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ROLE OF CBNAAT IN DIAGNOSIS OF TUBERCULAR SYNOVITIS

Orthopedics

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ABSTRACT

Aim: The aim of the present study was to assess the role of CBNAAT in early diagnosis of tubercular synovitis. **Methods:** A prospective cohort study was conducted among 30 patients attending OPD with sign and symptoms of non resolving unilateral synovitis of shoulder, wrist, hip, knee, ankle and elbow with failure of conservative treatment for 6 weeks. An informed and valid consent from the patient for arthroscopic guided synovial biopsy was taken. **Results:** Mean age was 36.1 years. Male: female ratio was 1: 0.8. Fever (70 %) & joint pain (96.6 %) were the most common symptoms. Hip joint (26.7%) was the most common involved joint. Sensitivity, specificity, PPV, NPV of CBNNAT in comparison with histopathology confirmation of extra pulmonary TB was 95.0%, 100.0%, 100.0%, 90.9% respectively. **Conclusion:** Extrapulmonary tuberculosis cases pose diagnostic challenge and its diagnosis cannot be relied on single test. CBNAAT detects TB in HIV patients with greater efficacy than ZN smear microscopy, both in PTB and EPTB. It gives early diagnosis in less than 2 hours. CBNAAT assay is a rapid test which identifies both the presence of Mycobacterium tuberculosis (with high sensitivity, specificity, positive predictive value and negative predictive value) and resistance to rifampicin in a single test. Thus, it decreases delayed or misdiagnosed cases, contributing to early start of treatment and thus decreasing the morbidity and mortality rates. It also detects rifampicin resistance and can be used for screening for MDR-TB.

KEYWORDS

CBNAAT, Extra-pulmonary TB, Histopathology, Sensitivity, Specificity

INTRODUCTION

Tuberculosis (TB) is still a major public health issue with significant social and economic consequences, especially in developing nations. India alone contributed the most to the worldwide burden of tuberculosis, accounting for 28% of the total TB cases.[1] Tuberculosis is caused by the bacteria Mycobacterium Tuberculosis (MTB). It is mainly transmitted through droplet infection from an open case of pulmonary tuberculosis. Mycobacterium Tuberculosis primarily affects the lungs, but can also affect other extrapulmonary organs.[2]

Extra pulmonary tuberculosis (EPTB) affects tissues and organs other than the pulmonary parenchyma and it contributes to 10–15% of total tuberculosis cases in India.[3,4] Extrapulmonary tuberculosis (EPTB) is caused by the hematogenous and/or lymphatic spread of MTB bacilli. Tubercular lymphadenitis (TBLN) is the most frequent form of EPTB tuberculosis, accounting for 20 to 40% of all cases followed by pleural tuberculosis which is the second most common form of EPTB after TBLN, accounting for 15 to 20%.[5]

Diagnosis of EPTB is sub-optimal in rural health facilities of developing countries. In developing countries, the diagnosis of EPTB remains a major diagnostic challenge due to the difficulty of acquiring samples for testing and experienced specialists for sampling. Fine needle aspiration cytology (FNAC) is an important tool in addressing these concerns and it is a quick diagnostic procedure due to its ease of use, low cost, rapid availability of results, accuracy, and minimal invasion. However, the laboratory diagnosis of EPTB has always been a challenge as invasive procedures may be required to obtain the required sample for analysis.[6]

Feasibility and acceptability of biopsy are limited for non-approachable sites of EPTB. There are several diagnostic tests for diagnosis of EPTB but most of the tests do not provide microbiological confirmation of MTB in case of low bacillary load and non-uniform distribution of microorganisms. Mycobacterial culture is the gold standard for tuberculosis diagnosis, but results can take up to eight weeks or longer which may further lead to delay in diagnosis and treatment. Due to the limitations of these tests for the diagnosis of EPTB, the role of the cartridge-based nucleic acid amplification test (CBNAAT) has been evaluated in several studies.[7] CBNAAT also tests for resistance to one of the most effective anti-tubercular drugs, i.e., rifampicin. The efficacy of CBNAAT for tuberculosis detection in extrapulmonary specimens has been found highly variable due to a very wide sensitivity range in different studies.[8]

The aim of the present study was to assess the role of CBNAAT in early diagnosis of tubercular synovitis.

MATERIALS AND METHODS

A prospective cohort study was conducted at the orthopedic department of MMMCH, Kumarhatti, Solan, Himachal Pradesh, India for the period of 12 months (June 2021-May 2022). Routine patients who presented to the Outpatient Department (OPD) of orthopaedics with signs and symptoms of unilateral synovitis.

Inclusion Criteria :-

- Non resolving unilateral synovitis of shoulder, wrist, hip, knee, ankle and elbow.
- Failure of conservative treatment for 6 weeks

Exclusion Criteria: -

- Septic Arthritis
- Consent not given

Detailed History and clinical examination was done. Demographic data including age, sex, socio-economic statutes, rural or urban background was obtained. Past history of Tuberculosis/contact with a TB patient was noted.

Routine blood investigations were done.
Radiological assessment of the lesion along with chest X ray (PA view) was done for all the patients. X ray was done for patients with neck swelling. CT scan/MRI was done for few selected patients subjected to their requirement and availability of resources.

Sputum, if present—ZN staining

During operative procedure among study subjects, 2 biopsy sample

collected for
1. One for histopathological confirmation and
2. Second for CBNAAT confirmation
After that, sensitivity, specificity, PPV, NPV of CBNNAT was compared with histopathological results.

The tissue was also analyzed by CBNAAT on XpertMTB/RIF manufactured by Cepheid endorsed by WHO (2010). It was performed according to the manufacturer's instructions [CEPHEID, Sunnyvale, CA, USA].

Detection of mycobacteria and rifampicin resistance was carried-out in the same setting.

Rifampicin resistant samples were further analysed by LPA. The three steps for LPA test included DNA extraction, multiplex polymerase chain reaction (PCR) amplification and reverse hybridisation.

Culture on solid media (Lowenstein–Jensen).

Procedure of Arthroscopic Guided Synovial Biopsies(AGSB):
AGSB's are performed in a dedicated facility, within the hospital's operation theatre complex of Maharishi Markandeshwar Medical College & Hospital.

Patient's change into hospital gowns in the ward and usually an intravenous cannula is sited. Cannulation facilitates phlebotomy, for both research bloods and the hospital laboratory to process relevant hematological and biochemical indices. The joint that is to be the site of sampling is marked with a skin marker. We start by switching the arthroscopy tower on, and by ensuring that both the camera and the light source are working. Patient's hospital identification and knee laterality is inserted for image capture. Karl Storz, Germany, equipment are used. A 2.7mm needle arthroscope is used. The operator scrubs and gowns using standard techniques.

All surgical instruments and the Karl Storz hardware kit which contain arthroscopy telescope, trocars, forceps are assembled in sterile packs and opened on a sterile draped table. In addition, sterile gauzes, syringes, needles, infusion system, sterile bowls and sterile drapes are opened by the theater nurse, received by the operator, and placed on the table. Chlorhexidine and sterile water are poured by the nurse into the sterile bowls on the table. A 20ml syringe is filled with lignocaine 2%, The local anesthetic products and expiry dates are checked by both the nurse and the operator. Before proceeding any further, a deliberate pause is undertaken to complete a reviewed "WHO Surgical Safety Checklist" for this procedure. Amongst the most important items on the list are a check that we have the correct patient, that the correct knee has been labeled, and that equipment has been arranged for this knee to be biopsied, as well as a final check to confirm the consent form has been completed, and that the patient is not on anti-coagulants/anti-aggregants, and an allergy check.

According to joint involved, standard approaches are followed. Example in case of knee:
A disposable sterile sheet is placed under the lower limb and the leg is raised to 45 ◦, with the assistance of the nurse who holds the patient's heel up. Sterile gauze is held in a pair of forceps and soaked in chlorexidine. The knee is sterilized by swabbing in ever widening circles from the lateral aspect of the knee, where the two small incisions will be made. The area from mid-thigh to mid-calf is disinfected circumferentially. A sterile sleeve closed at one end is placed over the foot and extended the length of the leg with care taken not to contaminate the cleaned field. The leg is next inserted through the fenestration in a sterile drape and the drape advanced to the hip. The two corners of the drape closest to the cephalic end are risen and attached to drip stands either side of the bed. This occludes the patient from inadvertently touching the sterile field. A sterile gauze bandage is applied circumferentially around ankle (which is covered by the sleeve). A window large enough to access the antero-lateral aspect of the knee is cut out of the sterile sleeve using a pair of scissors, taking care not to injure the skin.

The anatomical landmarks must now be identified. The knee is placed in 30–45 degrees flexion. Following palpation, a tissue marker can be used to delineate the lateral border of the infrapatellar tendon, the infero-lateral aspect of the patella, the anterolateral border of the tibial plateau, and the infero-lateral surface of the lateral epicondyle. The center of these markings is the site of entry for infero-lateral port. The landmark for the supero-lateral port is 1 cm above and 1 cm lateral to the supero- lateral aspect of the patella, the site used commonly for intra- articular injections. The joint capsule, soft tissues and skin is infiltrated with 10 ml of lignocaine 2%, for what will become the superior-lateral port site and the inferior-lateral port site. About 2–5 min is given to allow for this to take effect. Arthrocentesis is performed using a 21G needle, attached to an empty 10/20ml syringe through the site of the prospective supero-lateral port and synovial fluid is drained until no further fluid can be removed. Obtaining synovial fluid at this point gives high assurance that the tip of the needle is indeed in the joint cavity. Any synovial fluid removed is carefully placed on the sterile drape covered table. If no fluid can be removed, special care must be taken in the next steps.

The needle is left in situ while the syringe is detached. The 20 ml bupivacaine containing syringe is attached to the needle. There should be little or no resistance to the plunger advancing. If the operator encounters resistance, especially where no synovial fluid was obtained, the needle may be misplaced and may require adjustment. After placement of the bupivacaine into the joint cavity, the needle is left in situ and a further 2–5 min is given to allow the bupivacaine to take effect. In the next step, the empty syringe is detached from the needle and the 50 ml syringe containing sterile water is attached to the needle. The contents of the syringe are placed into the joint until resistance is felt. Typically, a joint will accommodate up to 60 ml more fluid. With the knee in a 30–45 degree flexed position, a scalpel is used to make a 1 cm incision in the infra-lateral patella space previously delineated, extending to the joint capsule. The trocar is introduced through the incision using blunt dissection into the joint cavity. It is imperative not to force the trocar if resistance is met. Once in situ, the trocar is removed, leaving the port in position, and the rigid camera is inserted through the infero-lateral port. The cavity of the knee joint can now be inspected. To establish the second port required to allow AGSB, the camera is placed such that it points toward to area where the superior-lateral port will be positioned. This can be found by using a finger to exert pressure over the site, and the operator can see the depression made by this action within the joint on screen. Once again, a scalpel is used to make a 1 cm incision extending to the joint capsule and then blunt dissection using a trocar allows the second port be sited. Sterile saline via a drip is connected to the camera port, and a drain connected to the grasper port with tubing to a basin or collection bag. A rigid grasper is inserted through the supero-lateral port and synovial biopsies can be collected under direct visualization. The biopsies are placed on saline soaked gauze. We check for any bleeding after biopsy collection and complete an effective joint lavage-usually approximately 1,500 ml thought the procedure. The superolateral trocar is removed after draining all the fluid from the joint. This is followed by the administration of 8ml of bupivacaine intra-articular to allow a sustained anesthetic benefit. The infrapatellar port (and camera) is removed. The two port sites are wiped clean, and single stich at each portal are applied to each incision. We next apply a small square dressing to each incision and apply a waterproof patch. Now the sterile drapes and sleeve are removed, and the knee is wrapped firstly with a cotton wool bandage and then with a crepe bandage.

Data Analysis: Collected data has been entered in the excel data sheet and data analysis has been done with the help of Epi. Info.7.2 software.

RESULT

Table 1: Patient Characteristics

Age Group (in year)	Number	%
18-30	10	33.3
31-45	8	26.7
46-60	7	23.3
>60	5	16.7
Mean ± SD	36.1 ± 7.3	
Gender		
Male	17	56.7
Female	13	43.3
Residence		
Urban Rural	7 23	23.3 76.7
Investigation	**TOTAL Number**	**Positive for EPTB**
HITOPATHOLOGY	30	20
CBNAAT	30	19

Out of 30 total patients, 10 patients (33.3%) were between 18-30 years of age, 8 patients (26.7%) were between 31-45 years of age, 7 patients (23.3%) were between 46-60 years of age and 5 patients (16.7%) were of age more than 60 years. The mean age of the patients was 36.1_+7.3 years. Out of 30 patients 17 patients (56.7%) were male and 13 patients (43.3%) were female. The ratio of male is to female patients were 1:0.8. Out of 30 patients 23 patients (76.7%) were residing in rural areas and 7 patients (23.3%) were residing in urban areas of the state. Out of 30 patients, 20 patients (66.6%) had histopathology report positive for EPTB and 19 patients (63.3%) had CBNAAT report positive for EPTB.

Table 2: Sign/symptoms Among Study Participants

Sign/symptoms	Number	%
Joint pain	29	96.6
Fever	21	70
Loss of weight	5	16.7
Headache	3	10.0
Dysuria	2	6.7
Weakness	3	10.0
Cough	6	20.0
Loss of appetite	2	6.7
Breathlessness	3	10.0
Chest pain	7	23.3

In the study most common system with which the patient presented were joint pain. 29 patients (96.6%) had complaint of joint pain. 21 patients (70%) had fever , 5 patients (16.7%) had loss of weight , 3 patients (10%) had headache , 2 patients (6.7%) had dysuria , 3 patients (10%) had cough , 2 patients (6.7%) had loss of appetite , 3 patients (10%) had breathlessness and 7 patients (23.3%) had chest pain.

Table 3: Joint Involved Among Study Participants

Joint Involved	Number	%
Hip	8	26.7
Knee	6	20.0
Elbow	6	20.0
Ankle	4	13.3
Wrist	3	10.0
Shoulder	3	10.0

The most common joint involved in the present study was hip joint in 8 patients (26.7%) followed by hip joint knee joint in 6 patients (20%), elbow joint in 6 patients (20%), ankle joint in 4 patients (13.3%), wrist joint in 3 patients (10%) and shoulder joint in 3 patients (10%).

Table 4: Sensitivity, Specificity, NPV, PPV Of CBNNAT vs Histopathology

CBNNAT	Histopathology		Total
	Positive for EPT	Negative for EPT	
Positive for EPTB	19	0	19
Negative for EPTB	1	10	11
Total	20	10	30

Sensitivity = 19*100/20 = 95.0% Specificity = 10*100/10 = 100.0%
PPV = 19*100/19 = 100.0%
NPV = 10*100/11 = 90.9%

The above table shows that the sensitivity of CBNAAT to diagnose tubercular synovitis in comparison to histopathology according to present was 95.0%, specificity was 100%, PPV and NPV was 100% and 90.9% respectively.

DISCUSSION

A total of 1,500,000 people died from TB in last many years. Worldwide, TB is the thirteenth leading cause of death and the 2nd leading infectious killer after COVID-19. In 2020, an estimated 10,000,000 people fell ill with TB worldwide. TB is present in all over world in all populations. But TB is curable and preventable. In 2020, 1.1 million children fell ill with TB globally.[9] Almost eighty six percent cases of new tuberculosis were registered in thirty high burden countries, with India leading the count.[9] According to WHO estimates, around 2.7 million people developed TB in India and over 400,000 people died due to TB in the year 2017.[10] By WHO estimates, India accounts for 27% of the global estimated 10 million cases and 25% of the estimated 1.6 million deaths. The global burden of disease analysis estimated the number of incident cases to be 3 million people in the year 2016.[11] A study based on data from the National family Health Survey (NFHS-4) estimates that the self-reported incidence of TB in India is 304/100,000.[12]

Out of 30 total patients, 10 patients (33.3%) were between 18-30 years of age, 8 patients (26.7%) were between 31-45 years of age, 7 patients (23.3%) were between 46-60 years of age and 5 patients (16.7%) were of age more than 60 years. The mean age of the patients was 36.1_+7.3 years. Present study found that highest number of participants (33.3%) was belonged to age group 18 to 30 years followed by 31 to 45 years (26.7%). A study done by Raj A et al[13] had noted mean age was 52 years. Out of 30 patients 17 patients (56.7%) were male and 13 patients (43.3%) were female. The ratio of male is to female patients were 1 : 0.8 .According to study done by Kandi S et al[14] and Bagdi T et al[15] the male:female ratio was 1:0.7 and 1:0.9 respectively in their studies. In the present study , majority of the patients were from rural areas. Out of 30 patients 23 patients (76.7%) were residing in rural areas and 7 patients (23.3%) were residing in urban areas of the state. A study done by Moore DF et al[16], Pai M et al[17] said that unfortunately, in rural areas there is no rapid test, and culture diagnostics and molecular line probe assays are costly, with inadequate biosafety measures and insufficient trained staff making detection of early TB difficult.

29 patients (96.6%) had complaint of joint pain. 21 patients (70%) had fever, 5 patients (16.7%) had loss of weight, 3 patients (10%) had headache, 2 patients (6.7%) had dysuria, 3 patients (10%) had cough , 2 patients (6.7%) had loss of appetite , 3 patients (10%) had breathlessness and 7 patients (23.3%) had chest pain. Present study found that fever (96.6%) & joint pain (70%) were the most common sign/symptoms noted among study participants followed by chest pain (23.3%). A study done by Bagdi T et al[15] observed that the among the presenting symptoms of the patients, the commonest was fever (98.8%), followed by loss of appetite (93.4%) which is similar to the study conducted by Devi et al[18] and Kumar et al.[19]

Present study found that hip joint (26.7%) was the most common involved joint noted among study participants followed by knee (20.0%) & elbow (20.0%). The sensitivity of smear microscopy and its inability to detect drug resistance limits its impact on TB control. Culture methods and drug susceptibility testing is complex, time consuming, and takes around 6-8 weeks. While patients await diagnosis, they are likely to receive inappropriate or in effective treatment and consequently disease may progress. This results in an increased chance of morbidity from tuberculosis. They continue to transmit drug-resistant TB to others; especially for family members and the resistance might have amplified.[14] A study done by Raj A et al[13] had observed sensitivity, specificity, PPV, NPV of CBNNAT of diagnosis of extra pulmonary TB was 92.6%, 95.7%, 83.3%, 98.3% respectively. A study done by Ioannidis P et al[20] the found the sensitivity and PPV of the CBNAAT was 91.4% and 86.5% respectively.

CONCLUSION

Extrapulmonary tuberculosis cases pose diagnostic challenge and its diagnosis cannot be relied on single test. CBNAAT detects TB in HIV patients with greater efficacy than ZN smear microscopy, both in PTB and EPTB. It gives early diagnosis in less than 2 hours. CBNAAT assay is a rapid test which identifies both the presence of Mycobacterium tuberculosis (with high sensitivity, specificity, positive predictive value and negative predictive value) and resistance to rifampicin in a single test. Thus, it decreases delayed or misdiagnosed cases, contributing to early start of treatment and thus decreasing the morbidity and mortality rates. It also detects rifampicin resistance and can be used for screening for MDR-TB.

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