JMGV004N01

January-March 2017 Volume 4 Number 1

ISSN 2347-7946
eISSN 2347-7962

MGM Journal of MEDICAL SCIENCES

MGMJMS

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The Official Publication of
Mahatma Gandhi Mission Institute of Health Sciences
(Deemed University u/s 3 of UGC Act 1956)
Kamothe, Navi Mumbai, Maharashtra, India

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January-March 2017 Volume 4 Number 1 ISSN 2347-7946

MGM Journal of Medical Sciences

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MGMJMS

January-March 2017 Vol. 4 No. 1

MGM Journal of Medical Sciences

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From the Editors' Desk

Increasing resistance of microorganisms to antibiotics is becoming a cause of great concern globally. We are already witnessing increase in morbidity, mortality, longer hospital stays and greater health care costs of treating patients suffering from infections. World Health Organization (WHO) has rightly taken this problem seriously and in May 2015, a "Global Action Plan for Antimicrobial Resistance" was initiated at the World Health Assembly. Main objectives of this plan were to improve awareness of antimicrobial resistance, strengthening surveillance, reducing incidence of infections and ensuring that antibiotics are used only on prescription by certified health professionals. In November 2015, WHO launched a global campaign titled "Antibiotics: Handle with Care" by celebrating first World Antibiotics Awareness Week. Hopefully, this campaign will yield effective results. Public needs to be made aware that antibiotic resistance is a big threat to global health. Misuse of antibiotics in humans and animals plays a major role in increasing this threat. Antibiotics are, no doubt, life saving drugs, if used judiciously. Their indiscriminate use must be stopped. Only then we can curtail the development of antimicrobial resistance. Health care professionals have a major role to play in putting an end to the ever-growing resistance of microbes to antibiotics, firstly by prescribing them judiciously in accordance with sensitivity reports for correct duration and secondly by educating people against self-use. Though, laws against selling antibiotics by druggists without valid prescriptions exist, these have to be implemented more forcefully.

We are pleased to present this latest issue of MGM Journal of Medical Sciences to our esteemed readers.

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January-March 2017 Volume 4 Number 1

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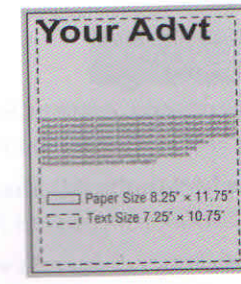

Technical Details

Paper size	8.25" × 11.75"
Text size	7.25" × 10.75"
Digital file format	EPS on CD (at 300 dpi resolution)

Printed on art paper using offset printing.

Schedule

Issues are published in the months of January, April, July and October.
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10.5005/jp-journals-10036-1128

ORIGINAL ARTICLE

Prospective Study of Percutaneous Nephrolithotomy in the Management of Renal Calculi

[1]Nandkishor Raut, [2]Piyush Singhania, [3]Nitin Joshi, [4]Sanish Shringarpure, [5]Saket Sathe, [6]Niraj Tiwari

ABSTRACT

Introduction: Kidney stones are a common problem affecting all population groups across the globe. Percutaneous extraction of renal stone – properly termed percutaneous nephrolithotomy (PCNL) which was invented over three decades ago – has become a standard, well-established procedure for the management of renal stones. This study will evaluate the role of PCNL in the management of renal calculi.

Materials and methods: A total of 107 cases of renal calculi who underwent PCNL from May 1, 2014 to April 30, 2016 were studied. Intraoperative findings and immediate postoperative complications were noted. They were followed up for 1 month after the surgical procedure.

Results: Mean age of cases was 43.64 years. Multiple calculi were seen in 43.9%, while a staghorn calculus was seen in 16.8%. Stone clearance was done through a single tract in 78.5%. Additional tracts were made in 21.5%. Tubeless PCNL was done in 45%; 12.1% of the cases had urinary tract infection. Pulmonary complications were noted in 4.67% in the form of hydrothorax. Urinary leak was noted in 4.6%; 70% of the cases were left stone free, with an overall success rate of 85.98%.

Conclusion: This study reveals that PCNL is a safe procedure with less complications and higher stone-free rates without compromising patient safety in a short period.

Keywords: Minimally invasive, Nephroscopy, Percutaneous nephrolithotomy, Renal calculi.

How to cite this article: Raut N, Singhania P, Joshi N, Shringarpure S, Sathe S, Tiwari N. Prospective Study of Percutaneous Nephrolithotomy in the Management of Renal Calculi. MGM J Med Sci 2017;4(1):1-5.

Source of support: MGMIHS

Conflict of interest: None

INTRODUCTION

Minimally invasive treatment options for treatment of kidney stones have evolved over the last several decades. Once the patient has history of urolithiasis, the risk of recurrence is 50% in next 5 years. The objective of stone clearance is to relieve obstruction, prevent further stone growth and any associated infection, and preserve kidney function.[1,2] Previously, the surgical options to the urologist for treatment of larger renal calculi were limited to open surgical techniques, with their inherent disadvantages of prolonged morbidity.

Percutaneous extraction of renal stone – properly termed percutaneous nephrolithotomy (PCNL) – has become a standard, well-established procedure for the treatment of renal stones.[3-6] Indications and limitations of PCNL have been well established. The most important indication for treating renal stone disease is the large stone burden.[7,8] This technique has high rates of success and acceptable morbidity.[9] The placement of a nephrostomy tube after completion of PCNL was initially considered a standard procedure. Recent reports from various authors have challenged routine need for nephrostomy tube. Tube-free PCNL has several purported advantages, including reduced hospital stay, decreased patient discomfort, earlier return to normal activities, and decreased hospital costs.[10,11]

If properly carried out, PCNL provides stone-free rates between 76 and 84%.[12] If not performed well, it can be associated with significant complications.[13-15] This study evaluates the role of PCNL in the management of renal calculi in our setup with respect to efficacy and attending complications.

MATERIALS AND METHODS

Prospective study of 107 patients of renal calculi, who underwent PCNL in our institution from May 1, 2014 to April 30, 2016, was carried out. Each patient's medical chart was reviewed to ascertain the history, examination findings, X-ray and ultrasonography of kidney, ureter, bladder (KUB), intravenous urography (IVU), and computed tomography (CT) KUB (plain or contrast). All patients were subjected to PCNL under strict aseptic measures. The procedure was performed in prone position under general anesthesia in a purpose-built operating room with state-of-the-art facilities of uroradiological imaging. The operative procedure comprised the following integral steps:

- Cystoscopy and retrograde ureteric catheterization in lithotomy position

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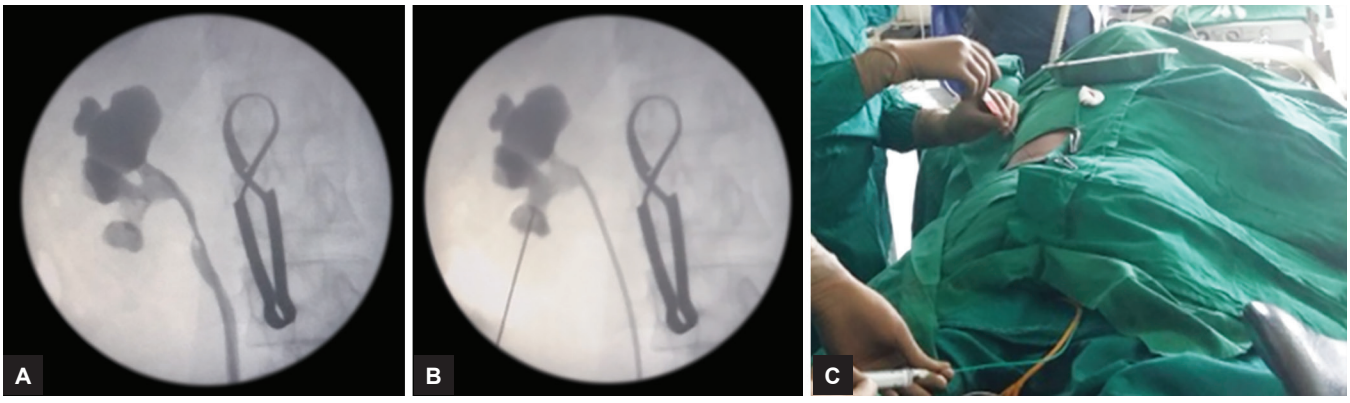
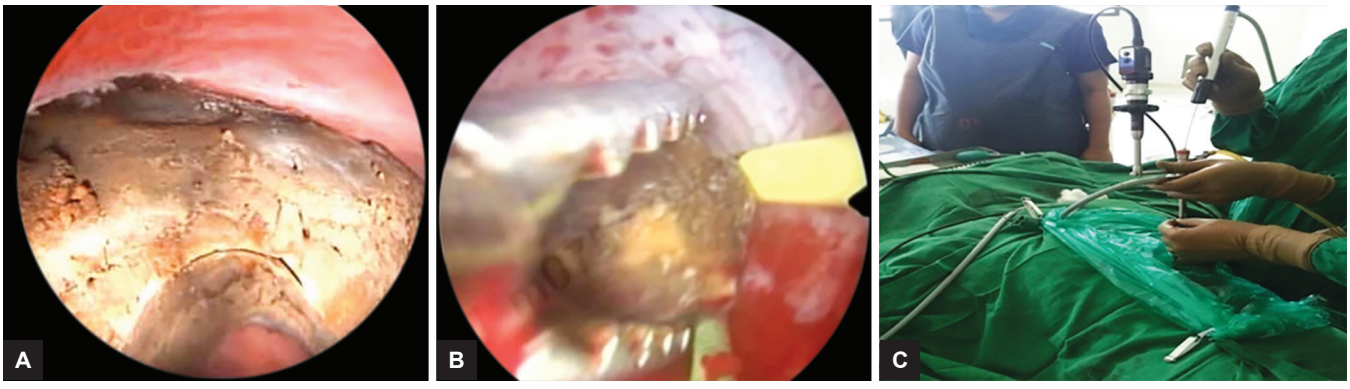


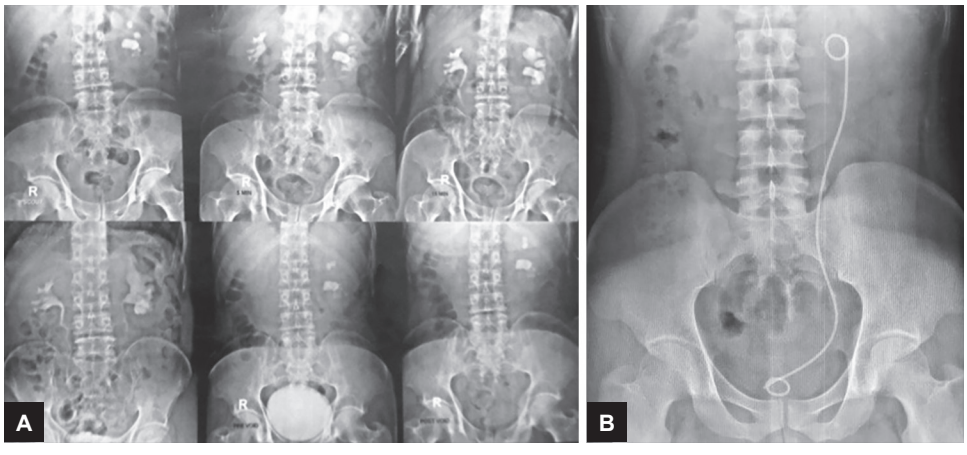
Figs 1A to C: Retrograde pyelography with puncture of the calyceal system under fluoroscopic guidance in prone position



Figs 2A to C: Nephroscopy with pneumatic lithotripsy (stone fragmentation with lithoclast) and removal of fragments

- Retrograde pyelography with puncture of the calyceal system under fluoroscopic guidance in prone position (Figs 1A to C)
- Dilation of the tract with Amplatz sequential fascial dilators and Alken metallic telescopic dilators till 24 F routinely or 28 F if large stone burden or single-step dilation
- Nephroscopy with pneumatic lithotripsy (stone fragmentation with lithoclast) and removal of fragments (Figs 2A to C)
- Confirmation of stone-free status visually and under fluoroscopy
- Antegrade DJ stenting/ureteric catheterization
- Placement of nephrostomy tube at the end of the procedure, if required.

Intraoperative findings and immediate postoperative complications were noted. Success rate was defined as patients who were stone-free or who were having clinically insignificant residual fragments (CIRF). The cut-off point of 4 mm was used to define the size of CIRF. Patients were reviewed 1 month following the surgical procedure with X-ray and ultrasonography of KUB, and requirement of any additional procedure was noted. The DJ stent was removed after 30 days if no stone was visible (Figs 3A and B).



Figs 3A and B: Preoperative IVU representing left renal calculi and postoperative X-ray KUB showing complete clearance with DJ stent *in situ*

The data were analyzed statistically using Statistical Package for the Social Sciences statistical software (version 22.0.0) and primer. All the outcome variables, i.e., quantitative data, were summarized in the form of mean ± standard deviation. Study results were statistically analyzed by using appropriate statistical methods, such as Cochrane test and Pearson test. The differences between proportions were analyzed using chi-square test. The levels of significance and αerror were kept at 95 and 5% respectively, for all statistical analyses. The p-values <0.05 were considered as statistically significant (S).

RESULTS

Mean age of cases considered for the study purposes was 43.64 years, with males comprising 60.7% and females 39.3%. Right side involvement was seen in 56 (52.3%) and left 51 (47.7%) cases. One patient had horseshoe kidney. Multiple calculi were seen in 43.9%. Another 11.2% had pelvic calculi. A staghorn calculus was seen in 16.8%. Stone clearance was done through a single tract in 78.5%. Additional tracts were made in 21.5%. Average operative time required for PCNL was 34 to 102 minutes with a mean of 57.67 minutes. Tubeless PCNL was done in 45%, 71% had postoperative fever, and 12.1% developed urinary tract infection (UTI). Hemorrhage occurred in 4%. One patient had sepsis, while 4.67% had pulmonary complications in the form of hydrothorax. Urinary leak was noted in 4.6% (Table 1); 70% of the cases were stone free with overall success rate of 85.98%. Residual stones were seen in 14.01% (Table 2). These patients were managed with additional procedures in the form of extracorporeal shock-wave lithotripsy (ESWL) (n = 13), PCNL (n = 1), and ureteroscopic lithotripsy (URSL) (n = 1).

Table 1: Postoperative complications

Complications	*Frequency*	*Percent*
Nausea	19	17.8
Vomiting	8	7.5
Fever	76	71
TUR syndrome	0	0
Urinary tract infection	13	12.1
Hemorrhage	4	3.7
Sepsis	1	1
Pulmonary complications	5	4.6
Urinary leak	5	4.6

Table 2: Results of surgery

Procedures	*Frequency*	*Percent*
Stone free (SF)	75	70.1%
Retained stone	15	14.01%
CIRF	17	15.89%
Total	107	100%
Success rate (SF + CIRF)	92	85.98%

DISCUSSION

Over the last three decades, PCNL has evolved into a safe and effective treatment of patients with large (>2 or >1.5 cm for lower calyx) or otherwise complex calculous disease.

Mean age of cases was 43.64 years. Sohail et al[16] did a study in September 2015 and found that most of the cases were around 40 years age group. More number of cases were males (60.7%) than females (39.3%). Khawaja et al[17] did a similar study in 2014 and found that males predominated, with male/female ratio 2.6:1 (86:33). Khan et al[18] did a study in 2005 and found that, out of 200 patients, 110 (55%) had right-sided stone and 90 (45%) had left-sided stone. Multiple calculi were seen in 43.9%, while another 11.2% had pelvic calculi. A staghorn calculus was seen in 16.8% cases.

In most of the cases kidney is approached through a subcostal access. However, in the presence of staghorn calculi or complex stones, supracostal access is preferable. Supracostal access offers optimal control and manipulation of stones in the mid and lower calyx.[19] Subcostal access was chosen in 46.7%, while supracostal access was preferred in 53.3% for the complete stone clearance. Stone clearance was done in maximum number of cases through a single tract (78.5%). Additional tracts were made in an attempt to clear the stones in 21.5%. Hegarty and Desai[20] in their study concluded that monotherapy with PCNL utilizing multiple percutaneous tracts is highly effective in the treatment of staghorn calculus and other large-volume renal calculi. It was found that average operative time required for PCNL was 34 to 102 minutes with a mean of 57.67 minutes, while the nephroscopy time on an average was 27 minutes. It seems that staghorn and multiple calculi required significantly more time than other calculi with p-value <0.05. Hayder[21] also noted the average procedure time of 57.40 ± 21.05 minutes.

Nephrostomy tube was inserted in 55% of the cases, while tubeless PCNL was done in 45%. Tubeless PCNL was associated with less postoperative pain and a shorter hospital stay than conventional PCNL with nephrostomy tube. Also, tubeless PCNL can be safely done in patients with a history of open nephrolithotomy and in those having a supracostal puncture without increased morbidity. Other published reports also recommend tubeless PCNL in selected uncomplicated case.[22-24]

The main complications of PCNL are residual calculi, bleeding, and renal perforation. Infectious complications related to PCNL are reported in up to 32.7%. In most of the cases, it is limited to postoperative fever, despite antimicrobial prophylaxis, and it usually resolves with continuing antibiotics for 48 hours. Although rare, postoperative septicemia or severe sepsis can induce

life-threatening situations,[12] and 71% of the cases had postoperative fever, while 12.1% had UTI. One patient had sepsis that was managed in the intensive care unit with higher antibiotics and supportive care.

Bleeding can occur at any step of the procedure: during the creation of the track, due to vascular injury after puncture, or after excessive dilation. In general, most of the bleeding is venous and is controlled by the Amplatz sheath. If the bleeding is excessive, the procedure should be stopped and a tamponading nephrostomy tube inserted. Requirement of blood transfusion is unusual. Hemorrhage was seen in 4% of our cases which was managed conservatively. Entry through the pleural cavity may lead to an accumulation of fluid, causing hydrothorax, which occurred in 4.6% of patients. Gupta et al[25] reported similar incidence (5%). Others have reported the incidence of hydrothorax to be 0 to 12%.[26,27] Pleural injury can be avoided by staying above the lateral half of the 12th rib.[28,29] Urinary leak was noted in 4.6%. It improved in majority of the cases without any intervention. In two patients nephrostomy tube slipped, which was managed by delaying removal of ureteric catheter by 24 hours. One patient developed persistent urinary leak for 3 days, which was managed conservatively with solifinacin 10 mg at bedtime without the need for DJ stenting. Ali et al[30] reported the incidence of urinary leakage in 8.57% of the patients.

In horseshoe kidneys, PCNL is a safe and effective method of stone removal in patients with calculi.[31] In the patient with horseshoe kidney, stone was removed through posteriorly placed upper pole puncture, and successful stone removal was achieved. Traditionally, post-PCNL radiographic imaging studies have been used to detect residual fragments (RF). The method for detecting RF in our study was a combination of ultrasonography KUB and plain radiography KUB. Most of the authors use sonography or KUB (sensitivity for RF: 47%), and only a few use CT as the most sensitive tool.[32] Both success rate and complication rate are important for determination of the surgical outcome of PCNL. Success rate is defined as sum of CIRF and stone-free rates,[33] where 70% of the cases were stone free, while only 16% had CIRF. The overall success rate was 85.98%. We attribute our high success rate to a well-organized team, where the anesthetist is prepared to deal with possible lengthy surgery and bleeding complications if any and the working staff are well trained with the equipment. Residual stone was seen in 14.01%. It was also noted that maximum residual stones were seen in cases having staghorn calculus and multiple calculi with a significant p-value (<0.005). Findings of the study were comparable to the study of Gupta et al[25] where the stone clearance was 75%. Aron et al[34] in 2004 found that stone clearance was seen in 72% patients. It was observed that as the size of the stone increases, and as the complexity of the situation increases, the stone-free rate decreases.[35,36]

Residual stone of varying size was seen in 15 (14.1%) cases. Re-PCNL was required in 1 patient, while 1 patient required URSL in whom the stone had descended into the ureter, and ESWL was given to 13 (12.1%) patients. In this study, most patients who required additional postoperative procedures had staghorn or multiple calculi. Farhan et al[37] in their study found that among patients with residual stones, six (29%) had additional treatments, with shock-wave lithotripsy in four and semi-rigid ureteroscopy and JJ stenting in one each. Average hospital stay was 5.5 days. Wickham et al[38] did a study on elective PCNL in 50 patients and found that the stone-free rate was 71% with the average hospital stay of 8.3 days.

With the development of new devices for renal access, lithotripsy, and renal drainage systems, PCNL has become the first choice of treatment modality for renal stones larger than 2 cm by urologists worldwide. As experience is gained in percutaneous stone surgery, there is going to be continuous improvement in the success rate and a decrease in operating time, complication rate, and hospital stay after treatment.

CONCLUSION

The findings of the study reveal that PCNL as first-line treatment modality for the management of the renal calculi offers the advantage of minimally invasive therapy with lower morbidity, shorter hospital stay, and higher stone-free rates without compromising patient safety. Data also suggest that the tubeless PCNL has better outcome. Advancements in technology, training, learning, experience of the urologist and availability of good, well-maintained instruments are critical in improving the success rate of PCNL.

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10.5005/jp-journals-10036-1129

ORIGINAL ARTICLE

Utility of GeneXpert *Mycobacterium tuberculosis*/Rifampin Assay for Extrapulmonary Tuberculosis Samples

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ABSTRACT

A total of 3,806 samples from suspected cases of extrapulmonary tuberculosis (EPTB) were subjected to GeneXpert *Mycobacterium tuberculosis* (MTB)/rifampin (RIF) assay. Samples consisted of body fluids, pleural fluids, pus and aspirates, lymph node (LN) tissues, and others. *Mycobacterium tuberculosis* positivity was detected in 18.10% and RIF positivity in 2.73% samples. The MTB/RIF positivity was found highest in pus and aspirates (40.38%). In this study, assay failure rate for GeneXpert MTB/RIF assay was very low (1.99%). It is concluded from this study that GeneXpert MTB/RIF is an efficient, reliable, simple, and fast technique for rapid diagnosis of EPTB in our country where incidence of tuberculosis remains high.

Keywords: Assay failure rate, Extrapulmonary tuberculosis, GeneXpert MTB/RIF assay, Positivity rate.

How to cite this article: Shetye S, Chheda P, Lad A, Matkar S, Yadav P. Utility of GeneXpert *Mycobacterium tuberculosis*/Rifampin Assay for Extrapulmonary Tuberculosis Samples. MGM J Med Sci 2017;4(1):6-9.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Tuberculosis (TB) is the world's most common infectious disease. According to the World Health Organization (WHO) report of 2015, there are 9.6 million people infected with TB. India accounted for 27% of global TB notifications in 2014.[1] Despite implementing Directly Observed Treatment Short-course strategy under the Revised National TB Control Programme in 1997, TB incidence in India continues to remain high, indicating that there could be substantial ongoing transmission.[2]

Extrapulmonary tuberculosis (EPTB) infections can affect any organ in the body. Diagnosis of EPTB infection is often difficult to establish because of the paucibacillary nature of *Mycobacterium tuberculosis* (MTB) bacilli in EPTB sites and the need for invasive procedures to secure appropriate sample.[3] Also, quick and reliable laboratory diagnostic methods for detecting tubercle bacilli in EPTB specimens are not easily available. This adds to the increased rates of morbidity and mortality in EPTB patients.[4]

In extrapulmonary samples, the WHO has recommended the use of GeneXpert MTB/RIF assay for rapid detection of MTB. The GeneXpert MTB/rifampicin (RIF) assay detects deoxyribonucleic acid (DNA) sequences specific for MTB and RIF resistance by polymerase chain reaction (PCR).[5] The GeneXpert MTB/RIF assay purifies and concentrates the MTB bacilli from extrapulmonary samples, isolates the genomic material, and amplifies the genomic DNA by PCR. The objective of our retrospective study was to evaluate the utility of GeneXpert MTB/RIF assay in the extrapulmonary TB samples.

MATERIALS AND METHODS

The study was conducted in the Department of Molecular Biology, Metropolis Healthcare, Mumbai, India.

Sample Collection

A total of 3,806 clinically suspected cases of EPTB were received in Global Reference Laboratory, Metropolis Healthcare Ltd, Mumbai, India. Extrapulmonary samples (pus and aspirates, body fluid, pleural fluid, Lymph node [LN] tissue, and others) were collected in plain universal 30 mL clear plastic container with white cap. Body fluids accounted for the largest type of specimen (n = 1,745). It was followed by pleural fluid specimen (n = 871) and pus and aspirate specimen (n = 586). The LN tissue formed least number (n = 195) of specimen type. Other specimens included biopsy specimens, brain tissue, computed tomography-guided fine-needle aspiration collection (FNAC), colon biopsy, fallopian tube, synovial tissue, and ultrasonography-guided FNAC. In total, other specimens accounted for 409 specimens (Table 1 and Graph 1).

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Table 1: Breakdown of EPTB samples used in the study

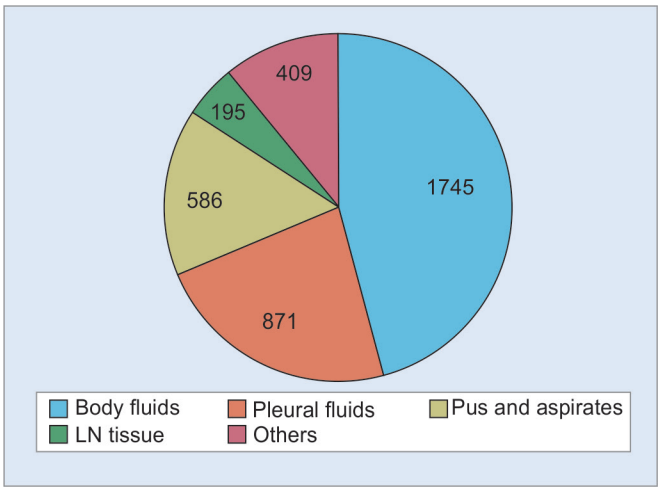
Specimen type	*Frequency*	*Percentage*
Body fluids	1745	45.84
Pleural fluids	871	22.88
Pus and aspirates	586	15.39
LN tissue	195	5.13
Others	409	10.76
Total	3806	100

Procedure for GeneXpert MTB/RIF Assay

The Xpert assay was performed as per the method described by Helb et al.[6] Sample reagent was added in a 3:1 ratio to 0.5 mL of decontaminated specimen. The closed tube was manually agitated twice during a 15-minute incubation period at room temperature before 2 mL of the inactivated sample reagent/sample mixture was transferred to the Xpert test cartridge. Cartridges were inserted into the GeneXpert device, and the automatically generated results were read after 90 minutes.

Feasibility Evaluation

The feasibility of GeneXpert MTB/RIF assay was evaluated in terms of proficiency of the assay to report a valid patient result. The absence of a valid test result for any given assay commenced was considered as a "test failure" irrespective of the underlying reason. The frequency of various reasons for the incidence of test failure was examined. The manufacturer has classified possible test failure causes as "error," "invalid," or "no result." An "error" result indicates that the GeneXpert MTB/RIF assay in a given test was aborted by internal quality control mechanisms including improper filling of the cartridge reaction tube, cartridge reagent probe integrity failure, cartridge internal pressure excess, or equipment malfunction. All "error" results are accompanied by specific error codes that provide additional information as to the underlying cause of failure (Table 2). An "invalid" result indicates that PCR has failed, usually due to the presence of PCR inhibitors. A "no result" outcome indicates that the test underway was prematurely terminated either by external or internal factors during cartridge loading process, such as power failure, manual termination of the test by the operator, or one of the equipment or cartridge component failures.[7] Under the study, for a patient, in case of "error" or "no result" outcome, repeat testing was performed on the same sample; for an "invalid" result, repeat testing was performed on a second fresh sputum sample due to concern over PCR inhibitors in the original specimen. The data from every test run were recorded by the GeneXpert software (GxAlert).



Graph 1: Diagrammatic representation of breakdown of EPTB samples used in the study

Table 2: Type of errors reported in the study

Error code	*Type of error*	*Number of cases*
5011	Postrun analysis error	22
5007		51
5006		0
2008		0
2005	Operation terminated error	0
2022		0
2025	Cartridge loading error	0
2037		0
1001		0
1002	Temperature-related errors	0
1004		0
Invalid results		03
Total		76

RESULTS

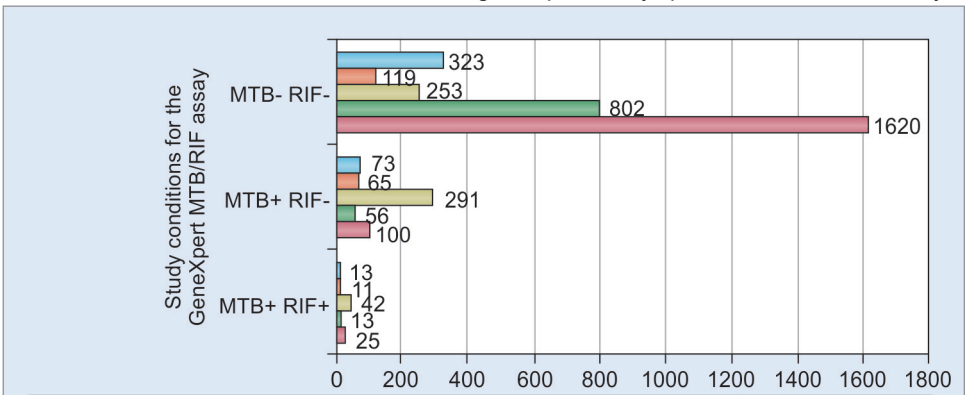
Out of the total number of extrapulmonary samples (n = 3,806) taken up for analysis, 81.89% (n = 3,117/3,806) cases were detected as MTB negative and RIF negative. Of these, body fluids (n = 1,620, 42.56%) accounted for the most of the MTB^-/RIF^- cases. This was followed by pleural fluids (n = 802, 21.07%), others (n = 323, 8.48%), pus and aspirates (n = 253, 6.64%), and LN tissue (n = 119, 3.12%) (Tables 3 and 4).

For the cases detected as MTB positive and RIF positive, the positivity rate of GeneXpert MTB/RIF assay was

Table 3: Performance of extrapulmonary specimens in GeneXpert MTB/RIF assay

	MTB^+/RIF^+	MTB^+/RIF^-	MTB^-/RIF^-
Body fluids (n = 1,745)	25	100	1620
Pleural fluids (n = 871)	13	56	802
Pus and aspirates (n = 586)	42	291	253
LN tissue (n = 195)	11	65	119
Others (n = 409)	13	73	323

Table 4: Distribution of MTB/RIF cases among extrapulmonary specimens used in the study



	MTB^+/RIF^+	MTB^+/RIF^-	MTB^-/RIF^-
Others (n = 409)	13	73	323
LN tissue (n = 195)	11	65	119
Pus and aspirates (n = 586)	42	291	253
Pleural fluids (n = 871)	13	56	802
Body (n = 1745)	25	100	1,620

recorded at 2.73% (n = 104/3,806). The maximum cases of MTB^+/RIF^+ were observed in pus and aspirates with 40.38% (n = 42/104). Second highest cases of MTB^+/RIF^+ was observed in body fluids 25.03% (n = 25/104), pleural fluids 12.50% (n = 13/104), others 12.50% (n = 13/104), and LN tissue 10.57% (n = 11/104) (Tables 2 and 3).

In the cases detected as MTB positive and RIF negative, the positivity rate of GeneXpert MTB/RIF assay was measured at around 15.37% (n = 585/3,806). Similar to the cases of MTB^+/RIF^+, the maximum cases of MTB^+/RIF^- were observed in pus and aspirates with 49.74% (n = 291/585), followed by body fluids 17.09% (n = 100/585), others 12.47% (n = 73/585), LN tissue 11.11% (n = 65/585), and pleural fluids 9.57% (n = 56/585) (Tables 2 and 3).

DISCUSSION

The study revealed that the GeneXpert MTB/RIF assay had a good diagnostic potential for specimens, such as pus and aspirates, which is difficult to diagnose by other laboratory techniques. Findings of the study supported the use of GeneXpert MTB/RIF assay in routine diagnosis for EPTB investigation, especially for pus samples.[8,9]

Similar studies were carried out by Lawn and Zumla[10] who employed the GeneXpert MTB/RIF assay for diagnosis of EPTB. Out of the total of 268 samples, the positivity rate was observed for tissue biopsies or fine-needle aspirates (35%), gastric aspirates (23%), pus (21%), urine (6%), cerebrospinal fluid (5%), and other body fluids, i.e., peritoneal, synovial, and pericardial (4%).

Test failure cause analysis: Failed tests for GeneXpert MTB/RIF assay accounted only 76/3,806 (1.99%) in our study. As per the test failure codes generated by the GeneXpert MTB/RIF assay, the leading cause of test failure was postrun analysis error, contributing to a total of 51 out of 76 test failures. The frequency of various factors contributing to test failures is described in Table 2. Literature studies[7,11] suggest that the leading cause of GeneXpert MTB/RIF assay failure results observed in the present study was due to inadequate sample processing and equipment malfunction. Like any other automated laboratory technology, GeneXpert MTB/RIF assay also require a stable electric power supply, and even a short-term interruption of power would result in test failures. The manufacturer recommends a maximum of 30°C ambient operating temperature for the operation of GeneXpert instrument. Data on the robustness of the device under prolonged periods of temperature exceeding 30°C are not available.[7] In our study, the GeneXpert MTB/RIF assay was error-free for Type error 1001, 1002, 1004, 2022, 2025, and 2037.

CONCLUSION

GeneXpert MTB/RIF assay is an efficient and reliable technique for the rapid diagnosis of EPTB. Its simplicity, sensitivity, and speed make this technique a good tool for diagnosis of MTB from extrapulmonary samples. The failure rate for GeneXpert MTB/RIF assay was acceptably low in our study. It is particularly useful for our country where the incidence of tuberculosis is high, as it provides a simple, reliable, and cost-effective diagnostic modality.

ACKNOWLEDGMENT

The authors would like to acknowledge the support and facilities provided by the management of Metropolis Healthcare Ltd, Mumbai, India.

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10.5005/jp-journals-10036-1130

ORIGINAL ARTICLE

Spectrum of Microbial Isolates from Wound Infections in Patients admitted in a Tertiary Care Hospital, Kolkata

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ABSTRACT

Increasing emergence of drug-resistant bacteria is becoming a major problem globally. A retrospective study of 790 culture and sensitivity reports on microbial isolates, from infected wounds was carried out in KPC Medical College and Hospital, Jadavpur, Kolkata, India. 504 patients were males and 286 females. Gram negative organisms were isolated in 561 and gram positive in 229. Among the gram negative organisms, *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Escherichia coli* were the most common, whereas *Staph aureus* was the only gram positive organism isolated. Antibiotic sensitivity tests revealed most gram negative organisms susceptible to carbapenems, polymyxin and colistin. *Staphylococci* showed sensitivity to tigecycline, clindamycin, vancomycin, teicoplanin and linezolid. Interesting differences in the type of organisms isolated in male and female patients were noted. For example *Enterococcus faecalis* was found only in female patients. Increasing resistance of microorganisms cultured from infected wounds to first line and even second line antibiotics is a matter of great concern and can be attributed to indiscriminate and irrational use of broad spectrum antibiotics. This has to stop forthwith if we want to prevent resistance to antibiotics; otherwise morbidity, mortality and health care costs in treating patients with wound infections are going to increase exponentially

Keywords: Blood culture, Gram-negative bacteria, Gram-positive bacteria, Sensitivity, Tertiary hospital.

How to cite this article: Saha AK, Nandi S, Dhar P. Spectrum of Microbial Isolates from Wound Infections in Patients admitted in a Tertiary Care Hospital, Kolkata. MGM J Med Sci 2017;4(1):10-18.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Commonly bacteria, fungi, and viruses invade the body defense, multiply, and produce respective symptoms.[1] Hence, the infectious diseases are most common cause of mortality and morbidity worldwide.[2] The bacteria invade the skin either directly through open-wound contamination or through the penetration of the intact skin.[3] The wound may be either postoperative, occurred after injury, or may be in birth-place.[4] These wound infection sources include first from nature, including exogenous microflora present all around or those presented as traumatic damage; secondly, skin microflora including *Staphylococcus epidermidis*, micrococci, skin diphtheroids and propionibacteria; and thirdly, endogenous sources (oropharyngeal, urogenital tract, and gastrointestinal tract).[5] Most of the open injuries are colonized by potentially pathogenic polymicrobes, but some experts considered the involvement facultative pathogens, like *Staphylococcus aureus*, beta-hemolytic *Streptococci* and *Pseudomonas aeruginosa, Enterococci, Escherichia coli*, and *Proteus* and *Klebsiella* species as essential drivers of prolonged recuperation and disease in both intense and constant injuries.[6-9] So, in case of clinically infected injuries, the aim of administration of antibiotics is not to target one particular pathogen, rather targeting aerobic or facultative aerobic and anaerobic pathogens.[10] In case of *S. aureus,* which is the most common organism in infected wound, cephalosporin, macrolide group of drugs, semisynthetic penicillin, clindamycin, and fluoroquinolone are the antibiotics of choice.[11,12] In case of open wound, surface bacteria enter and start multiplying locally at the moist edge of the gut. So, body's defense comes into action. Neutrophilic lymphocytes and other cytokines fight against these invaded bacteria producing local inflammation and ultimately white-colored liquid will be formed.[13,14] Ultimate complications will be wound dehiscence or wound breakdown.[15,16] But unfortunately the overuse, unjustified use, and missuse of the broad spectrum antibiotics may be responsible for spreading of infection resistant to those antibiotics and possibility of developing complications in future.[17] So, to prevent these multidrugs-resistant bacteria, regular updates of knowledge regarding the bacteriological review of pus culture and sensitivity is very much essential.[18] Hence, our aim in this study was to isolate the bacteria from pus and detection of its spectrum of antimicrobial sensitivity in our institution, which will definitely throw light of knowledge in the use of antibiotics in that type of organism.

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MATERIALS AND METHODS

This retrospective study was conducted in KPC Medical College and Hospital, Jadavpur, Kolkata only after getting permission from our local ethical committee. Most of the wounds were mainly infected injury, diabetic foot, and postoperative injuries. The data included here from the years 2010 to 2015, i.e., 6 years.

Sample collection: Samples were collected from our microbiology department. Total number of samples sent for culture and sensitivity and direct microscopy examination were 6,292. In 790 cases positive culture and sensitivity report were received.

Inoculation in broth and direct microscopy: After collection aseptically, the specimen was sent immediately to microbiological department for culture and sensitivity. The specimen was first inoculated in the thioglycollate broth and kept incubated for 24 hours at 37°C. On the following day, the broth was examined primarily to detect the growth of the bacteria, if any by doing direct gram stain smear. Then the smear was first examined in the low power field under oil immersion microscope (×100) to detect polymorph nuclear cells. Other smear was examined in high power field microscope under oil immersion (×1000) to detect the presence of bacteria.

Inoculation into the culture media: Some material was collected from the broth by using calibrated loop and inoculated in the blood agar, chocolate agar, and MacConkey's agar by four quadrant technique and incubated at 37°C for further 24 to 48 hours for the presence or absence of bacterial growth.

Identification of isolates by biochemical tests: After 48 hours the cultures was read out by observing four quadrant growth of bacteria – it is usually read as approximate number of colony forming unit of bacteria per mL (CFU/ML). Then, to measure variable biochemical behavior of bacterial strains, the following extensive biochemical tests were performed as per manual methods of general bacteriology by American Society of Microbiology, like triple sugar iron test (TSI), citrate utilization test, motility indole urease test (MIU), oxidase test, coagulase test, catalase test, and DNAse test.[19]

Antibiotic sensitivity tests: The obtained bacteria was diluted in 3 to 4 mL of sterile normal saline, which was then followed by swabbing the diluted bacterial sample onto the antibiotic disk by cotton swab as per direction of Clinical and Laboratory Standard Institute guideline.[20]

For Gram-negative bacteria, the following antibiotic disks were used: gentamicin, tobramycin, netilmicin, amikacin, ceftriaxone, cefixime, fluoroquinolone group of drugs, like, ciprofloxacin, ofloxacin, levofloxacin, co-trimoxazole, chloramphenicol, piperacillin-tazobactam, cefoperazone-sulbactam, ceftazidime, aztreonam, cefotaxime, imipenem, meropenem, ertapenem, polymyxin B, and colistin.

Again, for Gram-positive cocci, the following antibiotics were used: piperacillin-tazobactam, cefoperazone-sulbactam, semisynthetic penicillin group, like amoxicillin, oxacillin, amoxicillin-clavulanic acid, cefuroxime, ceftazidime, cefixime, ceftriaxone, carbapenem group, aminoglycoside group, chloramphenicol, co-trimoxazole, fluoroquinolone group of drugs, tigecycline, teicoplanin, vancomycin, clindamycin, linezolid, tetracycline, polymyxin B, and colistin.

After getting the data of antibiotic sensitivity spectrum of the different bacteria, they were analyzed in following sequences:

- Year-wise culture–sensitivity report between males and females with their statistical significance.
- Sex-wise distribution of bacterial isolates in pus.
- Incidence of Gram-positive and Gram-negative bacteria in pus.
- In bacterial isolates percentage of culture–sensitivity in different bacteria.

All the above data were analyzed with the help of statistical software [Statistical Package for the Social Sciences (SPSS)] version 17. Here the p-value of <0.05 was accepted as statistically significant.

RESULTS

Total number of samples sent were 6,292. In 6 years' study, total number of positive cases were 790, out of which 504 were males and 286 females (p = 0.00) (Table 1). In case of sex-wise distribution of bacterial isolates from pus, males were significantly affected by all bacteria (p = 0.00 to <0.02) except *Enterobacter* species (p = 0.35). Again in case of *Klebsiella oxytoca* and *Acinetobacter,* only males were affected, whereas only females were affected by *E. faecalis* (Table 2). These data demonstrated significant number of Gram-negative organism (n = 504) in comparison to Gram-positive organism (n = 229) (p = 0.00) (Table 3).

Table 1: Year-wise male–female distribution of bacterial isolates from pus

Years	*Total cases (790)*	*Males (504)*	*Females (286)*
2010	109 (13.79%)	71	38
2011	131 (16.58%)	89	42
2012	89 (11.26%)	62	27
2013	142 (17.97%)	102	40
2014	158 (20%)	98	60
2015	161 (20.37%)	82	79

Table 2: Sex-wise distribution of bacterial isolates from pus

Bacterial isolates (790)	*Males (504)*	*%*	*Females (286)*	*%*	*p-value*
K. pneumoniae (114) (14.43%)	76	66.66	38	33.33	0.00
MSSA (135) (17%)	86	63.70	49	36.29	0.00
P. aeruginosa (115) (14.55%)	67	58.26	48	41.73	0.01
E. coli (86) (10.88%)	56	65.11	30	34.88	0.00
C. freundii (26) (3.29%)	22	84.61	4	15.38	0.00
K. oxytoca (6) (0.75%)	6	100	0	0	■
E. coli (ESBL) (58) (7.34%)	35	60.34	23	39.65	0.02
Klebsiella (ESBL) (59) (7.46%)	36	61.01	23	38.98	0.01
Enterobacter (21) (2.65%)	9	42.85	12	57.14	0.35
E. faecalis (10) (1.26%)	0	0	10	100	■
P. mirabilis (55) (6.96%)	38	69.09	17	30.90	0.00
MRSA (53) (6.70%)	35	66.03	18	33.96	0.00
Acinetobacter (11) (1.39%)	11	100	0	0	■
CNS (41) (5.18%)	27	65.85	14	34.14	0.00

Methicillin-sensitive *S. aureus* (MSSA) was moderately sensitive to piperacillin-tazobactam (77.03%), netilmicin (77.03%), tobramycin (77.77%), moderately high sensitive to tigecycline and linezolid (80–88.14%), but high sensitive to vancomycin and teicoplanin (90.85%). Nonextended spectrum beta-lactamase (ESBL) producing *Klebsiella pneumoniae* and *Enterobacter* was not more than 50% sensitive to all the antibiotics, but ESBL producing *Klebsiella* were moderately to highly sensitive to carbapenem group of drugs (76.27–81.35%), tigecycline (88.13%), polymyxin B, and colistin (76.27%). *P. aeruginosa* were moderately high sensitive to imipenem (86.95%), meropenem (80.86%) and highly sensitive to polymyxin B and colistin (91.30%). Non-ESBL producing *E. coli* were moderate to moderately high sensitive to carbapenem group of drugs, polymyxin B, and colistin (77.90–86.04%), but less sensitive to aminoglycoside group (62.79–68.60%) except amikacin which was moderately sensitive (73.25%), whereas ESBL producing *E. coli* were moderately sensitive to carbapenem group (74.13–81.03%) but mildly increased sensitivity to polymyxin B and colistin (65.51%). Again, *K. oxytoca* (n = 6) were moderately sensitive to carbapenem groups, tigecycline (83.33%) but 100% sensitive to polymyxin B and colistin. Citrobacter were moderately high sensitive to piperacillin-tazobactum (73.02%), carbapenem group of drugs (76.92–84.61%) except imipenem which was highly sensitive (92.30%). *E. faecalis* (n = 10) was 100% sensitive to piperacillin-tazobactam, imipenem, chloramphenicol, tigecycline, vancomycin and linezolid, 90% sensitive to amoxicillin, but 70 to 80% sensitive to meropenem, ciprofloxacin, and gentamicin. *Proteus mirabilis* (n = 55) was highly sensitive to piperacillin-tazobactum (90.90%), moderately highly sensitive to imipenem (83.63%), meropenem (76.36%), levofloxacin (74.54%) and mildly increased sensitive to aminoglycoside group of drugs (60–69.09%). Methicillin-resistant *S. aureus* (MRSA) were highly sensitive to vancomycin, teicoplanin, and linezolid (94.33–98.4%), mildly increased sensitive to aminoglycoside group of drugs (66.03–69.81%), teicoplanin, and clindamycin (71.69%). *Acinetobacter baumannii* demonstrated high sensitivity to imipenem and meropenem (90.90%), polymyxin B, moderate to moderately high sensitivity to gentamicin and fluoroquinolone group of drugs (72.72–81.81%), but mildly increased sensitivity to other aminoglycoside group of drugs. Coagulase-negative *Staphylococcus* demonstrated very high sensitivity to tigecycline, vancomycin, teicoplanin (90.24–92.68%), moderately high sensitive to tetracycline, linezolid, chloramphenicol (78.04–87.80%) (Tables 4 to 7).

Table 3: Comparison between Gram-positive and Gram-negative bacteria in pus

Gram-negative organism (561)	*Gram-positive organism (229)*	*p-value*
K. pneumoniae (114)	Methicillin sensitive *Staphylococcus* (MSSA) (135)	0.00
P. aeruginosa (115)	Methicillin resistant *Staphylococcus* (MRSA) (53)	
E. coli (86)	Coagulase negative *Staphylococcus* (CNS) (41)	
C. freundii (26)		
K. oxytoca (6)		
E. coli (ESBL) (58)		
Klebsiella (ESBL) (59)		
Enterobacter (21)		
E. faecalis (10)		
P. mirabilis (55)		
Acinetobacter (11)		

DISCUSSION

Nowadays, surgery are well advanced, techniques are being modernized, good numbers of newly invented antibiotics

Table 4: Antibiotic sensitivity of bacterial isolates in penicillin, amoxicillin, oxacillin, ampicillin, piperacillin-tazobactam, cefoperazone-sulbactam, cefuroxime, cefotaxime, and cofoxitin

Organisms	*PEN*	*AMX*	*OX*	*AMC*	*PIPT*	*CES*	*CEF*	*CFT*	*CXT*
K. pneumoniae (114)	0	1 0.87%	0	15 13.15%	56 49.12%	55 48.24%	16 14.03%	18 15.78%	23 20.17%
MSSA (135)	11 8.14%	31 22.96%	83 61.48%	74 54.81%	104 77.03%	6 4.44%	65 48.14%	3 2.22%	13 9.62%
P. aeruginosa (115)	0	0	0	0	60 52.17%	56 48.69%	2 1.73%	0	1 0.8%
E. coli (86)	0	3 3.48%	0	22 25.58%	55 63.95%	47 54.65%	15 17.44%	22 25.58%	23 26.74%
C. freundii (26)	0	1 3.84%	0	7 26.92%	19 73.02%	14 53.84%	4 15.38%	9 34.61%	8 30.76%
K. oxytoca (6)	0	0	0	1 16.66%	1 16.66%	1 16.66%	0	0	1 16.66%
E. coli (ESBL) (58)	0	0	0	6 10.34%	33 56.89%	25 43.1%	0	1 1.72%	19 32.75%
Klebsiella (ESBL) (59)	0	0	0	9	31	17	0	0	21
Enterobacter (21)	0	5 23.8%	0	6 28.57%	12 57.14%	6 28.57%	2 9.52%	2 9.52%	0
E. faecalis (10)	0	3 30%	0	9 90%	10 100%	5 50%	1 10%	1 10%	0
P. mirabilis (55)	0	5 9.09%	0	20 36.36%	50 90.90%	36 65.45%	19 34.54%	21 38.18%	8 14.54%
MRSA (53)	0	0	7 13.20%	7 13.20%	20 37.73%	3 5.66%	3 5.66%	1 1.88%	1 1.88%
Acinetobacter (11)	0	0	0	0	4 36.36%	6 54.54%	2 18.18%	1 09.09%	0
CNS (41)	3 7.31%	11 26.82%	12 29.26%	16 39.02%	28 68.29%	0	11 26.82%	4 9.75%	5 12.19%

Table 5: Antibiotic sensitivity of bacterial isolates in ceftazedime, ceftriaxone, cefepime, azithromycin, erythromycin, aztreonam, ertapenem, imipenem, and meropenem

Organisms	*CFZ*	*CTRX*	*CFP*	*AZ*	*ER*	*AZT*	*ERT*	*IMP*	*MEP*
K. pneumoniae (114)	10 8.77%	9 7.89%	8 7.01%	3 2.63%	0	5 4.38%	49 42.98%	62 54.38%	54 47.36%
MSSA (135)	4 2.96%	66 48.88%	15 11.11%	57 42.22%	64 47.40%	19 14.07%	17 12.59%	23 17.03%	13 9.62%
P. aeruginosa (115)	16 13.91%	2 1.73%	12 10.43%	11 9.56%	0	7 6.08%	14 12.17%	100 86.95%	93 80.86%
E. coli (86)	24 27.90%	28 32.58%	24 27.90%	5 5.81%	3 3.48%	18 20.93%	67 77.90%	72 83.72%	74 86.04%
C. freundii (26)	9 34.61%	10 38.46%	9 34.61%	2 7.69%	0	5 19.23%	20 76.92%	24 92.30%	22 84.61%
K. oxytoca (6)	0	0	0	0	0	0	5 83.33%	5 83.33%	3 50%
E. coli (ESBL) (58)	0	0	0	1 1.72%	1 1.72%	0	43 74.13%	47 81.03%	45 77.58%
Klebsiella (ESBL) (59)	0	0	0	0	0	0	45 76.27%	49 83.05%	48 81.35%
Enterobacter (21)	3 14.28%	2 9.52%	2 9.52%	3 14.28%	3 14.28%	3 14.28%	3 14.28%	10 47.61%	6 28.57%
E. faecalis (10)	0	3 30%	3 30%	2 20%	4 40%	1 10%	5 50%	10 100%	7 70%
P. mirabilis (55)	21 38.18%	26 47.27%	21 38.18%	1 1.81%	0	24 43.63%	36 65.45%	46 83.63%	42 76.36%
MRSA (53)	0	7 13.20%	4 7.54%	9 16.98%	16 30.18%	7 13.20%	4 7.54%	5 9.43%	3 5.66%
Acinetobacter (11)	3 27.27%	3 27.27%	3 27.27%	1 9.09%	0	3 27.27%	3 27.27%	10 90.90%	10 90.90%
CNS (41)	1 2.43%	11 26.82%	12 29.26%	6 14.63%	4 9.75%	4 9.75%	13 31.70%	23 56.09%	11 26.82%

Table 6: Antibiotic sensitivity of bacterial isolates in gentamicin, tobramycin, netilmicin, amikacin, ciprofloxacin, ofloxacin, levofloxacin, cotrimoxazole, and chloramphenicol

Organisms	*GET*	*TOB*	*NIT*	*AMK*	*CIP*	*OF*	*LIV*	*COT*	*CHLO*
K. pneumoniae (114)	44 38.59%	42 36.84%	43 37.71%	43 37.71%	25 21.92%	26 22.80%	37 32.45%	16 14.03%	36 31.57%
MSSA (135)	108 80%	50 37.03%	104 77.03%	105 77.77%	76 56.29%	80 59.25%	94 69.62%	64 47.40%	93 68.88%
P. aeruginosa (115)	60 52.17%	57 49.56%	64 55.65%	69 60%	60 52.17%	36 31.30%	65 56.52%	5 4.34%	6 5.21%
E. coli (86)	58 67.44%	54 62.79%	59 68.60%	63 73.25%	41 47.67%	40 46.51%	55 63.95%	39 45.34%	59 68.60%
C. freundii (26)	5 19.23%	16 61.53%	15 57.69%	16 61.53%	13 50%	14 35.84%	17 65.38%	11 42.30%	11 42.30%
K. oxytoca (6)	3 50%	2 33.33%	1 16.66%	4 66.66%	0	0	0	0	3 50%
E. coli (ESBL) (58)	25 43.10%	24 41.37%	28 48.27%	32 55.17%	9 15.51%	11 18.96%	14 24.13%	12 20.68%	31 53.44%
Klebsiella (ESBL) (59)	30 50.84%	27 45.76%	32 54.23%	35 59.32%	12 20.33%	13 22.03%	17 28.81%	10 16.94%	35 59.32%
Enterobacter (21)	5 23.80%	1 4.76	5 23.80%	5 23.80%	6 28.57%	6 28.57%	10 47.61%	2 9.52%	11 52.38%
E. faecalis (10)	8 80%	1 10%	4 40%	2 20%	7 70%	6 60%	8 80%	1 10%	10 100%
P. mirabilis (55)	38 69.09%	34 61.81%	36 65.45%	38 69.09%	33 60%	30 54.54%	41 74.54%	18 32.72%	35 63.63%
MRSA (53)	31 58.49%	20 37.73%	37 69.81%	35 66.03%	17 32.07%	22 41.50%	32 60.37%	6 11.32%	40 75.47%
Acinetobacter (11)	8 72.72%	7 63.63%	7 63.63%	7 63.63%	8 72.72%	8 72.72%	9 81.81%	4 36.36%	6 63.63%
CNS (41)	23 56.09%	7 17.07%	24 58.53%	26 63.41%	18 43.90%	19 46.34%	25 60.97%	20 48.78%	33 80.48%

Table 7: Antibiotic sensitivity of bacterial isolates in tetracycline, tigecycline, clindamycin, vancomycin, teicoplanin, linezolid, polymyxin B, colistin, ticarcillin, and cefoperazone

Organisms	*TET*	*TIG*	*CLIN*	*VAN*	*TEI*	*LIZ*	*POL*	*COL*	*TIC*	*CEFOP*
K. pneumoniae (114)	20 17.54%	41 35.96%	1 0.87%	0	1 0.87%	0	65 57.01%	64 56.14%	1 0.87%	1 0.87%
MSSA (135)	107 79.25%	108 80%	82 60.74%	124 91.85%	124 91.85%	119 88.14%	1 0.74%	0	3 2.22%	8 5.92%
P. aeruginosa (115)	0	1 0.86%	0	0	0	0	105 91.30%	105 91.30%	5 4.34%	6 5.21%
E. coli (86)	35 40.69%	58 67.44%	0	0	0	0	70 81.39%	69 80.23%	7 8.13%	1 1.16%
C. freundii (26)	5 19.23%	15 57.69%	0	0	0	0	22 84.61%	21 80.76%	3 11.53%	0
K. oxytoca (6)	3 50%	5 83.33%	0	0	0	0	6 100%	6 100%	1 16.66%	0
E. coli (ESBL) (58)	15 25.86%	34 58.62%	0	0	0	0	38 65.51%	38 65.51%	9 15.51%	0
Klebsiella (ESBL) (59)	22 37.28%	52 88.13%	0	0	0	0	45 76.27%	45 76.27%	6 10.16%	0
Enterobacter (21)	8 38.09%	7 33.33%	0	9 42.85%	9 42.85%	8 38.09%	1 4.76%	1 4.76%	2 9.52%	1 4.76%
E. faecalis (10)	6 60%	10 100%	0	10 100%	1 10%	10 100%	2 20%	2 20%	2 20%	0
P. mirabilis (55)	3 5.45%	8 14.54%	0	0	0	0	1 1.81%	1 1.81%	15 27.27%	1 1.81%
MRSA (53)	34 64.15%	41 49.62%	38 71.69%	52 98.11%	52 98.11%	50 94.33%	0	0	2 3.77%	0
Acinetobacter (11)	6 54.54%	7 63.63%	0	0	0	0	11 100%	11 11%	0	0
CNS (41)	32 78.04%	38 92.68%	16 39.02%	37 90.24%	37 90.24%	36 87.80 %	0	0	0	0

CNS: Coagulase negative *Staphylococcus*; MSSA: Methicillin-sensitive *S. aureus*; MRSA: Methicillin-resistant *S. aureus*

are being used for prophylaxis, but with the inadvertent and irrational use of these antibiotics. The nosocomial bacteria get upper hand and are frequently encountered in the wound infections – these are mainly hospital-acquired. These bacterial infections are mostly responsible for worldwide morbidity and mortality.[21,22] According to Center of Disease Control (CDC), in USA and UK nosocomial infection surveillance, incidence of positive bacterial isolates was 15.45 and 11.32% respectively, which were very close to our study results because it showed 12.55% positivity.[23] It may be due to uncontrolled infections, which in turn may produce depressive type of illness, septicemia, and eventual death.[24,25]

In the study done by Rao et al[26] and Rameshkannan et al,[27] the most common bacteria isolated were *Staphylococcus* (24.29%) and *E. coli* (61%). Similarly, Verma[28] demonstrated in her study *Staphylococcus* as most common causative organism (40%). Similar incidence was found also in our study (MSSA – 17%, MRSA – 6.70%, and CNS – 5.18%, total being 29.88%). The second most common bacteria isolated in our study was *Klebsiella* species (14.43 + 0.75% +7.46% = 22.64%) followed by *E. coli* (10.88 + 7.34% = 18.22%) and *Pseudomonas* species (14.55%). Similarly, Verma[28] in her study demonstrated *Klebsiella* species as the second most common organism (33%) followed by *Pseudomonas* (18%) and *E. coli* (16%). Whereas Rameshkannan et al[27] in their study showed second most common bacteria as *S. epidermidis* (21%) followed by *S. aureus* (10%) and *Pseudomonas* (4%). So, from all the studies it can be interpreted that four most common bacteria responsible for infection are *S. aureus, E. coli, Pseudomonas* species, and *Klebsiella* species. These infections may be due to chronic morbid disease, like diabetes, chronic liver disease, immunosuppression, aging, low socioeconomic status, and poor nutritional status.

In our study MSSA was moderately sensitive to piperacillin-tazobactam, netilmicin, amikacin (≈ 77%), moderately high sensitive to tigecycline and linezolid (80–88%), and highly sensitive to vancomycin and teicoplanin (≈ 91%), whereas MRSA was very highly sensitive to vancomycin, teicoplanin, and linezolid (94–98%). In our study, MRSA was 6.70% and MSSA was 17%, but in other studies, the incidence of MRSA was 15 to 30%.[29,30] In the study of Perim et al,[31] the incidence of resistance of MRSA to vancomycin was 26%. Later on, in that study modified Kirby-Bauer disk diffusion demonstrated only three isolates resistant to vancomycin. So, in any diabetic wound infections without any risk factor for MRSA, the treatment should be started with vancomycin. More and more genetic studies should be performed to analyze nonvancomycin susceptible to MRSA.[32] In our study, 90 to 100% isolates of MRSA were resistant to penicillin and methicillin group of antibiotics, whereas in the study of Hailu et al,[33] 65.4 and 34.6% *S. aureus* demonstrated resistance to penicillin and oxacillin respectively with more or less similar results were found in the study done by Hwang et al,[34] Abera et al,[35] and Seid et al.[36] Our study as well as other different studies suggest that a large-scale study is required on the prevalence and spectrum of susceptibility of community-acquired MRSA. The study showed 40 to 90% resistance to co-trimoxazole, chloramphenicol, ciprofloxacin, erythromycin with only 30% resistance to clindamycin, whereas only 0 to 31% resistance to ciprofloxacin, chloramphenicol, clindamycin, erythromycin, and co-trimoxazole was evidenced in the study done by Hailu et al,[33] Seid et al,[36] Abera and Kibrad.[35]

Our study demonstrated 80 to 86% sensitivity of *Pseudomonas* to imipenem which was consistent with the study done by Rajalakshmi et al.[37] On the contrary, only 50% *Pseudomonas* was sensitive to imipenem in the study done by Perim et al.[31] Sivanmaliappan and Sevanan in their study demonstrated 100% resistance of *Pseudomonas* to ampicillin, 83% to tetracycline, 66.6% to gentamicin, and 16.6% to cefotaxime. There was some similarity as well as dissimilarity evidenced in our study.[38] More or less similarity in observations was demonstrated in the study of Perim et al.[31] In our study, *Pseudomonas* was 100% resistant to ampicillin, amoxicillin, tetracycline, erythromycin, cefotaxime, clindamycin, vancomycin, teicoplanin, linezolid and around 50% resistant to aminoglycoside group of antibiotics. In the study, of Hailu et al,[33] it was demonstrated that *P. aeruginosa* was highly sensitive to ciprofloxacin, gentamicin, amikacin, and chloramphenicol. This was contrary to our study where *Pseudomonas* was 52 to 55% sensitive to gentamicin, amikacin, ciprofloxacin, whereas 5.21% sensitive to chloramphenicol. Perim et al[31] demonstrated 25% *Pseudomonas* isolates were resistant to polymyxin B as determined with diffusion test using validated broth dilution method. Though different studies throughout the world demonstrated poor correlation among the different methods of testing for polymyxin B and colistin, but some studies including our study demonstrated good correlation because of use of validated broth dilution method.

Our study demonstrated that *P. mirabilis* (n = 55) was highly sensitive to piperacillin-tazobactam (90.90%), imipenem (83.63%), moderately sensitive to cefoperazone-sulbactam (65.45%), ertapenem (65.45%), aminoglycoside group of antibiotics (60–69%), chloramphenicol (63.63%) which was partially similar to the studies done by Hailu et al,[33] Seid et al,[36] and Wasihun and Zemune.[39] These studies demonstrated low level of resistance (5–28%) to

ciprofloxacin, piperacillin-tazobactam, ceftazidime, gentamicin, and ceftriaxone. Similarly, our study indicated very low level of sensitivity to ampicillin, amoxicillin, oxacillin which was also evidenced in the above studies.[33,36,39] The high resistance of *P. aeruginosa, S. aureus,* and *P. mirabilis* to ampicillin, amoxicillin, and oxacillin may be due to the following factors, like lack of up-to-date knowledge of antimicrobial resistance amongst nurses, physicians, lack of presence of proper antibiogram data, unnecessary, unethical, and irrational uses of antibiotics, self-intake by the patients, push by the pharmacists, irregular intake of antibiotics by the patients. Again, it is known fact that proteus species produces a unique beta-lactamase (cefuroximase) having high activity against cefuroxime, second-generation cephalosporin.

K. pneumoniae showed only 50% sensitivity to piperacillin-tazobactam and cefoperazone-sulbactam. But both *K. oxytoca* and ESBL producing *Klebsiella* demonstrated high sensitivity to carbapenem group (75–83%), tigecycline (83.33–88.13%), polymyxin B, and colistin (76.22–100%), which was similar to the study done by Rameshkannan et al[27] and Rao et al[26] where *Klebsiella* showed high sensitivity to meropenem, linezolid, and levofloxacin. On the contrary, our study demonstrated nearly 100% sensitivity and low level of resistance to levofloxacin.

Enterobacteriaceae group was resistant to most of the antibiotics as evidenced in the study done by Banashankari et al,[40] whereas the study done by Perim et al[31] demonstrated gentamicin and imipenem were most effective to this group. The latter study was nearly consistent with our own study where enterobacteriaceae was nearly 50% sensitive to piperacillin-tazobactam (57.14%), imipenem (47.61%), chloramphenicol (52.38%), vancomycin (42.85%). The fact for the resistance of these bacteria is the ability to produce highly effective beta-lactamase enzyme which make them resistant to all beta-lactam antibiotics except carbapenem, cephamycins (cefoxitin, cefotetan).[41]

Non-ESBL producing *E. coli* were moderate to highly sensitive to carbapenem group, polymyxin, and colistin, 62.79 to 75.25% sensitive to aminoglycoside group of antibiotics, levofloxacin, chloramphenicol, and piperacillin-tazobactam, and ESBL producing *E. coli* were moderately sensitive to carbapenem group (74.13–81.03%) and 65.51% sensitive to polymyxin and colistin. Our study was contrary to the study done by Ali et al,[42] where 100% sensitivity to piperacillin-tazobactam followed by carbapenem group. Again, Perim et al demoed in their study that *E. coli* was highly resistant to all the antibiotics except gentamicin and imipenem. The study by Rao et al[26] and Rameshkannan et al[27] demonstrated high sensitivity to vancomycin, linezolid in addition to other antibiotics as per our study. But our study specifically demonstrated 100% resistance of *E. coli* to vancomycin and linezolid. So, from the above studies, it was observed that *E. coli* were highly sensitive to carbapenem group.

CONCLUSION

In our study, males were significantly involved than females. Again, male patients were affected by all types of bacteria except *Enterobacteriaceae* species. Males were only affected by *Klebsiella oxytoca* and *Acinetobacter* species, whereas females were only affected by *Enterobacter faecalis*. The presence of gram-negative bacteria was higher than the gram-positive bacteria. It demonstrated that the incidence of most common bacterial isolates was MRSA, MSSA, and coagulase-negative *Staphylococcus,* followed by *Klebsiella* species and *E. coli* (both ESBL and non-ESBL producers) as 3rd and 4th most common bacterial isolates respectively. Carbapenem group was highly sensitive in case of ESBL producing *E. coli* and *Klebsiella, Acinetobacter, K. oxytoca* (except meropenem), *Pseudomonas* (except ertapenem), *E. faecalis* (except ertapenem), and *P. mirabilis*. Aminoglycoside group of antibiotics sensitivity was high in case of non-ESBL producing *E. coli, P. mirabilis, Acinetobacter*. Levofloxacin sensitivity was high in case of *E. coli, P. mirabilis, Acinetobacter*, coagulase-negative *S. aureus*. Polymyxin B and colistin were highly sensitive to *Pseudomonas, E. coli*, ESBL producing *Klebsiella, K. oxytoca*, Citrobacter, whereas *Staphylococcus* was highly sensitive to vancomycin, teicoplanin, linezolid, tigecycline, tetracycline, vancomycin (except coagulase-negative *Staphylococcus*). It provided a clear understanding of the spectrum of culture and sensitivity of bacterial isolates from pus or from wound with secondary infection and surgical wound infection. After a thorough review of the literature as well as our extensive study, it can be concluded that *E. coli, Pseudomonas, S. aureus, Klebsiella,* and *P. mirabilis* are the most common causative organism in the pus. Irrational, inadvertent use of broad spectrum antibiotics to treat infection is responsible for the emergence of resistance to ampicillin, amoxicillin, amoxicillin-clavulanic acid. So, very cautious as well as continuous monitoring should be carried out over the bacterial culture and sensitivity to choose most appropriate broad spectrum antibiotics, both for treatment as well as prophylaxis. If it happens so, then there will be better patient management. There should be continuous cooperation between bacteriologist, physicians, and surgeon for the sake of the treatment of the patients with wound infections.

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10.5005/jp-journals-10036-1131

ORIGINAL ARTICLE

Early Results of Total Condylar Knee Arthroplasty using Indian-designed Prostheses

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ABSTRACT

The present study was undertaken to evaluate the results of 50 total knee replacements performed at Military Hospital Kirkee, Pune, India, using Indian-manufactured prostheses, from November 2001 to November 2005. The study group consisted of 18 males and 28 females in the mean age of 63 years for osteoarthritis and 48 years for rheumatoid arthritis (RA): 41 knees of osteoarthritis and RA in 9 knees. The follow-up period was 6 months to 2 years, with a mean of 14 months. Good correction of deformities was achieved for all the knees. Postoperatively, there was improvement in Knee Society Score by 69 points for osteoarthritic knees and 65 points for rheumatoid knees. Excellent results were achieved in 88% of the cases. Average postoperative range of movements achieved was 90°. The results are comparable with those following use of far costlier imported prostheses.

Keywords: Osteoarthritis, Total condylar knee, Total knee replacement.

How to cite this article: Salgotra KR, Kohli S, Vishwakarma N, Chavan S. Early Results of Total Condylar Knee Arthroplasty using Indian-designed Prostheses. MGM J Med Sci 2017; 4(1):19-22.

Source of support: MGMIHS

Conflict of interest: None

INTRODUCTION

Advanced osteoarthritis (OA) and rheumatoid arthritis (RA) result in painful, deformed knees, thus compromising quality of life in these patients. Most of them cannot perform activities of daily living. Total knee replacement is a very rewarding surgery and has transformed the lives of many patients crippled with pain due to osteoarthritis, RA, or traumatic arthritis of the knee joint. First arthroplasty was performed by Gluck in as early as 1890 using ivory prosthesis in hip and knee. Hinge knee prosthesis was introduced in 1957 by Walldius. Due to poor results, Gunston introduced his polycentric knee in 1971. Insall et al[1] were the first to use unconstrained total condylar prosthesis with bone cement.

- More recently, 91 to 96% success rate has been achieved over a follow-up period of 11 years by Ranawat and Boachie-Adjei.[2]
- There is yet no ideal or universal total knee replacement prosthesis available.
- An endeavor is to produce an acceptable compromise to resurface the damaged knee joint.[3]
- The situation in India is different in many ways. Most of the patients come with very advanced disease and majority of them are unable to afford the cost unless backed by a free treatment facility.

Most of those in lower socioeconomic strata want to squat. Aim of this article is to compare the results of the more affordable Indian-designed prostheses with costlier imported ones. In our center, we have used Indian-made prosthesis, INOR total condylar knee, which has semi-constrained and posterior cruciate sacrificing design. The range of movement achieved in postoperative period and pain-free ambulation are important parameters to assess the surgical outcome. Knee Society Score has been used in our patients to assess the outcome.

MATERIALS AND METHODS

Fifty cases of cemented total knee arthroplasty using semi-constrained, posterior cruciate sacrificing Indian-made prostheses were evaluated. These surgeries were performed between November 2001 and November 2005 in Military Hospital Kirkee, Pune, India. The study consisted of 28 females and 18 males in the mean age group 63 years for osteoarthritis and 48 years for RA. Bilateral joint replacements were done in 4 patients. There were 41 cases of advanced osteoarthritis and 9 cases of RA. Preoperative and postoperative clinical and radiological assessment was done. Standing radiographs of both knees were used to assess the deformity preoperatively and its correction postoperatively. All operations were through middle line skin incision and medical para patellar arthrotomy. All the patients were managed with INOR II prosthesis which is semi-constrained, fixed bearing prosthesis. Posterior cruciate ligament was sacrificed in all the knees.

Fixed flexion deformity was corrected by soft tissue release and excision of osteophytes. Extra distal femoral

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resection was done in 3 cases (6%) to correct the fixed flexion deformity. Medial tibial condylar reconstruction with bone grafts was required in 5 patients (10%). Patella was replaced in 36 patients (72%). Lateral retinacular release was done in 5 patients. Continuous passive motion was started after drain removal on third postoperative day in all cases except those who could not tolerate the same. This was augmented by quadriceps exercises and active knee movements by the patient. Weight bearing with the help of walker was started as soon as patient was able to do active straight leg raising, usually on 5th postoperative day.

The cases were followed up for a period of 6 months to 2 years. Postoperative results were assessed clinically and radiologically using Knee Society Scoring System. These results were compared with various other results published in journals in India and abroad.

RESULTS

The present study comprises 50 total knee arthroplasties in 46 patients. Four (8%) patients underwent bilateral joint replacement. Nine (18%) patients had RA affecting knee joint, while 41 (82%) had osteoarthritis. There were 28 females and 18 males. Table 1 shows the distribution of age in the study group. The etiology of the group was tabulated in Table 2.

The average age of patients was 63 years for advanced osteoarthritis and 48 years for RA, the range being 29 to 74 years. Range of movement was more than 90° in 40 (80%) knees, 80° to 90° in eight (16%) knees, and less than 80° in two (4%) knees. More than 20° fixed flexion deformity was present in six (12%) knees and extradistal femoral resection to correct the same was required in five (10%) knees (Table 3). In others, deformity correction was achieved by soft tissue release and excision of osteophytes posteriorly.

Varus deformity of more than 20° was present in four (8%) knees as summarized in Table 4. All had significant lateral ligament laxity (>15°). Thicker tibial inserts were used in all patients [11 mm in 1 (2%) and 14 mm in 3 (6%) cases]. Three patients required reconstruction of medial condyle using bone graft from distal femoral or proximal tibial cuts.

The patients were followed up for 6 months to 2 years with a mean follow-up of 14 months. X-rays were taken preoperatively and postoperatively and at follow-up, as shown in Figures 1 to 3. Two patients (4%) complained of postoperative pain on ambulation. This was because of instability and local swelling. Two patients (4%) had

Table 1: Age distribution

Age group (years)	*Number*	*Percentage*
25–45	08	17.3
45–65	25	54.4
65	13	28.3

Table 2: Etiology

Etiology	*Number*	*Percentage*
Advanced osteoarthritis	41	82
Rheumatoid arthritis	09	18

Table 3: Preoperative fixed flexion deformity (FFD)

Range of FFD	*Number*	*Percentage*
<10°	28	56
10–20°	16	32
>20°	06	12

Table 4: Preoperative alignment (varus/valgus)

Alignment	*Number*	*Percentage*
<10°	14	28
10–20°	36	72
>20°	04	08

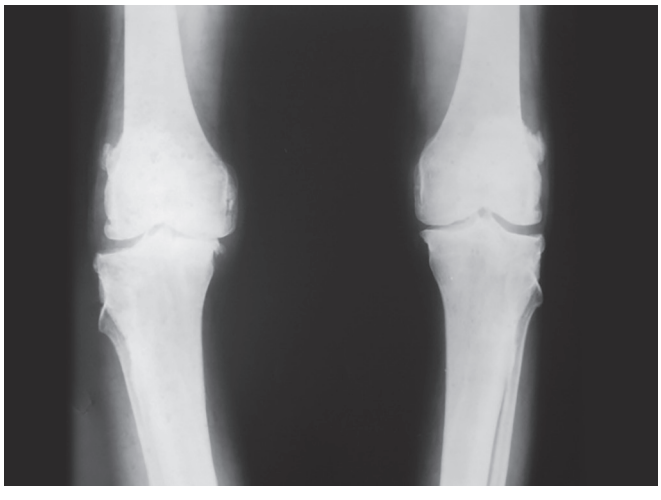

Fig. 1: Preoperative X-ray of knees

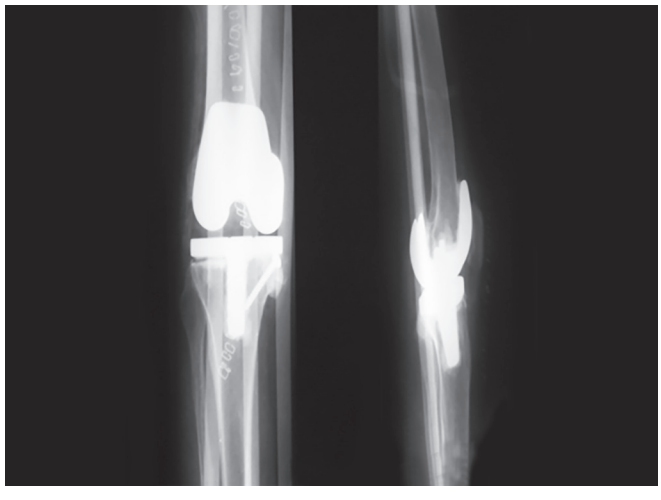

Fig. 2: Immediate postoperative X-ray

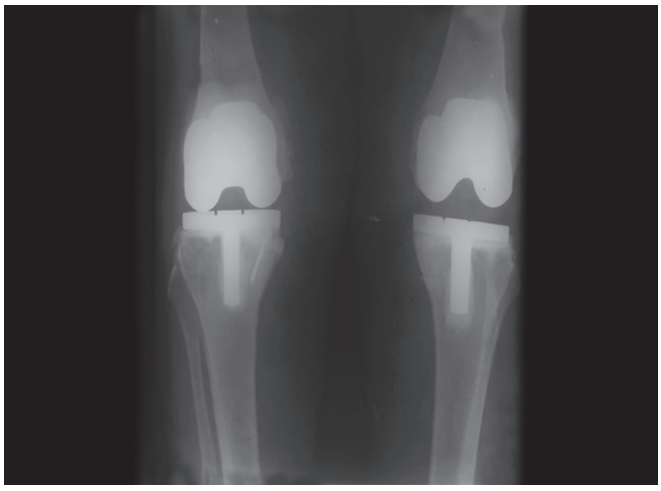

Fig. 3: Follow-up X-ray of knees

Table 5: Patient category as per Knee Society Score

Patient category	*Number of knees*	*Percentage*
A	08	16
B	32	64
C	10	20

A: Unilateral or bilateral (opposite knee successfully replaced); B: Unilateral, other knee symptomatic; C: Polyarthritis/associated medical conditions

Table 6: Knee Society Score – clinical results

Points	*Grade of results*	*Number of knees*	*Percentage*
<60	Poor	1	2
60–69	Fair	1	2
70–85	Good	4	8
85–100	Excellent	44	88

mild pain on climbing stairs after a follow-up of 2 years. Residual fixed flexion deformity of up to 10° was seen in two knees (4%) and this had corrected after 1 year of surgery.[6,7] Superficial wound infection was present in four knees which healed with dressings. Manipulation under epidural anesthesia was required for improving the range of motion in 2 patients. As per the clinical Knee Society Scoring System, 44 knees (88%) had excellent results, 4 knees (08%) had good results, 1 knee (2%) had fair result, and 1 knee (2%) had poor result. The fair result was in a grossly obese lady with bilateral knee replacement who is presently ambulant with a walking stick. The result was in a rheumatoid patient who developed analgesic nephropathy.

There was improvement in Knee Society Score by an average of 65 points in rheumatoid knees, and by an average of 69 points in osteoarthritic knees. Minimum postoperative range of movement of knee was 40° and maximum was 96°, the average being 90°. Postoperative functional score of 75 to 90 was achieved by 82% of patients with an average functional score of 80 in the series. The knee society category and clinical score distribution are summarized in Tables 5 and 6 respectively.

DISCUSSION

The results obtained in this study are comparable with other study groups in India using other fixed bearing prosthesis.[4,5] Postoperatively, no pain was present in 96% of patients in follow-up. This agrees with Chaudhary et al[5] series in which pain relief was present in 90% patients. Thirty one patients (62%) were of poor socioeconomic strata and 3 (06%) despite being cautioned were squatting while working or while passing stools. They preferred good range of movement to some amount of instability.[6] The average flexion in our study is 90.4°. Reddi et al[7] series on condylar gives an average flexion of 94.24°. Dhaon et al[8] have achieved an average flexion of 96° in varus knees and 97.4° in valgus knees.

In Dhaon et al[8] study, the postoperative alignment was 5.3° valgus. In our series the postoperative alignment achieved is 5.2° valgus; 48 (96%) had varus deformity of knee with only two knees (04%) having a valgus deformity in a polyarthritis patient with RA. Good correction was achieved in all. Residual fixed flexion deformity of up to 10° was seen in two knees (4%) and this had corrected after 1 year of surgery.[9,10]

In this study, average improvement in hospital for special surgery score for rheumatoid knee was 34. Patellar resurfacing is also a matter of controversy and in this study replacement of all patellae was done to prevent postoperative anterior knee pain. Most of the studies have shown no difference in results with or without replacement of patella.[11,12] Though the follow-up of period is too short to comment on the longevity of the prosthesis, there is no evidence of implant loosening, wear and tear of polythene, or wound infection. Superficial wound gaping was seen in four knees, of which two were in rheumatoid patients. Both these patients had been on long-term steroids and methotrexate which was stopped 6 weeks prior to surgery. In all these cases, the wound infection healed with local dressings.

The results of this study indicate that the use of Indian prosthesis, which are cheaper alternatives to the costly imported ones, can give good results if the basic surgical technique is correct and bio-mechanics are adhered to. Fixed bearing, posterior cruciate ligament sacrificing prosthesis gave satisfactory results in a population ranging from low socioeconomic strata to upper middle class group.

CONCLUSION

Total condylar knee replacement with INOR Indian-designed knee is suitable to provide pain-free, stable, and

mobile knee joint to patients suffering from advanced osteoarthritis and RA who cannot afford costlier imported prostheses.

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10.5005/jp-journals-10036-1132

ORIGINAL ARTICLE

Ultrasound Evaluation of Difference in Endometrial Thickness in Infertile and Fertile Females

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ABSTRACT

Endometrium has an important role in the success of a pregnancy, providing the site for implantation and supporting the pregnancy to fruition. There is a correlation noted between the thickness of the endometrium and the accomplishment of implantation. Endometrial thickness was measured on ultrasound examination of 50 women, who were being investigated for primary infertility and 50 age-matched healthy fertile women serving as control group, in all the three phases of the menstrual cycle. The endometrium of infertile women was found to be thinner during all the three phases of the menstrual cycle as compared with that of the fertile women in the control group. Difference in the thickness was found to be statistically significant in each phase of the menstrual cycle.

Keywords: Endometrial thickness, Infertility, Intracyclic endometrial response.

How to cite this article: Kumar S, Kapoor P, Nawre S. Ultrasound Evaluation of Difference in Endometrial Thickness in Infertile and Fertile Females. MGM J Med Sci 2017;4(1):23-25.

Source of support: MGMIHS

Conflict of interest: None

INTRODUCTION

"Infertility" is defined as failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [The World Health Organization (WHO) – The International Committee for Monitoring Assisted Reproductive Technology glossary].[1] Infertility may be primary or secondary. When a woman is unable to bear any child, either due to the inability to become pregnant or the inability to carry a pregnancy to a live birth (thus, including spontaneous miscarriage/birth of a stillborn child), she would be classified as having primary infertility.[2] When a woman is unable to bear a child, either due to the inability to become pregnant or the inability to carry a pregnancy to a live birth following a previous successful pregnancy (resulting in a live birth), she would be classified as a case of secondary infertility.

Imaging plays an important role in the workup for a case of female infertility. Ultrasound is readily available, inexpensive, noninvasive, radiation free, relatively less time consuming, and an easily repeatable mode of investigation. It helps in determining the morphology of the uterus and ovaries, in assessing the uterine and ovarian perfusion, and in evaluating endometrial thickness, volume, and vascularity among other things.

AIMS AND OBJECTIVES

- To measure intracyclical endometrial thickness in women with primary infertility during immediate postmenstrual, midcycle, and late menstrual periods.
- To measure intracyclical endometrial thickness on similar intracyclical days in age-matched group of fertile female patients.
- To compare findings in both the groups.

MATERIALS AND METHODS

Ethical clearance to conduct the study was obtained from MGM University ethical committee. Permission to conduct the study at MGM Radiology Department was obtained from MGM authorities. Written informed consent was taken from all participants. Information recorded in the questionnaire and clinical forms were used exclusively for studies. The study was carried out on females attending the outpatient department of the Department of Obstetrics and Gynecology, MGM Medical College & Hospital, Kamothe and Kalamboli, Navi Mumbai, India, who were referred to the Department of Radio-Diagnosis for ultrasonography (USG) examination.

Inclusion Criteria

About 50 women of child-bearing age matching the criteria for being diagnosed as cases of primary infertility (as per definition of infertility given by WHO)[2] were selected with due consent and ethical clearance to study endometrial thickness on three intracyclical days, namely immediate postmenstrual, midcycle, and late menstrual period. Simultaneously, age-matched, 50 healthy fertile females coming for nonpregnancy-related complaints to the USG outpatient department, who were willing to participate in the study, were included as the control group.

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Exclusion Criteria

Women with history of any previous operative manipulation, hormone replacement therapy, ovarian-stimulant drugs, and presence of any concomitant systemic disease were excluded from the study.

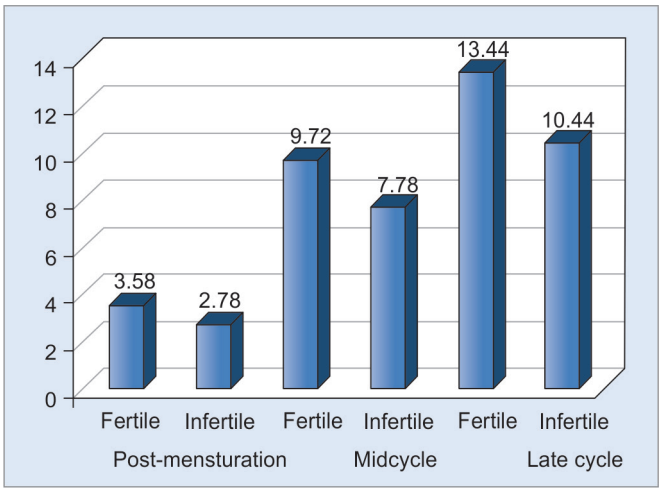
Detailed gynecological history about duration and pattern of the menstrual cycle was taken for each individual in both the groups of the women so as to determine the days for the USG examination for evaluation of the endometrial thickness.

The gray scale real-time USG examination was performed using GE Logiq P5 system and Philips HD 11 and HD 15 XE systems. Transabdominal scans in both groups of patients were performed using 3.5 to 5.5 MHz convex transducer.

Serial observations were recorded in both groups of patients. Analysis of findings in both the groups of women (using p value) was carried out.

RESULTS

There was significant difference in mean endometrial thickness of the two groups. In fertile women, endometrial thickness was greater than in the infertile women in all the three phases of menstrual cycle, as shown in Graph 1 and Table 1.



Graph 1: Diagrammatic comparison of mean endometrial thickness

Table 1: Mean endometrial thickness

Endometrial thickness	*Group*	*n*	*Mean*	*SD*	*p-value*
Postmensturation	Fertile	50	3.58	0.50	<0.01
	Infertile	50	2.78	0.46	
Midcycle	Fertile	50	9.72	1.47	<0.01
	Infertile	50	7.78	1.82	
Late cycle	Fertile	50	13.44	1.20	<0.01
	Infertile	50	10.44	2.70	

SD: Standard deviation

DISCUSSION

The prime role of the endometrium is to provide an optimal site for implantation and placentation. The functional capacity of endometrium and its ability to support a pregnancy can be assessed in many ways. Even though endometrial biopsy still remains the gold standard, physical characteristics of the endometrium can be effectively evaluated noninvasively with a USG examination and the measurement of the endometrial thickness. Many research studies have conclusively established a correlation between endometrial thickness and pregnancy outcome.[3,4] Endometrial growth may be considered as a functional bioassay for ovarian hormonal activity and can be mapped with USG. The endometrium responds to rising estrogen levels that accompany folliculogenesis.[5,6]

Ultrasound is the best modality to measure endometrial thickness as it is noninvasive, affordable, without danger of radiation-exposure, and is easily accessible. It has high specificity and sensitivity. Transvaginal ultrasound is the more reliable method to measure the endometrial thickness. However, in our study, we have restricted our study to only transabdominal as the asymptompatic group of volunteers that served as the control group was unwilling to get subjected to transvaginal sonography. Our findings in difference between mean endometrial thickness of fertile and infertile women match well with previous studies.[7]

Osemwenkha and Osaikhuwuomwan[8] concluded that a thicker endometrial lining is associated with higher pregnancy rates. Kader et al[9] concluded that when the endometrial thickness is less than 8 mm, and the trilaminar endometrial pattern not seen, pregnancy is unlikely and embryo transfer should be cancelled and embryos frozen for future transfer to increase the success rate. Dynamic change in endometrial thickness in assisted conception cycles was first described by Rabinowitz et al.[10] Using transvaginal scanning, Gonen et al[11] suggested that endometrial thickness, on the day before oocyte recovery, was significantly greater in the ladies, who got pregnant later, than in those women who did not get pregnant later, and postulated that it may be a good prognostic indicator to predict the likelihood of implantation.

Khalifa et al[12] reported that an endometrial thickness of 7 mm and below should be accepted as a reliable sign of suboptimal implantation potential.

CONCLUSION

Uterine receptivity is an important factor that affects embryo implantation. The two criteria for optimal uterine receptivity that are commonly used in studies are the thickness and the pattern of the endometrium, as assessed by USG. While in our study, we chose to

consider only the endometrial thickness, both endometrial thickness and pattern are generally acknowledged as predictors of the outcome of pregnancy.[13] The endometrial thickness was measured in this study for a group of 50 fertile and 50 infertile females in all three phases of the menstrual cycle and the results were compared using p value. The mean ± standard deviation for endometrial thickness was higher in fertile females than infertile females in all the three phases of menstrual cycle (Graph 1, Table 1).

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10.5005/jp-journals-10036-1133

REVIEW ARTICLE

Epithelial–mesenchymal Transition of Glomerular Podocytes: Implications in Proteinuria

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ABSTRACT

The kidneys play an essential role in filtration of blood plasma, regulation of water, electrolyte, and acid/base balance of the body, and thus maintain overall homeostasis. The glomerular filtration barrier serves as a size, shape, and charge barrier to ensue glomerular permselectivity, so that kidneys excrete almost protein-free urine. Podocytes are glomerular visceral epithelial cells and significantly contribute to the glomerular permeability owing to their unique structure and specialized function. Nevertheless, podocytes are susceptible to various insults, including altered metabolites, aberrant signaling molecules, and mutations to critical proteins that otherwise ensue normal function. Podocyte injury is a predominant indicator of several glomerular diseases that are manifested by proteinuria. Epithelial–mesenchymal transition (EMT) is considered as one of the responses of podocytes to the noxious stimuli, which consequently results in podocyte depletion and proteinuria. This review discusses the importance of podocytes in normal renal filtration and details the molecular and cellular events that lead to EMT of podocytes vis-à-vis impaired glomerular filtration.

Keywords: Epithelial–mesenchymal transition, Glomerulus, Kidney, Nephron, Podocytes, Proteinuria.

How to cite this article: Nishad R, Nakuluri K, Motrapu M, Pasupulati AK. Epithelial–mesenchymal Transition of Glomerular Podocytes: Implications in Proteinuria. MGM J Med Sci 2017;4(1):26-34.

Source of support: The work is funded by a grant from SERB, India (EMR/2015/002076) and DST-INSPIRE Faculty Scheme to AKP.

Conflict of interest: None

KIDNEYS ENSUE EXCRETION OF PROTEIN-FREE URINE

Over a million nephrons in each kidney work in concert to regulate water and acid/base balance of the body and to ensue excretion of protein-free urine. Thus, kidneys become vital organs to ensure homeostasis of the body. The two essential segments of a nephron are glomerulus and renal tubule. The glomerulus is essential for filtering water and small molecules from plasma. The tubular system ensues both selective reabsorption of glomerular filtrate and selective secretion of ions into glomerular filtrate. Therefore, both glomerulus and renal tubule work in concert and dictate the final composition of urine. The potential of kidney to excrete almost protein-free ultrafiltrated urine gets compromised during disease conditions, and as a result varying amounts of plasma proteins get excreted in urine. Albuminuria is an index of adverse renal outcome, which can be assessed by measuring albumin levels in urine, collected for 24 hours. According to the American Diabetic Association, microalbuminuria describes levels of urine albumin ranging from 30 to 300 mg/24 hours; and macroalbuminuria describes a urinary albumin excretion of ≥300 mg/24 hours. The condition of macroalbuminuria often progresses to overt proteinuria and even further to end-stage renal disease (ESRD), warranting renal transplant therapy.

Appearance of protein in the urine indicates a structural and/or functional artifact, particularly in the glomerular region.[1] The glomerular filtration barrier (GFB) of the kidney serves as a size, shape, and charge selective molecular sieve. The three critical components that constitute GFB are: (a) Fenestrated endothelium of glomerular blood vessels; (b) basement membrane that covers the blood vessels; and (c) the podocytes that provide epithelial coverage to basement membrane (Figs 1A and B). Though, all the three components contribute to the integrity of GFB, there is much debate on the critical role of each component toward size, shape, and charge-dependent permselectivity of GFB. It was proposed that endothelial dysfunction is a causal factor in the pathogenesis of proteinuria.[2] Thickening of glomerular basement membrane (GBM) by excess deposition of collagen and altered charge selectivity implicates the pathogenesis of proteinuria.[3,4] The third and final barrier that restricts entry of proteins from circulation into the urine is the podocytes, also known as visceral epithelial cells. There is increasing evidence for the crucial role of podocytes in this glomerular filtration process.[5]

PODOCYTES ARE UNIQUE CELLS WITH SPECIALIZED PROPERTIES

Podocytes are the major cell type of glomerulus and account for about 30% of all glomerular cells. Podocytes are highly branched epithelial cells and cover the urinary

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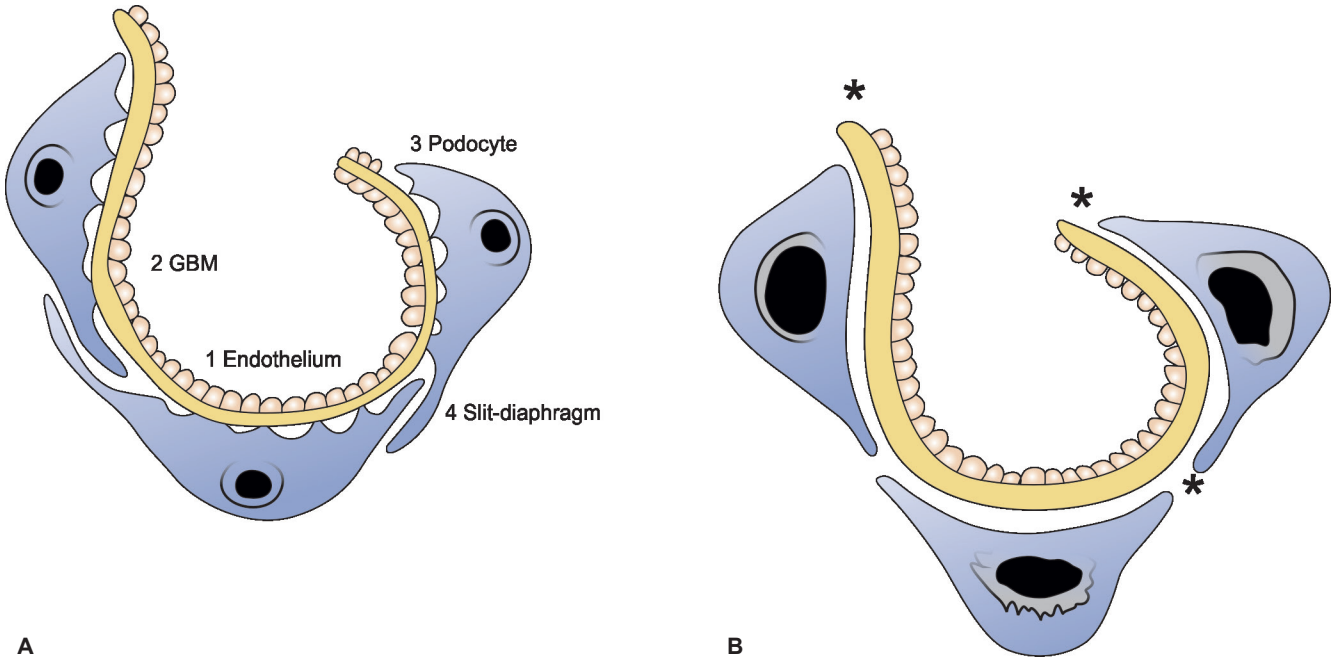


Figs 1A and B: Components of GFB. (A) The essential components of GFB are: (a) endothelium; (b) glomerular basement membrane; (c) podocytes; and (d) slit-diaphragm. (B) The major alterations of GFB during proteinuria conditions are indicated as * (asterisk), which include thickening of glomerular basement membrane, effacement of podocyte foot process, and damage to slit-diaphragm

side of the GBM. The important functions of podocytes are to (1) synthesize the components of GBM, including collagen; (2) provide structural support for the glomerular vasculature and filtration; (3) serve as a contractile apparatus together with basement membrane to counteract the expansive forces of the glomerular vasculature, (4) offer glomerular permselectivity, and (5) secrete several survival factors [vascular endothelial growth factor (VEGF) and angiopoietin] for endothelial cells. Therefore, podocytes are considered to be crucial in the regulation of glomerular architecture and function. Zimmerman[6] made the very first description of podocyte way back in 1929; he described podocytes as a heavily branched cell type within the glomerulus. The unique architecture of podocytes includes a voluminous cell body, from which long cellular processes extend, comprising primary and secondary processes. Secondary processes end in large number of foot processes, which constitute the main functional unit of the podocytes. The primary processes are composed of microtubules and vimentin filaments, while the foot processes are made of filamentous actin (F-actin). Foot processes play a critical role in cell/cell contact between podocytes, attachment of podocytes to the GBM and adjusting the shape of podocytes in response to the glomerular pressure.

The neighboring foot processes of podocytes are connected with an adherens junction, namely slit-diaphragm (SD), which represents the only cell/cell contact between podocytes. Though the SD is freely permeable to water and small solutes, it restricts the passage of large molecules, particularly proteins. Several proteins (Nephrin, Podocin, TRPC6 CD2AP, P-cadherin, etc.) constitute the SD and enable it to act as a charge, size, and shape selective glomerular barrier. The filtration slits of SD are 40 nm wide and smaller than the size of albumin, a predominant plasma protein. The apical membrane of podocyte, located above the SD, is negatively charged due to the presence of the glycocalyxin. Negatively charged glycocalyxin repels serum albumin and also helps maintain adjacent foot processes separate from each other. The basal membrane of podocytes, located below the SD, is associated with anchorage of podocytes to GBM, which is mediated by integrin family proteins.

A key feature that distinguishes podocytes from other renal cells is that they are terminally differentiated cells, postmitotic, quiescent in nature, and do not proliferate in response to injury or noxious stimuli. Whereas glomerular endothelial cells and mesangial cells readily proliferate in response to injury caused by an array of insults,[7,8] it is postulated that with a loss of critical proportion of the podocyte population in response to the injury or mutations, the remaining cells are unable to compensate for the glomerular filtration.[9] The range of podocyte injuries that can be caused by altered milieu, mutations in podocyte proteins, and also due to extrinsic stressors are collectively known as podocytopathy. Genetic podocytopathy [nephrotic syndrome (NS)] refers to the injury to the podocytes owing to mutations in key genes that encode proteins localized to SD. On the contrary, reactive podocytopathy refers to the podocyte injury triggered by

alterations in podocyte microenvironment during metabolic disorders (diabetes and obesity) or external agents (human immunodeficiency virus, immunoglobulin [Ig] A immune complexes, etc.). Nevertheless, podocytopathies manifest in considerable amount of proteinuria and, if left untreated, may progress to ESRD.

RESPONSE OF PODOCYTES TO INJURY DURING GLOMERULAR DISEASES

There are several diseases whose pathophysiological manifestation involves podocyte injury, which includes diabetic nephropathy (DN), membranous nephropathy, NS, and focal segmental glomerulosclerosis. One of the predominant ultrastructural manifestations of podocyte injury is effacement, characterized by flattening of podocyte foot process (Fig. 1). It leads to distortions of SD architecture and impairment of its permselectivity. Podocytes respond to the injury by secreting excess extracellular matrix (ECM) proteins, such as collagen IV, laminin, and fibronectin, leading to thickening of GBM. Altered composition of basement membrane leads to enhanced permeability. Reactive oxygen species secreted by injured podocytes damage the integrity of ECM, which increases the permeability to plasma proteins. Matrix metalloproteases secreted by injured podocytes selectively degrade target ECM proteins. Alternatively, podocytes, upon injury, fail to secrete sufficiently enough growth factors (e.g., VEGF) to promote the growth of glomerular endothelial cells. Endotheliosis, secondary to podocyte injury, limits the function of GFB.[10] Podocyte injury, therefore, results in concomitant morphological changes, such as effacement, thickening of GBM and endotheliosis. These events manifest in reduced function of GFB vis-à-vis proteinuria. Apart from the events discussed above, podocytes respond to injury by undergoing apoptosis, autophagy, anoikis and necrosis, or detachment from GBM. These events account for decreased podocyte number (podocytopenia). Neighboring podocytes respond to podocyte loss by undergoing hypertrophy. Compensatory hypertrophy of podocytes is an adaptation to cover the GBM exposed due to podocyte loss. Nevertheless, it leaves the GBM denuded and eventually results in loss of epithelial coverage to the GBM.[11]

Studies in both patients with DN and animal models of diabetes mellitus revealed that proteinuria is associated with decreased density and altered morphology of the podocytes.[12,13] Decrease in podocyte number predicts progressive decline in renal function and proteinuria in Pima Indians with diabetes mellitus.[14] Among several modes of podocyte depletion mentioned above, apoptosis was proposed as the major mode of podocyte loss, based on experiments pursued in transforming growth factor (TGF)-β1 transgenic mice, CD2AP$^{-/-}$ mice and puromycin aminonucleo side treated rats.[15-17] These studies argue that ~90% of the podocytes detected in urine are apoptotic.[12] An interesting finding is that podocytes that are shed in urine are viable and can be cultured. It is not readily explainable how podocytes from urine could be viable and can be cultured, if majority of the podocytes have undergone apoptosis.[18,19] Recovery of podocytes from urine strongly suggests that injured podocytes detach from GBM with intact renewable machinery of cells. Podocytes are anchored to GBM with the help of ECM proteins including laminin, integrins, dystoglycan, and collagen and alterations in cell–matrix adherence leading to podocyte detachment. Evidence for this mechanism is provided by data showing elevated expression of antiadhesive proteins and integrin receptors in DN.[19-22] Moreover, it is evidenced from diabetic rats that podocytes detach from GBM into urinary space.[21] Podocyte detachment could be explained by two possible mechanisms: Alterations in expression of ECM components; and enervated cell–cell and cell–ECM interactions. Since reduction in podocyte density and appearance of podocytes in urine is an early pathological feature in patients with diabetes and animal models of diabetes,[23-25] podocyte depletion could be considered as a hallmark of human and experimental DN and NS.

It was proposed that podocytes, in response to injury, are capable of undergoing a phenotypic switch to attain an embryonic form by shedding their specialized epithelial characteristics and by acquiring mesenchymal features. This phenotypic switch is known as epithelial–mesenchymal transition (EMT). It is conceivable that podocytes, after undergoing EMT, abandon their complex morphological architecture and relinquish their highly specialized functions, impairing GFB integrity, and altogether leading to the onset of proteinuria. Although it is debatable whether EMT contributes to decreased podocyte density in diabetic kidney disease, the presence of significant number of viable urinary podocytes in both experimental models of DN and in patients with DN suggest that podocyte dropout might be caused by decreased podocyte adhesion, which is a potential consequence of EMT.[19,26]

EPITHELIAL–MESENCHYMAL TRANSITION

Epithelial–mesenchymal transition is a tightly controlled cellular event during which an epithelial cell that otherwise interacts with basement membrane undergoes phenotypic switch and attains characteristics of mesenchymal cells, including enhanced migratory capacity, invasiveness, resistance to apoptosis, and increased production of ECM. Although EMT is considered as a pathological event in case of nephropathy, tissue fibrosis, and cancer metastasis, it is a fundamental process that occurs during several stages of development, such as mesoderm forma-

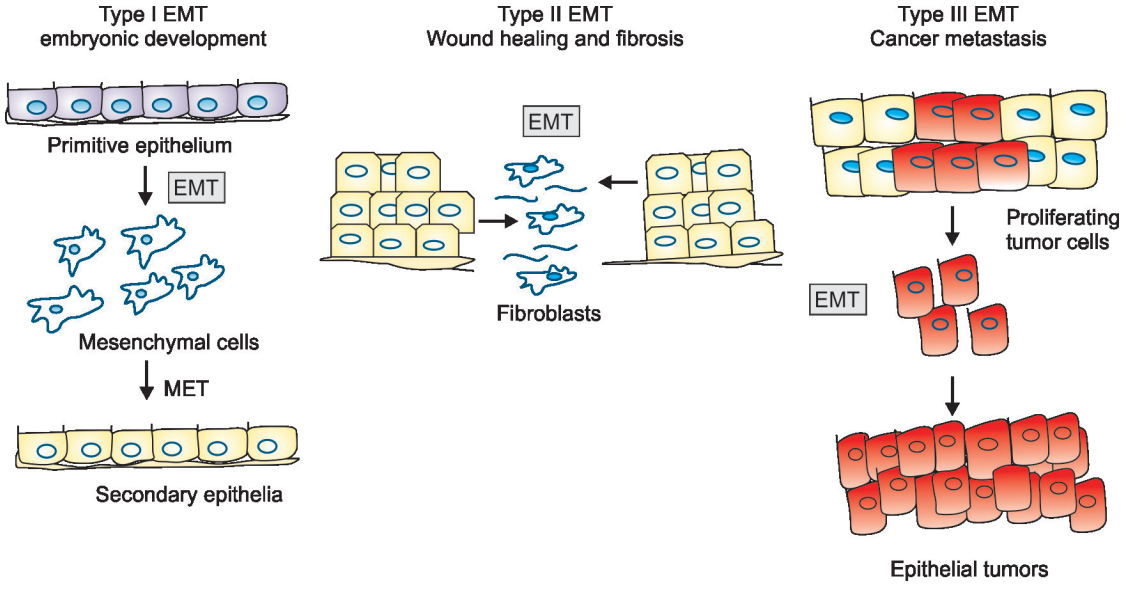


Fig. 2: Three types of Epithelial–mesenchymal transition (EMT). Type I EMT is associated with embryonic development, such as implantation and embryonic gastrulation. The primitive epithelium undergoes EMT to give rise to primary mesenchyme, which in turn undergoes MET to form secondary epithelia. Type II EMT is associated with inflammation and wound healing. If the primary inflammatory insult is not attenuated, type II EMT results in fibrosis. Type III EMT is associated with metastasis. Proliferating tumor cells in secondary epithelia undergo EMT that ensue their metastasis to form epithelial tumors

tion from embryonic epithelium and delamination of the neural crest.

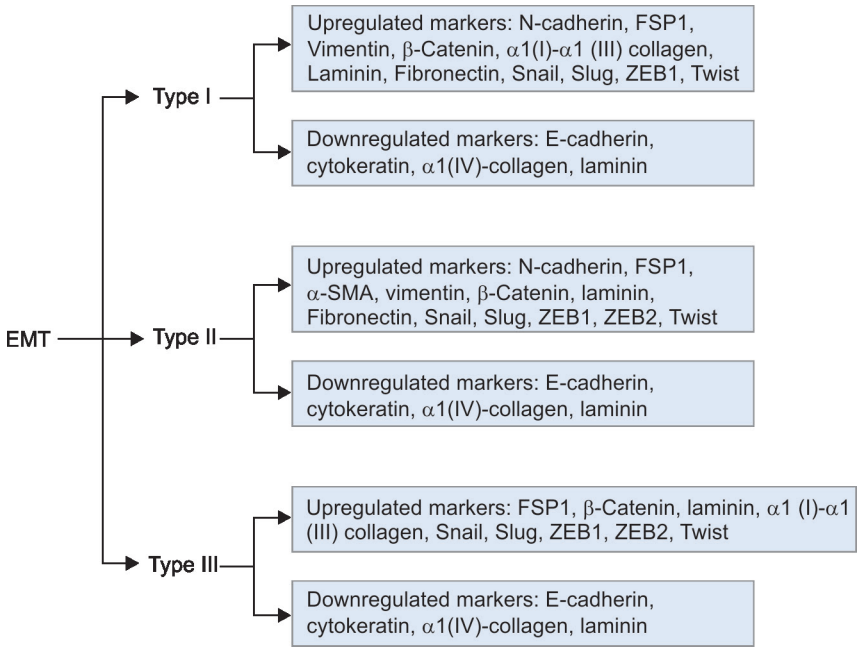
Epithelial–mesenchymal transition has been categorized into three different subtypes, based on functional consequences (Fig. 2). Epithelial–mesenchymal transition, i.e., associated with implantation, embryogenesis, and organ development are categorized as type I. Nevertheless, mesenchymal cells, known as primary mesenchyme, that arise as a result of type I EMT, have the potential to subsequently undergo a mesenchymal–epithelial transition (MET) to generate secondary epithelium. Secondary epithelia may further differentiate and undergo subsequent EMT to generate the cells of various lineages including astrocytes, adipocytes, chondrocytes, and osteoblasts. Epithelial–mesenchymal transition, i.e., associated with tissue regeneration and wound healing is of type II. Type II EMT is a repair-associated event that generates fibroblasts in order to reconstruct damaged tissue following a trauma and/or inflammation (Fig. 2). However, aberrations in type II EMT may eventually lead to fibrosis and organ destruction. Type III EMT occurs in neoplastic cells that may invade, metastasize, and ensue in tumor outgrowth. Further insights about the types of EMTs are detailed elsewhere.[27]

PODOCYTE UNDERGOES EMT

It is considered that phenotypic switch between healthy and diseased podocytes partially resembles type II EMT only.[28] Podocytes possess epithelial features, such as apical-basal cell polarity and tight junctions. Podocytes are anchorage dependent with a low invasive capacity.[28] Epithelial markers expressed by podocytes include E- and P-cadherin, WT-1, and ZO-1 (Flow Chart 1 and Fig. 3). The predominant manifestations of podocyte EMT are loss of their epithelial polarity, rearrangement of actin cytoskeleton, and injury to SD. Podocytes undergo cadherin switch from E- and P-cadherin to N-cadherin during EMT. On the contrary, podocytes express vimentin and intermediate filaments; and also possess high migration capacity. These later innate features of podocytes resemble that of mesenchymal cells and, therefore, podocytes are considered as specialized or atypical epithelial cells. List of acquired markers and attenuated markers during different types of EMT are provided in Flow Chart 1.

Elevated expression of fibroblast-specific protein-1 (FSP-1) in podocytes exposed to hyperglycemic conditions ensues EMT of podocytes.[29] Expression of increased collagen by injured podocytes also indicates that podocytes undergo EMT.[30] Although podocytes express vimentin, following an exposure to TGF-β1, a potent inducer of EMT, a further increase in vimentin was observed.[31] Injured podocytes express multiple transcriptional factors that ensue EMT, which include ZEB2, SNAIL, and SLUG. It was also reported that podocyte dedifferentiation is associated with attenuation of epithelial markers, such as P-cadherin and ZO-1. Despite the fact that podocytes undergo EMT upon noxious stimuli that are prevalent during various pathophysiological conditions, it has been proposed that the EMT of podocytes satisfies criteria of type II EMT partially.[28] The unique nature of differentiated podocyte further distinguishes them from the three types of EMT. Differentiated podocytes are spindle-

Flow Chart 1: List of acquired and attenuated markers during EMT. Various mesenchymal markers are upregulated and epithelial markers are downregulated during different types of EMT. The EMT of podocytes resembles type II EMT



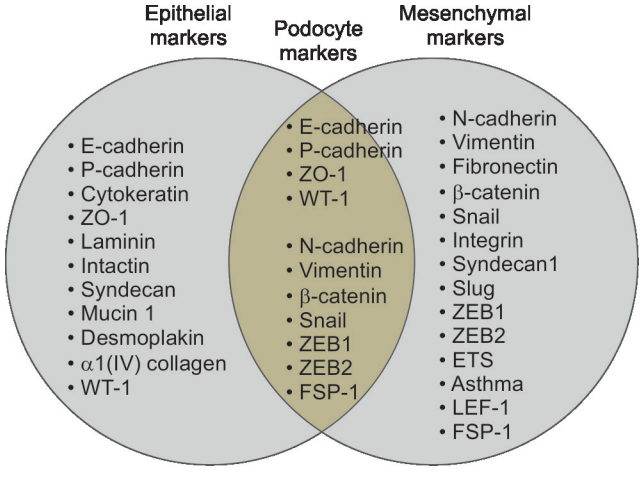


Fig. 3: Epithelial and mesenchymal features of the podocyte. Predominant characteristics of epithelial and mesenchymal cells are listed. The podocytes possess some of the features that are both epithelial and mesenchymal

shaped and arborized. Upon subjected to various insults, podocytes lose their apical-based polarity, and there is a compromise in their morphological features and function, as evidenced by redistribution of stress fibers occurs, and also in permselectivity. Features, such as redistribution of stress fibers and loss of polarity are unique to podocyte EMT and have not been seen in the other three types of EMT. Lists of epithelial and mesenchymal markers present in podocytes are provided in Figure 3.

FACTORS THAT INDUCE PODOCYTE EMT

Although TGF-β1 is a well-known inducer of type III EMT, the primary evidence for the role of TGF-β1 in podocyte EMT was provided by a study from Li et al.[30] The TGF-β1 treatment attenuated the expression of P-cadherin, ZO-1, and nephrin, while promoting the acquisition of mesenchymal markers, such as FSP-1 and Desmin. Nephrin, P-cadherin, and ZO-1 are constituents of SD; decreased expression of these proteins is expected to impair the integrity of the SD leading to foot process effacement and altered podocyte permselectivity to serum proteins. Increased transcriptional activity of Snail implicated in TGF-β1 triggered EMT of podocytes, whereas ectopic expression of Snail suppressed P-cadherin and nephrin. It is also reported that treatment with TGF-β1 resulted in retraction and shortening of podocyte foot processes and contraction of the cell body. Besides these morphological changes, TGF-β1 induced dedifferentiation of podocytes with increased motility. Following treatment with TGF-β1, attenuation of podocyte epithelial markers and adhesive proteins and acquisition of mesenchymal markers was observed.[31] The TGF-β1 suppresses α3 integrin expression in nephrotic rats.[32] These *in vivo* observations in nephrotic rats are supported by a study from cultured podocytes, wherein cells exposed to TGF-β1 showed loss of α3-β1 integrin expression. Since α3 integrin subunit regulates podocyte interaction with GBM, it is speculated that loss of α3-integrin expression by TGF-β1 ensues podocyte detachment and depletion.[33] In summary, the multiple effect of TGF-β1 on podocytes includes reduced expression of adhesion proteins (particularly integrins), attenuation of epithelial markers and acquisition of mesenchymal markers, and suppression of proteins that control the integrity of SD.[31]

Human pituitary growth hormone (GH) is another molecule, whose effect on podocyte EMT is well documented. In the setting of diabetes, particularly in type I DM, insulin deficiency is associated with reduced insulin-like growth factor (IGF-1) production by liver. Decreased IGF-1 secretion in concert with impaired IGF-1 action, due to increased secretion of hepatic IGF binding protein 1, elicits a negative feedback response to induce GH secretion by the pituitary gland.[34] Podocytes express GH receptor (GHR) and respond to GH by activation of canonical JAK-STAT signaling.[35] Elevated GH levels manifest in podocyte injury and proteinuria. Supraphysiological levels of GH in transgenic animals are associated with degenerative changes in the kidney.[34,36] A direct relationship has been observed between elevated GH levels and renal macroalbuminuria and glomerulosclerosis. On the contrary, GH deficiency or ablation of GHR activation conferred protective effect in diabetic conditions. In our study, we observed that GH induces ZEB2, a transcription factor that mediates EMT. It was also shown that GH-induced ZEB2 suppresses SD proteins and consequently increases podocyte permeability to albumin.[37] Furthermore, we have also demonstrated that administration of GH to rats induced podocyte EMT vis-à-vis decreased podocyte count, and increased proteinuria.[38]

Advanced glycation end-products (AGEs) that are derived from glucose via nonenzymatic reactions are also implicated in the pathogenesis of DN. Carboxymethyllysine (CML) is one of the predominant AGEs that accumulate in glomerular region of diabetic patients and animal models of diabetes. In our recent study, we demonstrated that CML induced the expression of ZEB2 in podocytes via activation of nuclear factor (NF)-kB signaling cascade. The CML treatment induced promoter activity of NF-kB and ZEB2 suppressed promoter activity of E-cadherin and increased podocyte permeability to albumin. Attenuation of NF-kB cascade prevented CML-dependent ZEB2 expression. It is interesting to note that shRNA-mediated knockdown of ZEB2 expression abrogated both CML-mediated invasiveness and permeability of podocytes.[39] Elevated CML levels are concurrent with increased expression of ZEB2 in glomeruli and proteinuria.

Glomerulus is composed of microvasculature, which is exposed to high volume and continuous perfusion. The kidney's demand for oxygen is very high. The low oxygen conditions that prevail during pathological conditions, such as diabetes and stroke induce alpha subunit of hypoxia-inducible factor-1α (HIF-1α) in the kidneys. In our recent study, we demonstrated that HIF-1α induced ZEB2 expression, both by directly interacting with ZEB2 promoter and by increasing expression of a ZEB2-natural antisense transcript. Elevated expression of ZEB2 resulted in suppression of E- and P-cadherin, which is implicated in podocyte EMT and proteinuria observed in hypoxic conditions.[40]

NEPHROTIC SYNDROME *VS* EMT OF PODOCYTES

Other than various insults that arise as a consequence of metabolic and physiological alterations, genetic defects are also associated with podocyte EMT, for instance, mutations in genes encoding podocyte SD proteins. In particular, single gene defects causing NS tend to cause irreversible damage to podocytes. Most of the genetic defects that cause NS occur in proteins that constitute SD or in proteins that are critical to the podocyte biology, such as nephrin, podocin, CD2AP, or alpha-actinin. The extracellular domain of nephrin protein forms a protein scaffold with the help of cysteine residues present in its eight IgG-like motifs.[41] This scaffold of nephrin interacts with other proteins in order to maintain the integrity of SD, whereas intracellular domain of nephrin interacts with actin cytoskeleton of the podocyte foot process.[42] Loss of extracellular domain of nephrin due to mutations results in aberrations in SD architecture.[43] Podocin is a raft-associated podocyte foot process protein, which is essential for nephrin transport to the podocyte membrane.[44] It is considered that podocin interacts with nephrin and CD2AP. CD2AP is an adaptor molecule, which possesses actin-binding sites. Nephrin, CD2AP, and podocin are capable of interacting with each other, thus contribute to the integrity of SD, and dynamic actin assembly.[45,46] Mutation in these SD proteins is associated with distortion of SD assembly and cause proteinuria.

OTHER MODES OF PODOCYTE DEPLETION

Although existing paradigm argues that podocytes are terminally differentiated and are unable to proliferate, it was suggested that they might proliferate in case of crescentic glomerulonephritis. Nevertheless, cells found in crescentic glomerulonephritis did not express predominant podocyte markers including WT-1.[47] Large body of evidence suggests that parietal epithelial cells and progenitors of podocytes are the major cell type in crescents.[48] This led to a new perception that podocytes undergo dedifferentiation during injury in order to engage in the cell cycle. All the evidence reiterates that mature podocytes are terminally differentiated, whereas parietal epithelial cells undergo proliferation and likely to contribute for the glomerular disease, such as crescentic and collapsing forms of glomerulopathy. In case of progressive glomerular diseases, podocyte loss cannot be matched by proliferation of

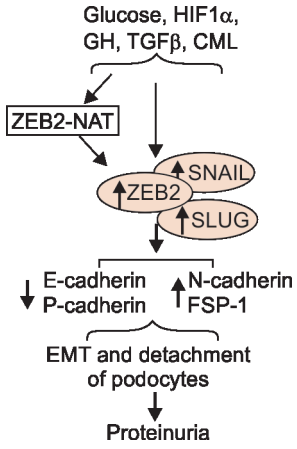


Fig. 4: Mechanism of podocyte EMT; TGF-β1, HIF-1α, GH, and CML induce expression of transcriptional factors, such as ZEB2, Snail, and Slug. These transcriptional factors suppress expression of epithelial markers and SD proteins while inducing expression of mesenchymal markers. A series of events lead to increased motility and consequent loss of podocytes. Together, these events manifest in proteinuria

parietal epithelial cells, which leads to overall podocyte depletion, with consequent glomerulosclerosis.

Another mode of podocyte injury that manifests in podocyte depletion is hypertrophy. The podocyte loss leaves a denuded area on GBM, which is covered by hypertrophy of neighboring podocytes, as podocytes are unable to proliferate. Podocyte hypertrophy involves various stages as evidenced in aged rats: Initial non-stressed podocyte hypertrophy (without proteinuria), followed by adaptive hypertrophy, and decompensated podocyte hypertrophy are characterized by reduced nephrin expression and proteinuria.[49] These events finally culminate in podocyte depletion. Several other modes of podocyte depletion have been described. Necrosis of podocytes occurs in membranous nephropathy. Anoikis, mitotic catastrophe, and apoptosis of podocytes have been documented in various glomerular diseases.[50]

CONCLUSION

Our understanding of podocyte biology has increased significantly in the past two decades. Nephrologists recognized the importance of podocytes in the glomerular filtration. Accumulated evidence highlights the novel mediators of podocyte injury, particularly which contributes to podocyte detachment by transforming these cells from epithelial form to more invasive and motile phenotype. Dearth of sufficient number of podocytes compromises glomerular permselectivity, which manifests in increased permeability to protein across GFB. Thus, the depletion of podocytes accounts for proteinuria observed in majority of glomerular diseases. Moreover, EMT is considered to be one of the predominant molecular mechanisms to explain podocytopenia in DN. The TGF-β1, HIF-1α, GH, and CML are some of the well-studied agents that trigger podocyte EMT, whereas ZEB2, Snail, and Slug are the key transcription factors that transduce EMT (Fig. 4). Our understanding of podocyte EMT with insights from cultured podocytes and animal models may enable us to target EMT as a therapeutic option.

ACKNOWLEDGMENT

Authors would like to thank Ms. Sneha Bheemireddy for technical assistance during preparation of this manuscript.

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10.5005/jp-journals-10036-1134

REVIEW ARTICLE

Fetal Surgery: A Basic Overview and a Glimpse into Its Future

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ABSTRACT

The routine antenatal screening for congenital disorders in the fetus has made a sea change the way we look at the fetus. With the availability of high-resolution ultrasound machines, we have technology to diagnose fetal structural defects, with high degree of certainty. Some of these babies can go through the entire pregnancy and can be operated upon after delivery without additional morbidity and mortality. Fetus with diaphragmatic hernia needs fetal surgery for better survival, while the fetus with myelomeningocele can be operated upon postnatally, but neurological outcome for the baby is better if operated upon *in utero*. Fetal surgery is performed in the second trimester of pregnancy either by open route or by endoscopy. Endoscopy route is still evolving and generally used to coagulate the communicating vessels in cases of twin–twin transfusion syndrome. Open fetal surgery involves hysterotomy, control of hemorrhage from edges of hysterotomy wound, aspiration of amniotic fluid, delivery of effected fetal part to the hysterotomy wound, corrective surgery, closure of uterine incision, and instillation of aspirated amniotic fluid back to uterus. Postoperatively, the patient is given tocolytics and antibiotics to avoid preterm labor and infection respectively. At appropriate date, the baby is delivered by cesarean section. Despite several benefits, fetal surgery cannot be considered safe for the mother and the fetus. It is associated with considerable maternal morbidity like hemorrhage, preterm delivery, chorioamnionitis, and so forth. It also needs coordinated team effort with a dedicated team of obstetrician, anesthetist, pediatrician, and other specialized surgeons of concerned deformity in the fetus. Currently, fetal surgery is a new frontier of fetomaternal medicine and may be labeled as evolving science, and the facility should be limited to highly specialized tertiary care centers to gain more experience. However, the future of fetal surgery as an effective tool to correct the congenital defects for the fetus is promising.

Keywords: Fetal surgery, Minimally invasive fetal surgery, Open fetal surgery.

How to cite this article: Kumar S, More M, Sharma S. Fetal Surgery: A Basic Overview and a Glimpse into Its Future. MGM J Med Sci 2017;4(1):35-38.

Source of support: MGMIHS

Conflict of interest: None

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INTRODUCTION

The unborn child has truly become a patient because of the availability of high-resolution imaging and screening procedures. Conditions like fetal malformations, genetic diseases, or *in utero* acquired conditions when suspected can be diagnosed and treated *in utero*. Certain conditions require surgical correction and in most cases, this is done after birth. Occasionally, fetal surgery is required to save the life of the fetus and to prevent permanent damage. There are around 600 fetuses requiring surgery per year, and many of them undergo fetal surgery. Fatal conditions in which the chances of survival of the baby are low like urinary tract obstruction, congenital diaphragmatic hernia (CDH), twin-to-twin transfusion syndrome (TTTS) are operated antenatally. Until the late 1990s, prenatal surgery was almost exclusively limited to life-threatening conditions. However, in 1994, the first prenatal surgery to treat myelomeningocele was performed, even though it is not a life-threatening condition.

HISTORY

Intrauterine transfusion of hydropic fetus to correct anemia in case of Rh isoimmunization was the first intrauterine procedure described in 1961. On April 26, 1981, the first successful open fetal surgery was performed for a urinary tract obstruction, under the direction of Dr Michael Harrison.[1] Congenital diaphragmatic hernia was first corrected successfully *in utero* in 1989. The resection of a congenital cystic adenomatoid malformation (CCAM) from a fetal lung was performed in 1990 for the first time. Fetal sarcococcygeal teratoma resectioning was first done in 1992. Between 1997 and 2004, more than 200 open surgeries were performed for myelomeningocele. In the last decade of development in fetal surgery, minimally invasive procedures like fetoscopy and laser ablation have come in.

DESCRIPTION

The decision to have prenatal surgery is taken when accurate diagnosis is made and associated anomalies excluded by carrying out echocardiogram, amniocentesis, and chorionic villi sampling (CVS). The cases selected are those with no possible effective postnatal therapy, and the specific surgery has a proven benefit with documented

animal studies. Interventions are performed in specialized multidisciplinary centers with strict protocols. Approval of local ethics committee and informed parental consent is taken. Consultations include a neonatologist, a pediatric surgeon, a clinical nurse specialist, and a social worker. Usually only fetuses with a very poor prognosis are candidates for maternal–fetal surgery. Only about 10% of those referred for evaluation actually undergo the surgery, as additional congenital defects preclude prenatal surgery. Prenatal surgeries usually are performed between 18 and 26 weeks of gestation. Prenatal surgery usually requires a general anesthesia. The fetus receives the anesthetic via the mother's blood. The anesthesiologist and a neonatologist monitor the heart rates of the mother and fetus respectively. Epidural anesthesia can sometimes be used instead of general anesthesia.[2] Prophylactic tocolysis (preoperatively and postoperatively) is required, as the mother can go into preterm labor.

Open Fetal Surgery

Open fetal surgery is a complex procedure and should be undertaken by experienced personnel. After opening the maternal abdomen, a narrow tube is placed through a puncture in the uterine wall, through which the amniotic fluid is drained out and collected in syringes. A procedure similar to cesarean section is performed, called hysterotomy, to open the uterus. Using ultrasound as a guide, the surgeon feels for the affected fetal part. The fetus must be moved away from the placenta. The first incision is made at a point away from the placenta to prevent damaging it. Specialized reabsorbable surgical staples are applied to the cut uterine edge to prevent maternal hemorrhage. The fetus is exposed or exteriorized and monitored. The fetus is kept warm with infusion of Ringer's lactate, at body temperature, into the uterine cavity. The specific procedure is then carried out. After the completion of the procedure, the uterus is closed. The amniotic fluid is then reinfused. An additional omental flap may be applied to cover the wound.

Amniotic fluid leakage, either from hysterotomy site or vaginally, is a common complication. Open fetal surgery has proven to be reasonably safe for the mother. All future pregnancies for the mother require cesarean delivery because of the hysterotomy. However, there are no presented data suggesting decreased fertility for the mother.[3,4] For the fetus, safety and effectiveness are variable, depends on the specific procedure, the reasons for the procedure, the gestational age, and condition of the fetus. Conditions that can potentially be treated by open fetal surgery include (i) CDH (if indicated at all, it is now more likely to be treated by endoscopic fetal surgery), (ii) CCAM, (iii) congenital heart disease, (iv) pulmonary sequestration, (v) sacrococcygeal teratoma, and (vi) myelomeningocele.

Minimally Invasive Fetal Surgery

Minimally invasive fetal surgery, also called as keyhole surgery, uses specially designed fetoscopes. They are flexible fiber endoscopes with high pixelated camera for better picture quality. Current scope diameters are between 1.0 and 2.0 mm with a 0° direction of view and an opening angle of 70 to 80°.[5] The intraamniotic access is facilitated by thin-walled, disposable semiflexible cannula or larger-diameter reusable rigid metal cannula to facilitate instrument change. Instrument insertion is done under local anesthesia.

Despite the minimally invasive nature of fetoscopy, it is associated with iatrogenic preterm rupture of membranes. Several initiatives have been taken toward treating and preventing this, including attempts to repair defects with tissue sealants. Use of amniopatch was first described by Quintero et al in 1996. Amniopatch is a procedure for sealing amniotic leakage after membrane rupture by using cryoprecipitate and platelets obtained after plasmapheresis.[6]

The first successful fetoscopic temporary tracheal occlusion for CDH[7] was performed in 1996. A small surgical incision was made in the uterus, and a tiny fiberoptic fetoscope inserted to guide the surgeon. A needle-like instrument carrying a balloon was then passed through the uterus. The balloon was placed in the fetus's trachea and inflated. This prevents lung fluid from escaping through the mouth, enabling the lungs to expand, grow, and push the abdominal organs out of the chest and back into the abdomen. The balloon is removed at birth. In a successful procedure, the lungs are developed enough for the baby to breathe on its own at birth.

For urinary tract obstructions, a needle may be used to insert a catheter through the mother's abdomen and the uterus, into the fetal bladder. The catheter drains the urine into the amniotic fluid. The catheter may have an expandable wire mesh, which is deployed in the bladder to prevent the catheter from plugging up or dislodging.

Fetoscopic Laser Coagulation

Laser coagulation is done in TTTS. Laser coagulation of the vascular anastomoses was first reported by De Lia et al.[8] They described coagulation of all vessels crossing the intertwining membrane between the twins. It became more popular when Nicolaides et al described a percutaneous approach, and since randomized trial proved this to be the most effective therapy.[9,10] The fetoscopic laser coagulation is performed at around 16 weeks gestation; before that, the amniotic membrane may still be separated

from the chorion, hampering amniotic access and increasing postoperative leakage.

Preoperatively, all patients undergo ultrasound study for disease staging and to exclude discordant anomalies. The cervical length is measured, because it is a strong predictor of preterm delivery. For most cases, fetoscopic laser coagulation is performed percutaneously through 3 to 4 mm incision with local anesthesia. A neodymium–yttrium aluminum garnet laser (minimal power requirement, 60–100 W) or a diode laser (30–60 W) with fibers of 400 to 600 μm provides optimal efficacy. Three fixed landmarks are used to identify the anastomosing vessels, i.e., the recipient and donor twin's cord insertions and the intertwining membranes. Coagulation of the anastomosing vessels is performed at a distance of 1 cm and ideally at 90° angle to the vessel, using a "no touch" technique starting at one placental border and finishing at the other end. The procedure is completed with amnioreduction in the polyhydroamniotic twin, until normal amniotic volume is measured ultrasonically.

Ex utero Intrapartum Treatment

Ex utero intrapartum treatment (EXIT) is a surgical delivery procedure done for babies who have severe respiratory disorder. It is used to permit controlled reversal of clipping of the fetal trachea, which was a treatment for CDH or disorders leading to congenital airway obstruction including laryngeal atresia (congenial high airway obstruction syndrome), large head and neck tumors, and other upper airway problems that might cause difficult intubation. The purpose of EXIT procedure is typically to establish functional and reliable fetal airway control while keeping the fetus attached to the uteroplacental circulation; EXIT is done under maximal uterine relaxation, typically provided by deep inhalational general anesthesia. Therefore, the maternal risks of this procedure are mainly hemorrhagic.[11]

The largest single center with 43 EXIT procedures is reported by Children's Hospital of Philadelphia. The most common indications were neck masses and reversal of tracheal clipping. Maternal complications included placental abruption, intraoperative blood transfusion, and chorioamnionitis. There were no cases of uterine atony or maternal death. One intraoperative fetal death occurred in a fetus with a large cervical lymphangioma who could not be intubated and whose parents had declined a tracheostomy. The maternal anesthetic protocol typically involves rapid sequence induction, followed by intubation and maintenance of anesthesia. To support adequate uteroplacental perfusion, effective maternal arterial pressure is maintained. Fetal umbilical artery and venous catheters ensure adequate vascular access for perinatal resuscitation. After EXIT, the fetal delivery is completed and the umbilical cord divided.

Extracorporeal membrane oxygenation (ECMO) is used for fetuses with severe cardiopulmonary pathology, where the fetal heart is unable to pump. The ECMO is similar to cardiopulmonary bypass machine, but the patient can be hooked up for longer duration. In severe disorders of the fetal airway, techniques have been developed to provide oxygenated blood to the fetus by maintaining fetoplacental circulation through ECMO, until the infant's airway is secured.[12] At times, EXIT is done along with ECMO for certain cardiac defects, for conjoined twins, or in surgery for CCAM of the lung.

THE FUTURE

Stem cell therapy was used to treat genetic diseases, metabolic disorders, hemoglobinopathies, and immunodeficiency.[13,14] In a newer study of myelomeningocele, spina bifida is combined with stem cell transplantation. Human placenta-derived mesenchymal stromal cells (PMSCs) are used. This combination has shown a significant improvement in motor function at birth. The intrauterine period is considered as the ideal time for stem cell therapy, because the fetal environment has poorly developed immunological system and more receptive to stem cells. The fetal MSCs have pluripotent stem cell markers and have greater expansion capacity than adult stem cells. The PMSCs have been shown to be immunomodulatory, neuroprotective and to improve wound healing, and are readily available from the placenta throughout pregnancy. Placenta is an autologous source of these cells.[15] There is a report of *in utero* transplantation of paternal bone marrow with hematopoietic cell progenitors to fetus having X-linked severe combined immunodeficiency, confirmed by CVS at 12 weeks gestation.[16]

CONCLUSION

Fetal surgery is one of the latest developments in the field of obstetrics and neonatology. From the first open fetal surgery conducted in 1981 to the minimally invasive techniques developed over the last four decades, fetal surgery has come a long way. During the past few years, the research and development has revolved around prevention of the complications of open fetal surgery like amniotic fluid leakage, preterm premature rupture of membranes, and preterm labor. This has been achieved with the use of minimally invasive procedures. With newer imaging modalities and procedures like fetoscopy and laser ablation, the need for open surgery has decreased tremendously. The use of fetal stem cell transplantation promises to extend the horizon of fetal surgery.[17] Although experimental currently, fetal surgery is a field with unending possibilities.

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10.5005/jp-journals-10036-1135

CASE REPORT

Undiagnosed Cesarean Scar Pregnancy: A Nightmare

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ABSTRACT

Ectopic pregnancy is one of the leading causes of morbidity and mortality among fertile women. Cesarean scar pregnancy (CSP) is the rarest type of ectopic pregnancy. It is a life-threatening abnormal form of implantation of a gestational sac in the myometrium at the site of a previous cesarean scar. A case of 23-year-old woman with previous cesarean section, torrential hemorrhage during dilatation, and evacuation carried out for retained products of conception is being reported. The patient finally required hysterectomy to stop the hemorrhage. The provisional diagnosis of CSP was made during laparotomy and later confirmed by histopathological examination.

Keywords: Cesarean scar pregnancy, Methotrexate, Myometrium, Obstetric hysterectomy.

How to cite this article: Mande SA, Dank GA, Shiradkar SS. Undiagnosed Cesarean Scar Pregnancy: A Nightmare. MGM J Med Sci 2017;4(1):39-42.

Source of support: MGMIHS

Conflict of interest: None

INTRODUCTION

Ectopic pregnancy is one of the leading causes of morbidity and mortality among fertile women, accounting for 9% of pregnancy-related deaths. Among ectopic pregnancy, there is a clinical entity called cesarean scar pregnancy (CSP). It is the rarest type of ectopic pregnancy. It is a life-threatening abnormal form of implantation of a gestational sac in the myometrium at the site of a previous cesarean scar.

Cesarean scar pregnancy was first described by Larsen and Solomon in 1978.[1] It is estimated that CSP constitutes about 6% of all ectopic pregnancies in patients with a history of at least one cesarean section. The incidence of this pathology ranges from 1/1,800 to 1/2,200 pregnancies, and its prevalence rate is 0.15% in women with previous cesarean sections.[2]

CASE REPORT

A 23-year-old woman, Gravida 2, para 1, living 1 (1 previous cesarean section), came to the hospital on August 8, 2015 with bleeding from the genital tract since 5 days. Her menstrual history did not reveal any period of amenorrhea. Last menstrual period narrated by the patient was 5 days back; previous cycle was on July 15, 2015. Past cycles were regular. On admission, the physical examination demonstrated the patient in good general health, pulse – 72/minute, blood pressure values – 110/80 mm Hg, respiratory rate – 16 breaths/minute. Systemic examination did not reveal any abnormality. Abdomen was soft and nontender. Bleeding through the Os was visible on the speculum examination. Bimanual examination revealed a softened and enlarged uterus of size of about 8 weeks gestation, and the Os was closed. The laboratory results showed hemoglobin – 11.7 gm/dL, hematocrit – 33.1%, red blood cells – 4.35 million/mL, platelet count of 3,34,000/mm.[3] Blood group was B positive. Urine examination was normal. Urine pregnancy test was positive. Liver and kidney function tests were within the normal limits. Ultrasonography (USG) revealed retained products of conception and endometrial thickness of 13 mm.

In view of uterus size of 8 weeks (not correlated to her menstrual history) and bleeding through the os with USG report of retained products of conception, patient was posted for emergency evacuation and curettage. As soon as the dilator was introduced, torrential bleeding started. Attempt was made to evacuate the uterus with ovum forceps. Even after evacuation, bleeding continued despite giving uterotonics. There was no clinical suspicion of perforation. In view of history of previous cesarean, continuous bleeding, and some evidence of the products of conception being adherent to uterus at probable scar site, diagnosis of CSP was considered.

Decision of Laparotomy

A hysterectomy vertical incision was taken from the fundus downward and a trial for removal of products of conception was made with the Karman's cannula introduced from above downward. Bleeding decreased transiently. Hence, the hysterectomy incision was closed with intermittent stitches with Vicryl in an attempt to conserve the uterus. Still the bleeding continued. Hence, obstetric hysterectomy was done. The estimated blood loss was 2000 mL. Intraoperative photograph and photograph of operative specimen are shown in Figures 1 and 2 respectively.

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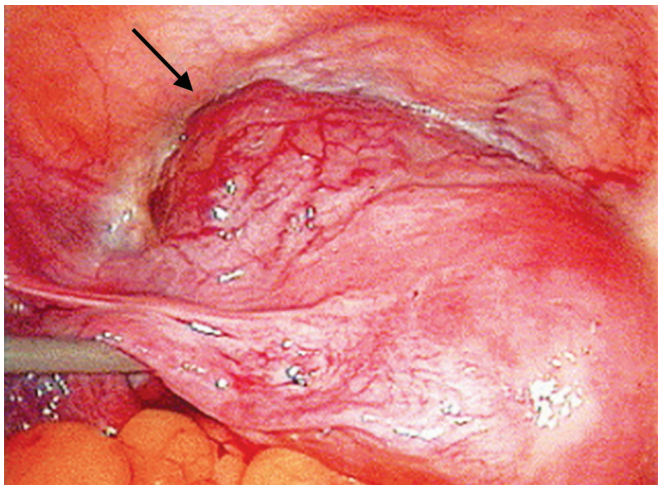


Fig. 1: Cesarean scar pregnancy marked by the arrow

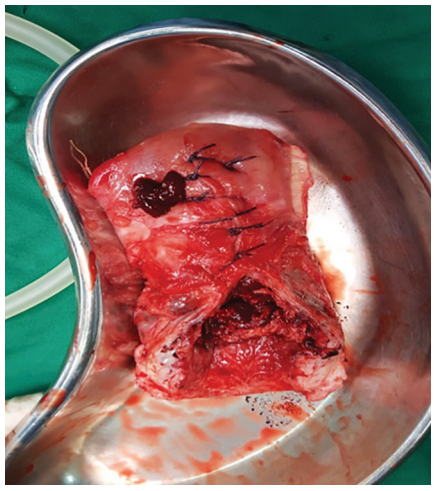


Fig. 2: Posthysterectomy specimen of the uterus

Patient had an uneventful postoperative recovery. She was given two packed cell transfusions postoperative. She was discharged from the hospital after 8 days with hemoglobin level of 9.2 gm/dL. Definitive histologic examination revealed the presence of mature chorionic villi infiltrating the myometrium. No gestational tissue was found in the entire uterine cavity.

DISCUSSION

Prior cesarean is not the only risk factor for CSP. A history of uterine infections and prior dilatation and curettage (D&C) procedures are also risk factors, as is a short interpregnancy interval after a cesarean. Treatment with *in vitro* fertilization may also be associated with CSP, although this is not clear. Some authors have speculated that recent uterine suturing technique changes (single layer, various suture materials) may have an effect, though there are little data to support or refute this. Obviously, having a prior cesarean scar is the most important risk factor for CSP. Transvaginal sonography is a useful tool for diagnosing CSP, probably in woman who underwent a previous cesarean section. An evaluation of the scar very early in pregnancy could help in early diagnosis of CSP. In this way, a conservative treatment of the uterus and of the reproductive function could be feasible by medical or surgical approach. Because the symptoms are unclear and easy to ignore at first, many cases of CSP go undetected initially. Even when the patient presents with symptoms to a care provider, the diagnosis may be missed. The 2012 review found that about 13% of CSPs are missed or misdiagnosed at first.

According to a recent 2012 review,[3] the following sonographic findings should raise the suspicion level for a CSP:

- No fetal parts in the uterine cavity or cervix;
- A thin myometrial layer between the bladder and gestational sac;
- A triangular-shaped gestational sac;
- A gestational sac, i.e., close to the bladder and uterine wall, presentation of arteriovenous malformation in the area.

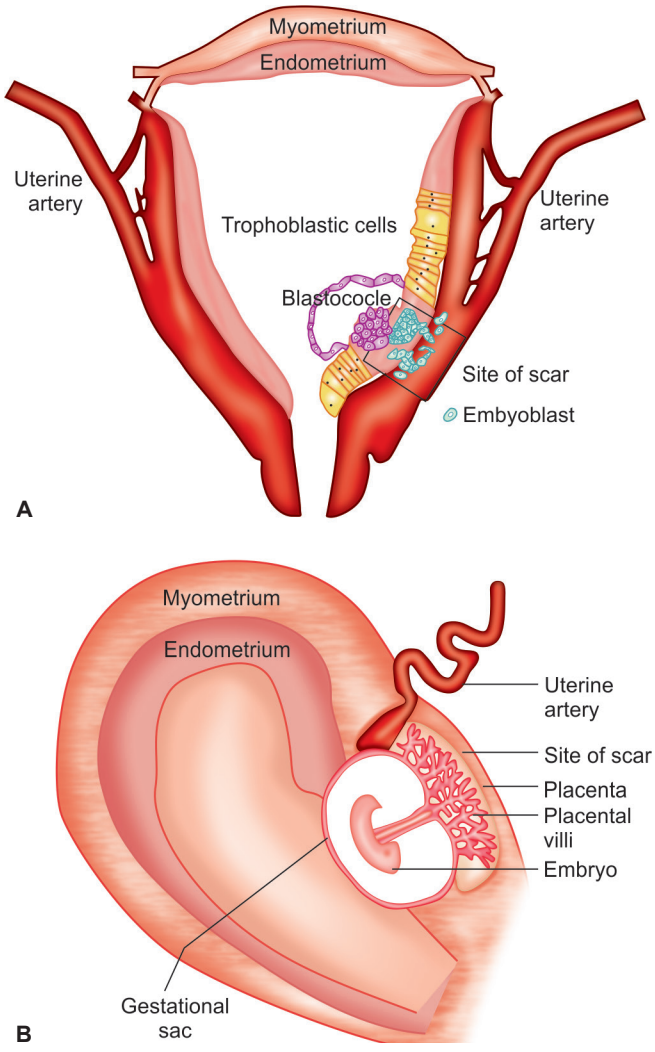
Pathological Aspects of CSP

The most recent data indicate that CSP and placenta accreta are the continuum of the same pathology rather than separate diseases.[4] In CSP, the conception product can penetrate the endometrium through the microscopic dehiscences in the cesarean scar (Figs 3A and B). If the wait-and-see attitude is accepted in the first trimester of CSP, it is most likely to evolve into placenta percreta. In almost each case, this leads to postpartum hemorrhage and requires a hysterectomy. Early diagnosis and appropriate interventions are likely to substantially improve the prognosis.

It is important to diagnose scar pregnancy as early and accurately as possible, but it is very difficult because there are other clinical entities that can confuse, such as spontaneous abortion and/or cervicoisthmic pregnancy. The differential diagnosis of CSP and cervicoisthmic pregnancy is based on the absence of physiological myometrium between the bladder and the gestational sac in scar pregnancies.

TREATMENT OPTIONS

Available data suggest that termination of pregnancy shortly after the diagnosis of CSP is the treatment of choice in the first trimester. Postponed treatment is usually associated with poor prognosis. Cesarean scar pregnancy can lead to massive hemorrhages, uterine rupture, and disseminated intravascular coagulation or death. Treatment options of CSP include D&C as well as excision of trophoblastic tissues using laparotomy or laparoscopy. There are literature case reports describing successful treatment of



Figs 3A and B: Diagrammatic representation of cesarean scar pregnancy

CSP by systemic and/or local administration of methotrexate (MTX) with subsequent D&C.

Conservative treatment can be considered the first-line treatment in many early, unruptured ectopic pregnancies. Treatment options include the following.

Systemic Administration of MTX

It is a standard treatment for tubal ectopic pregnancy. There should be no reason to doubt its efficacy on CSP.[5]

Local Injection of Embryocides

This has been successfully reported with local injection of MTX, potassium chloride, hyperosmolar glucose, and crystalline trichosanthin.

Combined Medical Treatment

Combined medical treatment in varying regimens have been described by many authors, e.g., local injection of 8 mEq potassium chloride (2 mEq/mL) followed by 60 mg of MTX injected into the gestation sac.

Medical Treatment Combined with Surgical Sac Aspiration

Medical treatment – systemic or local, single agent or combined regimen – can interrupt the pregnancy, but symptoms can continue with bleeding, sometimes heavy. Also, it is difficult to rule out some scar dehiscence already developing at the time of treatment, as the very thin myometrium could be in a state of prerupture.

Uterine Curettage

To date, a total of 12 cases of CSP managed by uterine curettage as primary therapy have been reported in the English medical literature, and another 4 cases have been cited in a case series of 8 CSPs.[6]

Hysteroscopic evacuation

In 2006, Wang et al[7] have described a successful treatment of CSP by operative hysteroscopy and suction curettage, the first of its kind reported in English literature. At 4-week follow-up, serum βhuman chorionic gonadotropin level became normal, with restoration of normal echotexture of the uterus on ultrasound scan. But this facility will not be available at all the places.

Laparoscopic Removal

Wang et al[8] were the first to perform a successful laparoscopic resection of a CSP. The operative laparoscopy should be performed only after an ultrasound confirms the diagnosis of a CSP. During laparoscopic removal, the CSP mass is excised and the pregnancy tissue is removed in an endobag.

Hysterectomy

In a review until August 2002, hysterectomy was performed in 7 out of 19 cases.[9] From then, six more hysterectomies have been reported in the literature either as a primary procedure or because other treatment modalities failed. This shows that CSP is a potentially serious condition despite advances in many of the diagnostic techniques and therapeutic measures.

Many cesareans are truly life-saving and necessary, and many others are probably prudent. However, cesareans are not without risks and should not be taken lightly. The extremely high cesarean rates in certain areas of this country and around the world have very distinct public health implications, both in the immediate period around the cesarean and for years afterward. In particular, the long-term implications of cesareans are underrecognized.

CONCLUSION

Without a high index of suspicion and correct early diagnosis, CSP can lead to uterine rupture and/or hysterectomy, with consequent maternal morbidity and loss of future fertility. If the location of such an implantation is misdiagnosed, a common gynecological operation, such as D&C can be met with catastrophic hemorrhage as happened in our case. Sonologists and trainee doctors should be aware of this condition. Senior obstetricians should be involved in the management plan. Since there is scarcity of reliable data, patients should be given information to make an informed choice for management.

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10.5005/jp-journals-10036-1136

CASE REPORT

Severe Metabolic Alkalosis in an Infant: Bartter Syndrome

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ABSTRACT

Metabolic alkalosis is an uncommon acid/base disorder in children in which serum bicarbonate concentration is increased. Two most important causes of metabolic alkalosis are emesis and diuretic use. However, in the absence of these two etiologies, a thorough investigative workup is of paramount importance to reach a definitive diagnosis. A case having severe metabolic alkalosis diagnosed as a case of Bartter syndrome is being reported.

Keywords: Bartter syndrome, Hypokalemia, Metabolic alkalosis.

How to cite this article: Gavhane J, Markanda K, Dogra S, Jafri N. Severe Metabolic Alkalosis in an Infant: Bartter Syndrome. MGM J Med Sci 2017;4(1):43-45.

Source of support: MGMIHS

Conflict of interest: None

INTRODUCTION

Metabolic alkalosis is an uncommon acid/base disorder that occurs in critically ill children. Without treatment, severe metabolic alkalosis may result in significant adverse consequences, including impaired perfusion, diminished respiratory drive, cardiac arrhythmias, seizures, and death. Identifying the underlying pathophysiology is essential to the management of this disorder.[1] Metabolic alkalosis occurs when a primary pathophysiologic process leads to the net accumulation of base within or the net loss of acid from the extracellular fluid; typically, the intracellular compartment becomes more acidic in potassium-depletion alkalosis. Unopposed by other primary acid/base disorders, metabolic alkalosis is recognized by increases in both arterial blood pH – alkalemia – and plasma bicarbonate concentration.[2]

A case in pediatric intensive care unit, with severe metabolic alkalosis, was eventually diagnosed as a case of Bartter syndrome (BS).

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CASE REPORT

A four-and-a-half-month-old male child was brought to the Pediatrics outpatient department with complaints of refusal to feed since 3 days and labored breathing and vomiting since 1 day. The child vomited twice after feed which was nonbilious, nonblood stained, and contained milk. Simultaneously, he started having a little labored breathing, which was persistent and associated with restlessness.

Child had attained developmental milestones appropriate for the age. On examination, child was afebrile, dehydrated, and tachypneic. Oxygen saturation on nonrebreathing mask was normal. Pulses were well felt. Urine output monitoring was done, which showed polyuria. On head to toe examination, the child had triangular face with low set and protruding ears. On anthropometry, his weight, height, and head circumference were below –3 standard deviation. Systemic examination was normal. Patient was started on maintenance intravenous fluids, along with symptomatic treatment, and lab investigations revealed hyponatremia (119 mEq/L), hypokalemia (2.5 mEq/L), and hypochloremia (53 mEq/L).

In view of tachypnea, arterial blood gas was ordered. It showed: pH 7.64, pCO_2 47, pO_2 70, HCO_3 50.6, tCO_2 52. Double potassium correction was started in view of hypokalemia. Common causes of metabolic alkalosis like excessive vomiting, use of bicarbonate (baking soda), and use of diuretics were ruled out. Urinary electrolyte levels were sent, which were as follows: Urinary Na – 16, K – 37.3, Cl – 20.

In view of high chloride levels in urine in the background of metabolic alkalosis (chloride-resistant metabolic alkalosis), blood pressure monitoring was done. It was within normal limits. Ultrasonography (abdomen and pelvis) was normal. Renal Doppler did not show any evidence of renal artery stenosis. So causes like adrenal adenoma, renovascular disease, renin-secreting tumor, Cushing syndrome, 17β-hydroxylase deficiency, 11β-hydroxylase deficiency, and Liddle syndrome (all associated with high blood pressure) were ruled out. In the setting of normal blood pressure, metabolic alkalosis, hypokalemia, high urinary chloride levels, hypochloremia, and young age of the patient along with the presence of dysmorphic features mentioned above, diagnosis of BS was established. Child was started on oral potassium.

With continued treatment, child became better and started accepting feeds well. Serum electrolytes normalized soon.

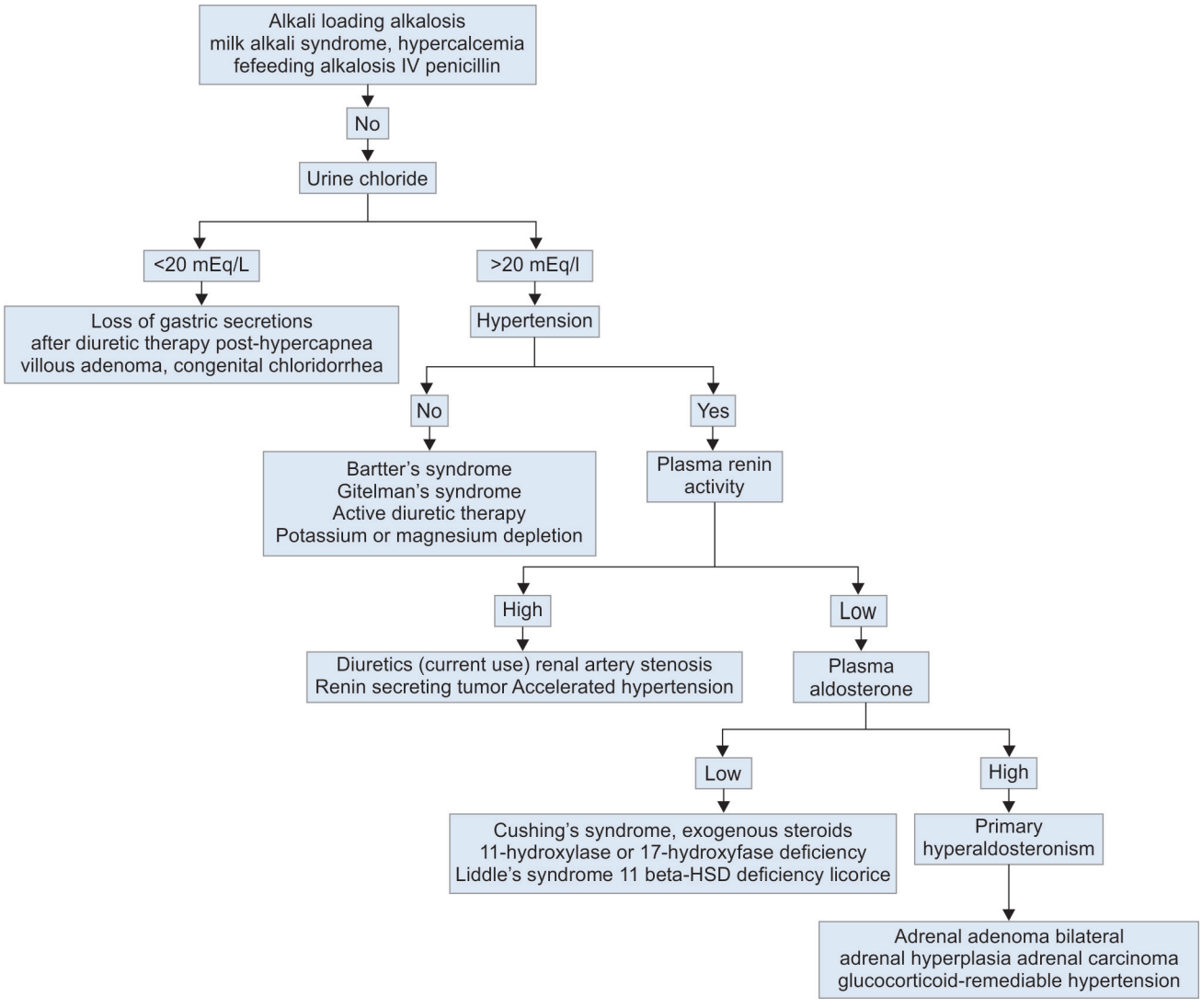
DISCUSSION

Metabolic alkalosis is classified as chloride responsive or chloride resistant. Etiologies of chloride-responsive metabolic alkalosis are chloride-depleting diuretic therapy (e.g., furosemide and chlorothiazide) and gastrointestinal loss (e.g., vomiting and nasogastric suctioning). Chloride-resistant metabolic alkalosis commonly occurs secondary to excessive mineralocorticoid activity or severe hypokalemia.[1] Alkalosis in BS and Gitelman syndrome (GS) and their variants are associated with both potassium and chloride depletion.[2]

In an approach to look for cause of metabolic alkalosis in a child, common causes like emesis, diuretic use, or excess base administration should be asked for. This is followed by estimation of urine chloride levels. If urine chloride levels are less than 20 mEq/L, the cause can be emesis, repeated nasogastric suctioning, diuretic use, chloride losing diarrhea, chloride-deficient formula, cystic fibrosis, or posthypercapnia state. If urine chloride level is more than 20 mEq/L, it is suggestive of chloride-resistant metabolic alkalosis. Measurement of blood pressure at this point is crucial in clinching the diagnosis. In the presence of hypertension, the cause can be adrenal adenoma, renovascular disease, renin-secreting tumor, Cushing syndrome, Liddle syndrome, licorice ingestion, 17β-hydroxylase deficiency, or 11β-hydroxylase deficiency. If blood pressure is normal, the cause can be GS, BS, autosomal dominant hypoparathyroidism, epilepsy, ataxia, sensorineural hearing loss, tubulopathy syndrome, or base administration.[3] Algorithm for approach to metabolic alkalosis is depicted in Flow Chart 1.[4]

In 1962, Bartter et al[5] described a new disease entity in two African Americans who presented with metabolic alkalosis, hyperplasia of juxtaglomerular apparatus, and normotensive hyperaldosteronism. Over the years, several phenotypic and genotypic variants of the original descriptions of BS have been identified. It is an uncommon

Flow Chart 1: Algorithm for metabolic alkalosis



inherited renal tubular disorder with hyponatremia, hypokalemia, hypochloremic metabolic alkalosis, hyperreninemia with normal blood pressure associated with increased urinary loss of sodium, potassium, calcium, and chloride. The primary defect in BS is an impairment in one of the transporters involved in sodium chloride reabsorption in the thick ascending limb of loop of Henle, viz., Na-K-2Cl cotransporter (NKCC2) or apical K channel (ROMK) or basolateral chloride channel (ClCNKB). Bartter syndrome is transmitted as an autosomal recessive disorder. The estimated prevalence is approximately 1 per million in the Western population.[6]

The current classification includes type I and II (neonatal or antenatal BS) due to defective NKCC2 and ROMK genes respectively, affecting the Na–K–2Cl symporter predominantly. Type III, or "classic" BS, is due to CLCNKB genetic defect causing abnormal basal chloride channel. Type IV is rare and the most severe combined loop and distal tubule dysfunction with associated sensorineural deafness and is due to CLCNKA impairment or their beta subunit BSND genetic mutation.[7]

Dysmorphic features include triangular facies, protruding ears, and large eyes. Strabismus and drooping mouth may be present on examination. Older children can have history of recurrent episodes of polyurea with dehydration, failure to thrive, nonspecific fatigue, dizziness, and chronic constipation. Blood pressure is usually normal. Renal function is typically normal. Urinary calcium levels are typically elevated, as are urinary potassium and sodium levels. Establishment of hypokalemia and hypochloremia with metabolic alkalosis is vital for diagnosis. Although renal biopsy is not essential for diagnostic purposes, the cardinal feature will be hyperplasia of juxtaglomerular apparatus in most specimens. A definitive diagnosis can be reached by genetic mutation analysis.[7] The treatment consists of proper hydration, potassium supplementation, and indomethacin therapy, which will blunt the prostaglandin overproduction and correction of hypokalemia. Potassium-sparing diuretic spironolactone may benefit transiently. Nephrocalcinosis, chronic renal failure, and short stature are a few known complications and should be kept in mind and, if encountered, addressed accordingly.[7]

CONCLUSION

Bartter syndrome should be suspected in any child with history of failure to thrive and metabolic alkalosis. Early diagnosis and treatment with potassium supplementation are lifesaving.

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10.5005/jp-journals-10036-1137

CASE REPORT

Hyperhomocysteinemia with Anticoagulant-related Acute Kidney Injury

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ABSTRACT

A case of 40-year-old young woman with an extensive, acute thrombosis of left distal brachial artery following an elective laparoscopic cholecystectomy was reported. The patient underwent urgent surgical intervention for brachial artery thrombosis and was started on oral anticoagulant. Within a week, the patient presented with bleeding diathesis and acute renal insufficiency with sepsis. She was found to have markedly increased serum homocysteine level. No other thrombophilic factors could be found. On investigation, a genetic defect of homocysteine metabolism was found to be the underlying cause. The patient recovered completely on treatment with pyridoxine, cyanocobalamin, and folate.

Keywords: Acute kidney injury, Anticoagulant, Heterozygous methylenetetrahydrofolate reductase gene mutation, Thromboembolic event.

How to cite this article: Gadekar KG, Paike N, Bhange N, Kulkarni S. Hyperhomocysteinemia with Anticoagulant-related Acute Kidney Injury. MGM J Med Sci 2017;4(1):46-48.

Source of support: MGMIHS

Conflict of interest: None

INTRODUCTION

Thrombophilias, inherited or acquired, are conditions associated with hypercoagulable state and increased risk of arterial and venous thrombosis, which represent a significant cause of mortality and morbidity worldwide.[1] There may be interaction of genetic and environmental factors.[2] Investigating for thrombophilia requires an initial evaluation of classical prothrombotic risk factors, such as smoking, dyslipidemias, arterial hypertension, or diabetes mellitus. Extended profile of investigations is necessary in patients with arterial or venous thrombosis, which occurs repeatedly in unusual sites or at young age, also when family aggregation of thrombotic events is identified, as well as in women with recurrent idiopathic pregnancy loss. It must include a complete blood count and erythrocyte sedimentation rate, blood film examination, prothrombin time (PT) and activated partial thromboplastin time, factor V Leiden, antithrombin and fibrinogen levels, protein C and S, prothrombin gene mutations, homocysteinemia, methylenetetrahydrofolate reductase (MTHFR) gene mutations, and antiphospholipid antibodies.[3]

Mild to moderate hyperhomocysteinemia (HHC), meaning mildly to moderately increased plasma homocysteine (15–50 µmol/L), is uncommon in the general population. This condition is caused by either genetic factors (mutations of homocysteine metabolism enzymes) or acquired conditions, such as deficiencies in B vitamins, renal insufficiency, and some medications.[4] Two common mutations involving the MTHFR gene have been identified: C677T and A1298C.

CASE REPORT

The case of a 40-year-old nondiabetic and nonhypertensive female admitted with clinical picture of acute kidney injury (AKI) has been presented. Her medical history started 2 weeks prior to her admission, when she underwent an elective laparoscopic cholecystectomy. On the second postoperative day, she developed painful swelling of the left arm with clawing of the hand and ischemia of the fingers. Color Doppler study of left upper limb revealed acute thrombosis in left distal brachial, radial, ulnar, and median arteries with absent flow. She underwent urgent vascular intervention with left brachial artery embolectomy. She was heparinized and started on oral anticoagulant Acenocoumarol 3 mg twice a day. 1 week after embolectomy, she developed generalized swelling involving the face, arms and lower limbs, oliguria, hematuria, bleeding gums, hematemesis, shortness of breath, and fever.

On examination, she was febrile, conscious, oriented with pulse rate 124/minute, blood pressure 120/70 mm Hg, and relative risk 28/minute. She was pale, with facial and pedal edema. She had bleeding gums and left upper limb swelling. Her systemic examination was normal except bilateral fine crepitations on chest auscultation. Her investigations revealed hemoglobin (Hb) 2.9 gm/dL, total leukocyte count (TLC) 28,100/mm^3, platelets 600,000/mm^3, urea 124 mg/dL, creatinine 6.6 mg/dL, Na 118 mEq/L, K 4.4 mEq/L, PT 120 seconds, international

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normalized ratio (INR) 7.5, total serum proteins 5.2 gm/dL, serum albumin 1.8 gm/dL, Ca 9.5 mg/dL, PO_4 7.2 mg/dL, and uric acid 9.7 mg/dL. Urine analysis showed 4+ proteinuria, plenty of red blood cells (RBCs), and 30 to 40 pus cells/hpf. Liver function test, lipid profile, electrocardiogram, and two-dimensional echocardiogram were normal. Anticardiolipin antibodies and lupus anticoagulant tests were negative. Thrombophilia tests showed that protein C, protein S, and antithrombin III levels were within normal limits. Serum C3 complement was normal. Her homocysteine level was 43.08 µmol/L (normal 3.36 to 20.44 µmol/L in females).

The patient was negative for factor V Leiden and prothrombin gene mutation. However, she was found to have MTHFR gene polymorphism in the form of compound heterozygous for C677T and A1298C. Abdominal ultrasound found both normal-sized kidneys with increased echogenicity. Kidney biopsy was not performed due to risk of bleeding. She was treated conservatively with five packed cell volume (PCV) and eight fresh frozen plasma transfusions, intravenous vitamin K, injection Meropenem, injection Tranexamic acid, pyridoxine, cyanocobalamin, and folate supplements. Anticoagulants were discontinued. She did not need hemodialysis. By the end of 2 weeks, patient showed gradual improvement and was discharged with normal clinical and biochemical parameters. At the time of discharge, her laboratory tests showed PT 27.5 seconds, INR 2.29, normal renal functions, Hb 8.7 gm/dL, TLC 12,600/mm^3, PCV 26%, mean corpuscular volume 70 fL, mean corpuscular hemoglobin 18 pg, mean corpuscular hemoglobin concentration 26 gm/dL, and normal urinalysis.

DISCUSSION

The mechanism by which MTHFR gene mutations produce prothrombotic states is represented by elevated levels of plasma homocysteine due to decreased enzymatic activity of MTHFR that participates in regulating homocysteine metabolism, and a mutation of MTHFR may be a marker for possible elevated homocysteine levels. At present, HHC is considered to represent a risk factor for deep vein thrombosis and a common risk factor for recurrent venous thrombosis.[5] Heterozygotic status for two polymorphisms of the MTHFR gene, the C677T and A1298C, was found in our case. There are studies which suggest supplementation with folic acid; vitamin B6 and B12 may help in lowering the homocysteine concentrations, and even in reversing endothelial dysfunction regardless of the underlying cause of HHC.[5]

Acute kidney injury resulting from glomerular hemorrhage has been described in patients with glomerular lesions in the absence[6-8] and presence[9,10] of coagulopathy (INR 6–9 range). A biopsy study in patients who developed otherwise unexplained AKI in association with anticoagulant overdose revealed the predominant lesion of distal tubular injury and obstruction with RBCs and RBC casts.[11] The glomeruli show little or no abnormalities by light, immunofluorescence, or electron microscopy.[11] The recognition of a characteristic histologic lesion that was associated with the clinical presentation of otherwise unexplained AKI in the setting of overanticoagulation led to the term "anticoagulant-related nephropathy."

The pathogenesis event appears to be glomerular hemorrhage[12,13] resulting in the formation of obstructing RBC casts within renal tubules, which is the most conspicuous histologic feature of anticoagulant-related nephropathy.[11] The diagnosis of anticoagulant-related nephropathy should be suspected among patients who present with AKI in the setting of excessive anticoagulation. A definitive diagnosis is made by renal biopsy. However, biopsies are usually not performed, at least initially, among patients who are anticoagulated because the risk of bleeding is high.

Among patients who develop AKI and are on anticoagulant therapy, a presumptive diagnosis of anticoagulant-related nephropathy may be made if a severe warfarin coagulopathy is present and if other causes of AKI have been excluded by clinical features and serologic tests. Restoration of a therapeutic INR may limit the extent of AKI and chronic kidney injury that results from glomerular hemorrhage. The patient was discharged from the hospital with folic acid, vitamin B6, and vitamin B12 supplements. The peculiarities of the present case were the thrombotic events and the extensive arterial thrombosis in a young patient with HHC due to two heterozygotic mutations in the MTHFR gene. Anticoagulant nephrotoxicity presented as AKI, which was successfully treated conservatively.

CONCLUSION

In patients with unexplained arterial or venous thrombosis, it is appropriate to investigate for the possible coexistence of multiple predisposing factors for thrombosis, including measurement of the serum homocysteine level, in addition to investigations for mutations of the MTHFR, the prothrombin, and the factor V genes.

ACKNOWLEDGMENT

Authors would like to thank the Dean, Dr Ajit Shroff, MGM Medical College and Hospital, Aurangabad, for giving permission to publish this case report.

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10.5005/jp-journals-10036-1138

CASE REPORT

Pediatric Catatonia in Early-onset Schizophrenia and Treatment Implications

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ABSTRACT

A 13-year-old girl presented with symptoms of catatonia during second episode of early-onset schizophrenia. Catatonic features seen were motoric immobility, extreme negativism, mutism, ambitendency, and refusal to take food. She was initially treated with antipsychotic drugs but developed side effects. In view of life-threatening situation and absence of improvement, she was treated with electroconvulsive therapies (ECTs). Nine adequately spaced ECTs were given using propofol as the anesthetic agent. She showed significant response to ECTs with respect to her symptoms of catatonia and activities of daily living.

Keywords: Catatonic symptom, Electroconvulsive therapy, Pediatric catatonia, Schizophrenia.

How to cite this article: Vispute CD, Nayak AS, Kedare JS, Vanjari NA. Pediatric Catatonia in Early-onset Schizophrenia and Treatment Implications. MGM J Med Sci 2017;4(1):49-51.

Source of support: MGMIHS

Conflict of interest: None

INTRODUCTION

Pediatric catatonia has been reported to be a potentially life-threatening but treatable syndrome. A study by Cohen et al[1] has shown an incidence of catatonia in 0.6% of inpatient adolescents. It has been found to be associated with various disorders like psychotic, mood, autistic, developmental, and tic disorders. In some of the cases, pediatric catatonia was idiopathic and not associated with psychotic, affective, or medical disorder. Following mood disorders, schizophrenia has been found to be the most frequent diagnosis in cases of pediatric catatonia.

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Early-onset schizophrenia (before the age of 18 years) is prevalent in 1 in 10,000 and has longer episode duration and a deteriorating course. Catatonic symptoms have not been frequently reported in these patients. The symptoms predominantly consist of delusions and hallucinations.[1,2] Green et al[3] examined 38 children with schizophrenic disorder who were younger than 12 years of age, and indicated that catatonia or other grossly disorganized behavior was present in 31.6% of the cases. In an Indian study by Thakur et al,[2] 5.5% of the entire sample and 17.7% of the patients with affective and nonaffective psychotic disorders had at least two signs of catatonia.

Treatment in these cases poses a unique challenge. Use of antipsychotic drugs has been reported to result in side effects in the form of sedation and extrapyramidal reaction.[4] Electroconvulsive therapies (ECTs) have been rarely used due to stigma and risks of side effects. However, an estimated 75% of patients with catatonia have been reported to improve immediately after ECTs, whereas 46% were found to function at the premorbid level 6 months after ECTs.[5] In children or adolescents, no fatalities as a consequence of ECTs have been published. In spite of the successful and safe use of ECTs in adult populations, its use in the child and adolescent population has been limited.[5] We are reporting a case of pediatric catatonia in a girl of early-onset schizophrenia with onset at the age of 9 years.

CASE REPORT

The patient is a 13-year-old girl, right-handed, born out of nonconsanguineous marriage, full-term normal delivery with normal developmental milestones, educated up to fourth standard, menarche at the age of 12 years, with adequate social support. She was brought by mother for the chief complaints of withdrawn to self, disturbed sleep, refusal to accept food, not interacting with family members, and maintaining postures for long hours since 1 month. On examination on admission, she was found to have catatonic features in the form of ambitendency, mutism, negativism, posturing, immobility, rigidity, withdrawal, and flattened affect. Her score on 23-item Bush-Francis Catatonia Rating Scale (BCRS) was 28 and Columbia Impairment Rating Scale score (CIRS) was 40. Her electroencephalography (EEG) and magnetic resonance imaging (MRI) scan of brain were normal.

According to her mother, altered behavior was first observed at the age of 9 years, in the form of complaints of academic difficulties like lack of concentration in studies and staying aloof in class. She had started muttering to self and smiling inappropriately occasionally. She had also started becoming suspicious that some of her classmates were stealing her pencil and lunch box. She used to sleep with pencil and lunch box under her pillow every night. She used to close the doors and scream "thieves are coming." Her school attendance had gradually decreased and she stopped studying. She stopped going to school eventually. She also reported auditory hallucinations of "God" and her dead father. She had been treated with oral antipsychotics (olanzapine, risperidone, amisulpride, haloperidol) and mood stabilizer sodium valproate over a period of 1.5 years. Improvement had been noted in the form of improved sleep and decreased auditory hallucinations. She continued to be withdrawn to self. Her speech output remained low. Her mother reported that these negative symptoms persisted till current episode.

They discontinued medications for 1.5 years after which she had the current exacerbation with catatonic features. In the current episode, she was treated with oral and injectable lorazepam. Injectable haloperidol was started due to lack of response. She developed side effects in the form of tremors and rigidity, hence, was shifted to tablet olanzapine. She was also treated for this extrapyramidal reaction with promethazine and benzodiazepines. She did not respond to the antipsychotic medications and her physical condition deteriorated, as refusal to food intake continued. Electroconvulsive therapy was considered. Second opinion to review the diagnosis, confirm illness severity, and treatment resistance was taken to corroborate the advisability of ECT. The adequacy of the workup was also reviewed. Her preanesthetic workup was done. Intravenous propofol (60–70 mg) was administered as anesthetic agent along with 25 mg of succinyl choline. Electroconvulsive therapies were administered (duration: 0.6 seconds, frequency: 70, pulse width: 1, current: 0.66 millicoulomb) and seizure duration between 20 and 25 seconds was obtained. Nine adequately spaced ECTs were given. Patient's catatonic symptoms improved. Her BCRS scores declined to zero. Patient was discharged on 12.5 mg of tablet olanzapine in divided dosages. No memory disturbances were noted. Her mini mental status examination score was 25 on discharge. 6 months after follow-up, patient is maintained and can independently carry out all tasks of basic activities of daily living scale like dressing, bathing, feeding self etc. On CIRS her scores has been reduced to 2.

DISCUSSION

Catatonic features in early-onset schizophrenia have been reported in very few studies.[1,2] Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) lists five clinical features of catatonic disorder: Motoric immobility; excessive motor activity; extreme negativism or mutism; peculiarities of voluntary movement; and echolalia or echopraxia.[6] Though echolalia and echopraxia were absent in this patient, other severe catatonic features in the form of mutism, negativism, posturing, immobility, rigidity along with ambitendency, withdrawal, and refusal to eat and take medications were present.

The differential diagnosis of pediatric catatonia includes both psychiatric and neurological conditions. It is most commonly associated with mood disorder.[2] Other psychiatric conditions that should be considered are schizophrenia and pervasive developmental disorder. Neurological conditions like seizure disorder, juvenile Parkinson disease, metabolic disorders, and psychoactive substance use need to be ruled out. In our patient, detailed history, physical examination, EEG, and MRI were not suggestive of any abnormality. Metabolic parameters were within normal limits.

This patient also had positive family history of schizophrenia in two first-degree relatives. A strong genetic vulnerability in cases of early-onset schizophrenia has also been reported in other studies[7] and may be responsible for the early onset and severity of the illness. Pathophysiological mechanisms indicated in catatonia are dysfunction in frontal lobe circuits and lesion in thalamic or parietal lobe, leading to disruption of connections from perceptual-integrating brain systems. The role of neurotransmitters dopamine and γ-aminobutyric acid has also been implicated.[8]

In the first episode, the positive symptoms responded to antipsychotic medications, albeit with side effects. However, severe catatonic features in the second episode did not show significant response to oral or parenteral typical or atypical antipsychotics. Sedation and extrapyramidal side effects have been reported in children and adolescents with schizophrenia in similar studies.[4] In view of persisting life-threatening symptoms of catatonia like refusal to accept food, water, and medication, presence of severe side effects of antipsychotics, patient was treated with ECT. Electroconvulsive therapy has been effectively used in children and adolescent in severe mood disorders, catatonia, and intractable psychotic disorders.[5,9] In this patient, good response was seen with nine sessions of bilateral, brief pulse ECT. No memory deficits were observed after ECTs. Tardive seizures are a rare but potentially serious side effect commonly associated with the use of ECTs in children.[9] No tardive seizures were noted in this case, as the ECTs were adequately spaced. The drug propofol was used as anesthetic agent that has been associated with shorter seizures,[7] which might also explain the absence of prolonged seizures.

CONCLUSION

Life-threatening catatonic features can be seen in patients of schizophrenia in children and adolescents. Electroconvulsive therapy has been infrequently used in children due to stigma and risks of side effects. We feel it can be used safely in cases of pediatric catatonia with potentially life-threatening symptoms using newer and safer anesthetic techniques. Electroconvulsive therapy may be a life-saving procedure in such cases.

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10.5005/jp-journals-10036-1139

CASE REPORT

Kyrle's Disease: A Rare Presentation in Diabetic and Hypertensive Patients

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ABSTRACT

Two rare cases of Kyrle's disease in diabetic patients who presented with papules on legs, back and abdomen, are reported. Pathology of this disease and management are described in detail. Importance of treating the underlying condition associated with this disease is highlighted.

Keywords: Diabetes, Hyperkeratosis follicularis, Kyrle's disease.

How to cite this article: Dhar R, Wani AS, Sahu S, Borkar DB, Tambekar M, Jadhav P, Ambrish PI, Agarwal S. Kyrle's Disease: A Rare Presentation in Diabetic and Hypertensive Patients. MGM J Med Sci 2017;4(1):52-53.

Source of support: MGMIHS

Conflict of interest: None

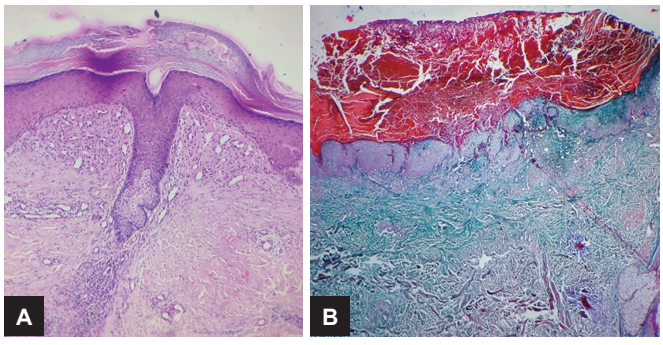
INTRODUCTION

Kyrle's disease is a rare dermatologic perforating disorder, which is characterized by transepidermal elimination (TEE) of abnormal keratin. It can affect both men and women throughout life, but female preponderance is usually seen. Lesions typically begin as small papules with scales that eventually grow and form red brown nodules with central keratin (horny) plug. Lesions are not painful but cause intense itching. Treatment is directed at the underlying disease. Lesions may self-heal without any treatment, but new lesions usually develop.

CASE REPORTS

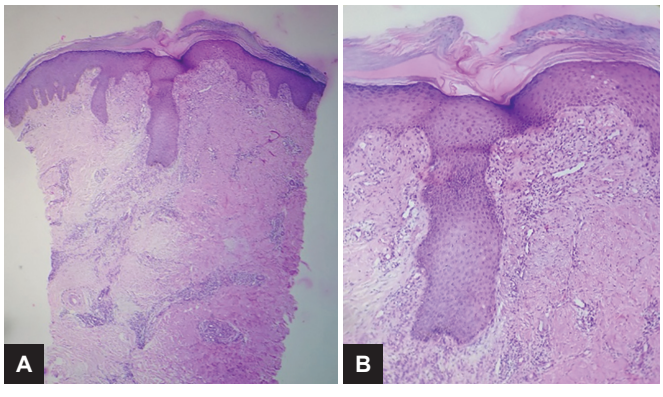
Two cases of Kyrle's disease in a duration of 6 months were reported. One was a 53-year-old male patient who presented with raised reddish skin lesions over both lower limbs, back and abdomen associated with itching since 2 weeks (Figs 1A and B). He was a known case of type II diabetes mellitus and hypertension since 8 years. Biopsy was taken from a single localized papule with keratotic plug on the back, which had been clinically suspected to be acquired perforating dermatosis (APD). Second patient was a 48-year-old female who presented with complaints of recurrent itchy hyperpigmented papules and pustules over upper and lower extremities and trunk since 6 months (Figs 2A and B). She was a known diabetic since 7 years and hypertensive since 4 years. Biopsy was taken from hyperpigmented papule over the left leg. She was also suspected to be a case of APD or atopiform eczema.

Case 1



Figs 1A and B: (A) 10× view: Epidermal depression filled with keratin. Perforation occurring away from hair follicle, thus ruling out perforating folliculitis; and (B) 40× view: Special stain – Masson trichrome is negative, ruling out perforating collagenosis

Case 2



Figs 2A and B: (A) Scanner view; and (B) 40× view: A column of dyskeratotic cells, basophilic debris, and superficial perivascular lymphohistiocytic infiltrate

DISCUSSION

The perforating disorders comprise a group of disorders sharing the common characteristic of TEE. This phenomenon is characterized by the elimination or extrusion of altered dermal substances and, in some cases, by such material behaving as foreign material. Traditionally, four

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diseases have been included in this group: Kyrle's disease (hyperkeratosis follicularis et parafollicularis in cutem penetrans), perforating folliculitis, elastosis perforans serpiginosa (EPS), and reactive perforating collagenosis (RPC). A fifth entity, APD, which is usually associated with renal disease and/or diabetes mellitus, in which clinical and histologic findings may resemble any of these four diseases, has been added to this group.[1] Although TEE is a prominent feature in all of these conditions, it has also been described as a secondary phenomenon in other entities, like granuloma annulare, variant of pseudoxanthoma elasticum, and chondrodermatitis nodularis helicis. Elastic fibers can be transepidermally eliminated over sites of healing wounds. Collagen may be eliminated through keratoacanthomas.[2]

Clinically, it is characterized by an eruption that presents with a large number of papules, some coalescing into plaques and often distributed on the extremities. Although some may appear to involve the follicular units, these lesions are more likely to be extrafollicular. The typical patient is young to middle aged and often has a history of diabetes mellitus. The essential histopathologic findings include:

- A follicular or extrafollicular cornified plug with focal parakeratosis embedded in an epidermal invagination;
- Basophilic degenerated material identified in small collections throughout the plug with absence of demonstrable collagen and elastin;
- Abnormal vacuolated and/or dyskeratotic keratinization of the epithelial cells extending to the basal cell zone;
- Irregular epithelial hyperplasia; and
- An inflammatory component, i.e., typically granulomatous with small foci of suppuration.

In most instances, it is important to perform elastic tissue stains and even trichrome stains to exclude perforating elastic fibers, as in EPS, or collagen fibers, as in RPC.[3]

The histogenesis is attributed to a primary event of disturbance in epidermal keratinization characterized by the formation of dyskeratotic foci and acceleration of the process of keratinization. This leads to the formation of keratotic plugs with areas of parakeratosis.[4-6] Because the rapid rate of differentiation and keratinization exceeds the rate of cell proliferation, the parakeratotic column gradually extends deeper into the abnormal epidermis, leading in most cases to perforation of the parakeratotic column into the dermis. Perforation is not the cause of Kyrle's disease, as originally thought, but rather represents the consequence or final event of the abnormally accelerated keratinization.

This rapid production of abnormal keratin forms a plug that acts as a foreign body, penetrating the epidermis and inciting a granulomatous inflammatory reaction. A certain similarity exists between the parakeratotic column in Kyrle's disease and that observed in porokeratosis of Mibelli.[7] In both conditions, a parakeratotic column forms as a result of rapid and faulty keratinization of dyskeratotic cells, but, whereas in Kyrle's disease the dyskeratotic cells are often used up so that disruption of the epithelium occurs, and the clone of dyskeratotic cells can maintain itself in porokeratosis Mibelli by extending peripherally. Studies on lectin binding showed that the glycosylation process was impaired in both the epidermis and basement membrane zone of the leisonal skin. In addition, electron microscopic examination revealed diabetic microangiopathy of the dermal blood vessels as well as marked ultrastructural alteration of the dermo-epidermal basal lamina. These findings confirm the association of diabetes mellitus with Kyrle's disease.[8]

CONCLUSION

Although rare, Kyrle's disease should be considered in the differential diagnosis of all perforating dermatoses in diabetics. Epidemiological, clinical, and special stains will help in the diagnosis of this disease to provide better patient management. Kyrle's disease is treated with retinoic acid preparations, salicylic acid, corticosteroids, electrocautery, and cryotherapy. But the main treatment lies in treating the underlying cause. Thus, in case of diabetics, glycemic control can help in alleviating the disease symptoms and prevent recurrence.

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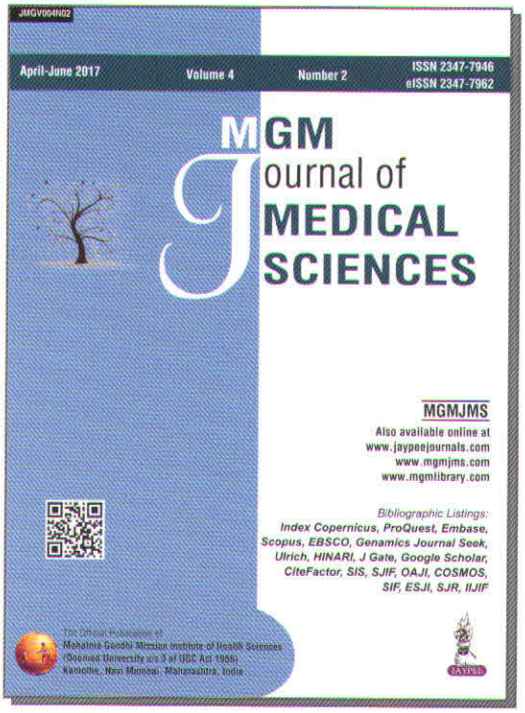

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