DOI: 10.7860/IJNMR/2023/62064.2387

Original Article

Paediatrics Section

Clinical Features of Urinary Tract Infection in Neonates with Hyperbilirubinemia: A Cross-sectional Study

SYED MUSTAFA HASAN[1], GAURAV JAIN[2], J MEENA[3], SAMEER PUNIA[4]

ABSTRACT

Introduction: Neonatal hyperbilirubinemia is a common physiological finding in neonates but sometimes Urinary Tract Infections (UTI) can occur in these neonates and it can be asymptomatic or may lead to complications. Many causative factors are listed out for development of neonatal jaundice but the UTI is less mentioned in previous studies.

Aim: To study the prevalence of UTI and its clinical features in the neonates with hyperbilirubinemia.

Materials and Methods: This cross-sectional study was conducted in Aakash Healthcare super specialty Hospital, Dwarka, New Delhi, India, between June 2019 and May 2020. Total 116 infants with neonatal hyperbilirubinemia were included in the study. The demographic features including date and time of admission, age at presentation of jaundice, mode of parturition, type of assistance for delivery (if any used), presence of cephalohaematoma, bruising or caput succedaneum, weight at birth, age at onset of jaundice (days of life), baby's and mother's blood group, any metabolic diseases in mother and father etc. were studied. A thorough haematological work-up was done and urine was collected in a sterile container by catheterisation. All samples were sent to the laboratory for microscopic analysis and culture. Data was statistically analysed using Mann-Whitney U-test and level of significant p-value was considered as less than 0.05.

Results: A total of 116 cases of neonatal hyperbilirubinemia were included in this study. Out of the 116 cases, 66 cases (56.89%) were male neonates and infants and 50 cases (43.11%) were female neonates and infants. In this study, out of 116 neonates with hyperbilirubinemia, only 20 babies showed pus cells >5 //hpf (high power field microscope) (suggesting UTI), out of the 20 babies, 08 babies showed culture negative and pus cells >5 /hpf and remaining 12 babies showed culture positive and pus cells >5 /hpf. Out of 12 cases of culture and sensitivity, 8 cases showed culture for Escherichia coli (*E.coli*) and remaining four cases, organism cultured was *Klebsiella pneumonia*.

Conclusion: Hyperbilirubinemia may be the initial sign of UTI in neonates; it may be asymptomatic in jaundiced newborns. It is recommended that, evaluation of UTI should be made in cases of asymptomatic hyperbilirubinemia cases which helps the paediatrician for early detection and treatment of these affected newborns reducing the hospital stay and long term complications.

Keywords: *Eschericia coli*, Jaundice, *Klebsiella pneumonia*, Phototherapy, Serum Bilirubin

INTRODUCTION

Hyperbilirubinemia has generally been regarded as a pathologic consequence of UTI and diagnosis of UTI can sometimes be challenging in newborns particularly if laboratory tests are not routinely performed [1]. Furthermore, due to multiple possible causes of jaundice in the neonatal period, it is important to have a good clinical orientation regarding the UTI in neonates to guide diagnosis and prevent the complications. Various conditions can lead to increased level of bilirubin in the serum. In newborns, hyperbilirubinemia can be due to haemolysis, birth trauma, infection or sepsis, metabolic and endocrine disorders, errors in galactose metabolism etc., [1]. Most of the time hyperbilirubinemia in neonates is physiological and is present during the first week of life; sometimes it can persist beyond a week and up to two weeks and is referred to as breast milk jaundice [1].

UTI is one of the most common infections in neonates and can present with hyperbilirubinemia and this is more predominant in preterm infants. About 60% to 80% of preterm newborns present a transient hyperbilirubinemia during the first week of life but few may have a masked pathological disorder [1,2]. But sometimes in some cases, jaundice may co-exist with UTI. They present with fever, irritability, vomiting, refusing feeds, failure to thrive, lethargy, oliguria or polyuria and yellowish urine. The predisposing factors for UTI in infants include underdeveloped uroepithelial bactericidal activity, low levels of local immunoglobulin A, low urinary acidification capacity, and high periurethral colonisation in the neonatal period lead to increased susceptibility to UTI [1].

During the first week of life, most of the infants have apparent jaundice due to the increased levels of unconjugated bilirubin concentration and it is termed as physiological jaundice. Mechanisms involved in this type of jaundice are relatively low activity of the glucoronsyltransferase which normally converts unconjugated bilirubin to congujated bilirubin that can be excreted into the gastrointestinal tract. Secondly, shorter life span of the foetal Red Blood Cells (RBC), and thirdly due to relatively low conversion of bilirubin to urobilinogen by the intestinal flora resulting in relatively high absorption of bilirubin back into the circulation [2].

Garcia FJ and Nager AL in their study reported that neonates who had hyperbilirubinemia after the postnatal 8th day had higher incidence of UTI [2]. In another study conducted by Ghaemi S et al., the rate of UTI in patients with prolonged jaundice was similar to that of the febrile cases of similar age, and therefore assessing routine urinalysis and urine culture were recommended in patients with prolonged jaundice [3,4]. Presently, there are very few clinical studies on hyperbilirubinemia and UTI to evaluate the effects of

hyperbilirubinemia on the course of UTIs [2-4]. Hopefully, this present study throws some light into the clinical aspects of jaundice and UTIs. Hence, present study was conducted to understand the significance of UTI as one of the causative factors in neonatal hyperbilirubinemia and also want to access the role of raised bilirubin as a cytoprotective pigment.

MATERIALS AND METHODS

This cross-sectional study was done in Aakash Healthcare super specialty hospital, Dwarka, New Delhi, India, between June 2019 and May 2020. Institutional Ethics Committee approval was taken before commencement of the study (IEC approval number 1602 /2019).

Inclusion criteria: Newborns with hyperbilirubinemia, total bilirubin levels ≥12.5 mg/dL (as per American Academy of Pediatrics (AAP) Guidelines for phototherapy in hospitalised infants of 35 or more weeks' gestation were included [5].

Hyperbilirubinemia is defined as increased bilirubin in the blood due to increased breakdown of the RBCs and other additional risk factors like gestational age, maternal health and diseases etc., according to the American Paediatric Academia and Turkish Neonatology Committee, Newborn Jaundice Guide [6].

Exclusion criteria: Newborns with fever, lethargy, hypotonic or high pitched cry with bilirubin levels of <13 mg/dL, blood culture positive, Complete Blood Count (CBC) with increased total leukocyte count or neutrophil count above the normal range, infants less than 24 hours of life and more than three weeks of life, UTI not coinciding with the time of onset of jaundice or neonates with any other infection (Other than UTI) were excluded.

Sample size estimation: Total 116 infants with neonatal hyperbilirubinemia, who presented in the department, within the study duration were enrolled in the study.

Study Procedure

The demographic features including, gender of the baby, mode of delivery, type of assistance for delivery (if any used), presence of cephalohaematoma, bruising or caput succedaneum, weight at birth and at admission, age at onset of jaundice (days of life), baby's and mother's blood group, any metabolic diseases in mother and father etc.,

A thorough haematological work-up was done which included CBC, peripheral smear with reticulocyte count, venous (total and direct) bilirubin levels, levels were performed in all patients (routinely done). Capillary blood bilirubin levels during remission period were also recorded everyday of phototherapy or once in two days.

Urine was collected in a sterile container by catheterisation. All samples were sent to the laboratory for microscopic analysis and culture. UTI was defined as positive urine culture (>10,000 in bag collection of a single organism) related with pyuria and bacteriuria. Pyuria considered to >5 pus cells /hpf of centrifuged urine [6]. Culture was considered positive when a single pathogen with more than 10,000 colony forming units/ml was discovered by catheterisation [7]. Urine culture was repeated if more than one pathogen was discovered or if the number of colonies did not match the above criteria.

STATISTICAL ANALYSIS

Data were statistically analysed by using the free version of stalstat statistics. Mean, standard deviation was calculated and the p-value is calculated using the sampling distribution of the test statistic under the null hypothesis from the sample data. Data were statistically analysed using Mann-Whitney U-test and level of significant p-value was considered as less than 0.05.

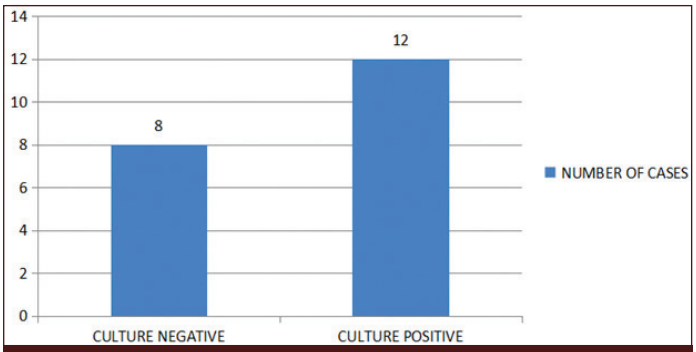
RESULTS

A total of 116 cases of neonatal hyperbilirubinemia were included in this study. Out of the 116 cases, 66 (56.89 %) were male infants and 50 (43.11 %) were female infants. In this study, preterm babies were 21 (18.10%) and remaining 95 (81.90%) were term babies. Mode of delivery in majority of the cases was caesarean section. It was observed that the mean birth weight for preterm and term infants was 1.97 Kg and 3.14 kg, respectively. In this study, majority of the neonates were exclusively breast fed. The mean age of onset of jaundice was 9.64 days and the mean total bilirubin seen in the infants' was 14.89 (preterm and term infants) and the mean indirect bilirubin was 14.12 mg/dL. The mean total leukocyte count 11,800±3400 cells /cu.mm [Table/Fig-1].

Parameters	n (%)	Mean (range seen in study population)
Gender		
Male	66 (56.89)	
Female	50 (43.11)	
Gestation		
Preterm	21 (18.10)	<37 weeks (33-37 weeks delivery)
Term	95 (81.90)	(≥38 weeks delivery)
Mode of delivery		
Normal vaginal delivery	37 (31.89)	
Caesarean section	79 (68.11)	
Birth weight (kg)		
Preterm	21 (18.10)	1.97 Kg (1.85 to 2.3 Kg)
Term	95 (81.90)	3.14 Kg (2.65 to 3.42 kg)
Feeding history		
Exclusively breast fed	73 (62.93)	
Formula feeds	09 (07.76)	
Both	34 (29.31)	
Age of onset of jaundice (days)	--	9.64 (8 days to 14 days)
Bilirubin at admission		
Total bilirubin (mg/dL)	--	14.89 (6.1 to 22.8 mg/dL)
Direct bilirubin (mg/dL)	--	0.77
Indirect bilirubin (mg/dL)	--	14.12 (13 to 21.15 mg'dL)
Complete Blood Count (CBC)		
Total leukocyte count (in cu.mm)	--	11,800±3400 (11,200 to 23500 cells /cu.mm)
Mean neutrophil count (in cu.mm)		63 cells /cu.mm

[Table/Fig-1]: Showing demographic, birth weight, feeding history, total bilirubin and leukocyte count.

In present study, out of 116 cases, 20 (17.25%) had UTI. Hence, the prevalence of UTI in this study was 17.25%. In term babies, the levels of total bilirubin were lower (12.06 mg/dL) when compared to the preterm babies with hyperbilirubinemia (17.4 mg/dL). In this study, out of 116 neonates with hyperbilirubinemia, only 20 babies showed pus cells >5/hpf (suggesting UTI), out of the 20 babies, 08 babies showed culture negative and pus cells >5 /hpf and remaining 12 babies showed culture positive and pus cells >5/hpf [Table/Fig-2].



[Table/Fig-2]: Showing diagnosis of UTI by microscopy and culture and sensitivity.

Out of 12 cases of culture positive, 8 cases (66.66 %) showed culture for *E.coli* and remaining 4 cases (33.33%), showed organism cultured was *Klebsiella pneumoniae*.

All culture negative and positive cases were treated with antibiotics injection cefotaxim and amikacin along with other symptomtic drugs. All the culture positive cases were treated according to the sensitive drug like amikacin, cefixime, cefpodoxime, cefprozil or cephalexin etc.,

When bilirubin levels were taken into consideration with antibiotic and phototherapy treatment, it was observed that approximately 1.72 mg/dL decrease was noted in neonates with UTI and 1.84 mg/dL decrease was noted in neonates without UTI on the first day of treatment. When compared to the group with UTI, bilirubin levels of neonates without UTI responded better to the phototherapy treatment and shown a significant p-value [Table/Fig-3].

Days	Bilirubin level decreased in neonates with UTI (n=20)	Bilirubin level decreased in neonates without UTI (n=96)	p-value
1	1.72 mg/dL±0.23	1.84 mg/dL±0.24	0.0028
2	1.91 mg/dL±0.26	2.01 mg/dL±0.27	0.0017
3	2.02 mg/dL±0.29	2.14 mg/dL±0.30	0.0019
4	2.14 mg/dL±0.33	2.23 mg/dL±0.34	0.0024
5	2.46 mg/dL±0.35	2.54 mg/dL±0.36	0.0031

[Table/Fig-3]: Effect of phototherapy in reducing the bilirubin levels in neonates with UTI and without UTI.
*Mann-Whitney U test

Average duration of hospital stay was taken into consideration, most of the infants i.e., 16 (80%) cases required phototherapy upto 7 days in neonates with UTI and 88 (91.7%) cases without UTI needed photo therapy up to 07 days and remaining 04 (20%) cases in UTI group and 8 (8.3%) cases in the non UTI group needed little longer stay of 8-9 days [Table/Fig-4].

Duration of hospital stay	Neonates with UTI (n=20)	Neonates without UTI (n=96)	p-value
3 days	-	12	-
4 days	-	21	-
5 days	3	19	0.001
6 days	8	23	0.003
7 days	5	13	0.004
8 days	3	7	0.003
9 days	1	1	0.002

[Table/Fig-4]: Showing duration of hospital stay.
A p-value <0.05 was considered to be significant

When the blood groups were taken into consideration, it was found that most common maternal blood group was O^+ followed by B^+ and A^+ and least common was AB^+. Among the negative groups common O^- was common and AB^- was least common. Among the infants blood group, most common was B^+ group followed by O^+ group and remaining were A^+. Only 8 infants had Rh^- group and the common was O^- group, followed by B^- and A^- [Table/Fig-5]. The mother and father of the neonate did not report the metabolic disorders.

Maternal blood group	Number	Infant blood group	Number
O^+	49	O^+	30
B^+	31	B^+	59
A^+	23	A^+	19
AB^+	7	AB^+	0
O^-	5	O^-	5
AB^-	1	B^-	2
		A^-	1
Total	116		116

[Table/Fig-5]: Blood group of the mother and neonates in general.

DISCUSSION

Bilirubin is a product of breakdown of haemoglobin in old RBCs and prematurely destroyed erythroid cells in bone marrow. Newborns have a higher rate of haemoglobin catabolism and increased production of bilirubin because of their elevated haematocrit or packed cell volume and RBC volume per body weight, and their shorter life span of RBCs when compared to older children and adults. Because of the increased destruction of RBCs, bilirubin levels remain elevated and also bilirubin clearance is delayed because of conjugation of bilirubin. When bilirubin molecule undergoes a reaction with diazo reagents causing the breakdown of the tetrapyrrole to two azodipyrroles and is measured spectrophotometrically. This reaction is termed as the Van den Bergh reaction [1].

According to the researchers and clinicians, hyperbilirubinemia is a prevalent condition among newborns and also have antioxidant and cytoprotective properties [4,8]. Newborns are more prone to get infections by various bacteria. Newborns also have high rate of UTIs and of renal scarring following pyelonephritis [9,10]. Garcia FJ and Nager AL reported that infants with the reported onset of jaundice after 8 days of age, when physiologic jaundice is expected to have improved or resolved, had a higher incidence of UTIs [2]. It was also reported that the newborns over three days of life can develop UTI in the setting of hyperbilirubinemia without any evidence of renal scarring. Hyperbilirubinemia in UTIs has been reported to be unconjugated and related to haemolysis caused by E.coli and other gram-negative organisms, or conjugated secondary to cholestasis. However, the relationship between UTI and hyperbilirubinemia has not been clearly defined [11].

In the present study, the prevalence of UTI was 20/116 which is lower that the incidence reported by the author Garcia FJ and Nager AL and higher than the incidence reported by Chen HT et al., [2,12]. Shahian M et al., studied 120 neonates <four-week-old with asymptomatic jaundice and reported UTI in 12.5% [13]. In present study, preterm babies were 21 (18.10%) and remaining 95 (81.90%) were term babies. In term babies, the levels of total bilirubin were lower (12.06 mg/dL) when compared to the preterm babies with hyperbilirubinemia (17.4 mg/dL). Male predominance was seen in this study which is in correlation with the studies done by Aygun E and Firinci F et al., [6,14] and this male predominance of neonatal UTI may be explained by some factors such as anatomical abnormalities, phimosis, periuretheral colonisation and overall increased susceptibility to infections by bacteria. Circumcision as a risk factor still remains unclear as few authors like Ghaemi S et al., considered it as a risk factor in male infants and authors Singh-Grewal D et al., reported that it has a very low risk [3,15].

Mode of delivery in majority of the cases was caesarean section 79 cases (68.11%) and normal vaginal delivery in 37 cases (31.89%) which is in correlation with the study done by Aygun E where they have reported 64.7% caesarean section and 35.3% normal deliveries. Whereas in another study by Bahat Ozdogan E et al., it was reported only 39.69% caesarean section and 60.31% were normal vaginal deliveries [16].

It was observed that the mean birth weight for preterm and term infants 1.97 kg and 3.14 kg, respectively which is in tandem with the findings of Aygun E where they reported that birth weight of the new born ranged between 1750 and 4270 grams [6]. In this study, majority of the neonates were exclusively breast fed (73 cases- 62.93%), 34 cases (29.31%) were breast fed and were given formula feeds. Only 9 (7.76%) were exclusively formula fed when compared to the study done by Omar C et al., where 48.4% of the newly born were exclusively breast fed and similar percentage (48.4%) were given both breast milk and formula feeds and only 3.2% given exclusively formula feeds [17].

The mean age of onset of jaundice was 9.64 days whereas Omar C et al., reported that majority of the cases (84.3%) age of onset was before eight days and 15.6% of the cases, age of the onset were after eight days [17]. In this study, out of 116 neonates with hyperbilirubinemia, only 20 babies showed pus cells >5 /hpf (suggesting UTI), out of the 20 babies, 08 babies showed culture negative and pus cells >5 /hpf and remaining 12 babies showed culture positive and pus cells >5 /hpf. In this study, 18.10% of the UTI were culture positive which is in correlation with the study done by Omar C et al., [17]. Majority of the cases, UTI was diagnosed on microscopy with more than 5 pus cells/hpf in others studies done by Garcia FJ and Nager AL; Aygun E, Firinci F et al., [2,6,14].

Out of 12 cases of culture and sensitivity, 8 cases showed culture for E.coli and remaining 4 cases, organism cultured was *Klebsiella pneumoniae* which is in contrast with the findings reported by Omar C et al., Aygun E and Rashed YK et al., [6,17,18]. Aygun E also reported that 12% UTI cases were due to *Enterobacter cloacae*, 6% cases were due to Methycillin-Resistant Coagulase Negative Staphylococci (MRCoNS), 4% cases were due to *Proteus mirabilis* and remaining were due to *enterococcus faecalis* (2%), gram negative bacilli (2%) and *candida albicans* (2%). The maximum duration of treatment in the was 4 days with the majority of newborns (44 cases) receiving three days of phototherapy which is in tandem with the findings of the author Omar C et al., where the cases responded well to two days of phototherapy [17].

Limitation(s)

Sample size in this study is small.

CONCLUSION(S)

In present study, prevalence of UTI in cases with hyperbilirubinemia was 17.25%. UTI can occur in neonates with hyperbilirubinemia and may present as initial sign of UTI. This study shows there was a significant decrease in the hospital stay and betterment of bilirubin levels in the neonates without UTI. It is recommended that testing for a UTI should be a part of the diagnostic protocol or evaluation of asymptomatic jaundiced newborns as this will lessen the hospital stay and urogenital complications. Further research with large sample size and more parameters to be added for better understanding.

REFERENCES

[1] Kasap B, Soylu A, Kavukçu S .Relation between hyperbilirubinemia and urinary tract infections in the neonatal period. J Nephrol Therapeutic. 2014;S11:009.
[2] Garcia FJ, Nager AL. Jaundice as an early diagnostic sign of urinary tract infection in infancy. Pediatrics. 2002;109(5):846-51.
[3] Ghaemi S, Fesharaki RJ, Kelishadi R. Late onset jaundice and urinary tract infection in neonates. Indian J Pediatr. 2007;74(2):139-41.
[4] Adin CA, Croker BP, Agarwal A. Protective effects of exogenous bilirubin on ischemia-reperfusion injury in the isolated, perfused rat kidney. Am J Physiol Renal Physiol. 2005;288(4):F778-84.
[5] American Academy of Pediatrics Steering Committee on Quality Improvement and Management Classifying recommendations for clinical practice guidelines. Pediatrics. 2004;114(3):874-77.
[6] Aygun E. Clinical significance of urinary tract infection among newborns with hyperbilirubinemia. 2020;9(6). AJBSR. MS.ID.001459.
[7] Bilgen H, Ozek E, Unver T, Biyikli N, Alpay H, Cebeci D. Urinary tract infection and hyperbilirubinemia. Turk J Pediatr. 2006;48(1):51-55.
[8] Clark JE, Foresti R, Sarathchandra P, Kaur H, Green CJ, Motterlini R. Heme oxygenase-1-derived bilirubin ameliorates postischemic myocardial dysfunction. Am J Physiol Heart Circ Physiol. 2000;278(2):H643-51.
[9] Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics. Committee on Quality Improvement. tee on Urinary Tract Infection. Pediatrics. 1999;103(4 Pt 1):843-52. Erratum in: 2000 Jan; 105(1 Pt 1):141. Erratum in: Pediatrics 1999 May; 103(5 Pt 1):1052, 1999 Jul; 104(1 Pt 1):118.
[10] Schlager TA. Urinary tract infections in infants and children. Infect Dis Clin North Am. 2003;17(2):353-65
[11] Maisels MJ, Newman TB. Neonatal jaundice and urinary tract infections. Pediatrics. 2003;112(5):1213-14.
[12] Chen HT, Jeng MJ, Soong WJ, Yang CF, Tsao PC, Lee YS, et al. Hyperbilirubinemia with urinary tract infection in infants younger than eight weeks old. J Chin Med Assoc. 2011;74(4):159-63.
[13] Shahian M, Rashtian P, Kalani M. Unexplained neonatal jaundice as an early diagnostic sign of urinary tract infection. Int J Infect Dis. 2012;16(7):e487-90.
[14] Firinci F, Soylu A, Ozturk C, Gulay Z, Demir BK, Turkmen M, et al. Hyperbilirubinemia and urinary tract infection: the effect of indirect hyperbilirubinemia on the in vitro growth of uropathogen Escherichia coli in newborn urine. Ren Fail. 2014;36(1):55-57.
[15] Singh-Grewal D, Macdessi J, Craig J. Circumcision for the prevention of urinary tract infection in boys: a systematic review of randomised trials and observational studies. Arch Dis Child. 2005;90(8):853-58.
[16] Bahat Ozdogan E, Mutlu M, Camlar SA, Bayramoglu G, Kader S, Aslan Y. Urinary tract infections in neonates with unexplained pathological indirect hyperbilirubinemia: Prevalence and significance. Pediatr Neonatol. 2018;59(3):305-09.
[17] Omar C, Hamza S, Bassem AM, Mariam R. Urinary tract infection and indirect hyperbilirubinemia in newborns. N Am J Med Sci. 2011;3(12):544-47.
[18] Rashed YK, Khtaband AA, Alhalaby AM. Hyperbilirubinemia with urinary tract infection in infants younger than eight weeks old. J Pediatr Neonatal Care. 2014;1(6):11-12.

PARTICULARS OF CONTRIBUTORS:
1. Director and Head, Department of Paediatrics, Aakash Healthcare Superspecialty Hospital, New Delhi, India.
2. Senior Consultant Neonatology, Department of Paediatrics, Aakash Healthcare Superspecialty Hospital, New Delhi, India.
3. Senior Consultant, Department of Paediatrics, Aakash Healthcare Superspecialty Hospital, New Delhi, India.
4. Consultant, Paediatric Intensive Care, Department of Paediatrics, Aakash Healthcare Superspecialty Hospital, New Delhi, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Gaurav Jain,
Senior Consultant , Neonatology, New Delhi, India.
E-mail: go4gauravjain@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Dec 06, 2022
- Manual Googling: Mar 15, 2023
- iThenticate Software: Apr 13, 2023 (17%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? No
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Dec 05, 2022**
Date of Peer Review: **Jan 12, 2023**
Date of Acceptance: **Apr 14, 2023**
Date of Publishing: **Jun 30, 2023**