than 3 years of age.[1] The American Academy of Pediatrics also recommends the use of TST over IGRA in children less than 2 years of age.[4] While recent studies have shown a high degree of concordance between IGRA and TST-results in children less than 2 years of age, several factors hinder the widespread use of IGRA in this age group. A high proportion of indeterminate (up to 35%) and invalid results have been reported in children less than 2 years of age.[1] This is believed to be due to younger children being unable to develop a sufficient immune response for achieving an adequate positive control, thus leading to the reporting of indeterminate or invalid results. This issue may be further compounded in immunocompromised children who would be unable to mount a sufficient immune response.[5] In addition, technical issues such as difficulties in phlebotomy, hinder the use of

Table 1. Investigations of the patient.

Parameters	Patient's Values	Reference Range
Hemoglobin (gm/dL)	9.1	11.5-15.5
TLC (cells/cumm)	7950	5000-13,000
ANC (cells/cumm)	1638	2000-8000
ALC (cells/cumm)	5780	1000-5000
Platelets (10^6 cells/cumm)	4.52	1.50-4.50
ESR (mm/hr)	47	<15
CRP (mg/dL)	1	<1

Note: TLC- Total leukocyte count, ANC- Absolute neutrophil count, ALC- Absolute lymphocyte count, ESR-Erythrocyte sedimentation rate, CRP- C-reactive protein.

IGRA in this age group.[1] The studies reporting on the use of IGRA in children less than 2 years of age, were largely performed in non-endemic countries, in immunocompetent children, and their results were inconsistent, thus resulting in the conditional recommendation of TST over IGRA in this age group.[1] However, despite this, our patient had undergone an IGRA test at an outside centre which was found to be incidentally positive. This begs the question of whether this asymptomatic child, without any evidence of active TB disease, should receive treatment for latent TB in view of the IGRA results? Considering the high sensitivity of IGRA, this result is unlikely to be falsely positive. IGRA titres are known to increase over time with progression to active disease, and as the child had no history of TB contact and had radiologically documented resolution of disease, we decided to repeat IGRA testing to check for conversion to negative results or persistent positive results, rather than start antitubercular therapy for LTB.

Compliance with Ethical Standards

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Conflict of Interest None

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