Sacrococcygeal Teratoma

V. Raveenthiran

Department of Pediatric Surgery, Sri Ramasamy Memorial (SRM) Medical College, SRM University, Chennai 603203, India

(Athena stands for abbreviation of Abstracting and Thoughtful Evaluation of Neonatal Articles; but it is also personified by the contributor. Like Athena of Greek mythology, she distills wisdom from published literature)

Athena is fascinated by the tailbone (coccyx) for more than one reason: it is named poetically after the beak of a cuckoo; it is the key Darwinian link between the tail of primates and the tailless Homo sapiens; notwithstanding its tiny size it plays a vital role in anal continence by giving attachment to anal sphincters; and above all it harbors totipotent stem cells giving rise to a peculiar tumor - the Sacrococcygeal Teratoma (SCT). This tumor is peculiar because it is almost always benign to start with and it turns malignant with passage of time. This emphasizes the importance of early surgery and the need to excise coccyx in SCT. Athena believes that studying the natural history of SCT may unravel the secrets of oncogenesis. Her curiosity is perpetuated by recent reports [1 - 16] describing as to how these tumors have been mistaken for a variety of other lesions and vice versa (Table 1).

Recently, Shalaby et al [17] reported a mysterious vanishing of mid-urethra in girls undergoing excision of SCT. In a series of 53 SCT collected over a period of 30 years, they described 5 girls who had “vanishing mid-urethra”. In all of them the proximal urethra had fistulous communication with vagina. In 4 of them the external urethral meatus was normal and the distal urethra was ending blindly; one had complete absence of the distal urethra. Interestingly, in none of them the anomaly was recognized preoperatively despite the fact that all of them had been catheterized in the perioperative period. The diagnostic delay ranged from 6 weeks to 13 years after SCT excision. All of them presented with voiding dysfunction (2 with retention of urine and 3 with incontinence). Importantly, the diagnosis was elusive even after initial cystoscopic examinations. This phenomenon has also been previously reported in 2 girls [18]. Hypothetical explanations of this phenomenon include: (i) congenital malformation of the urogenital sinus due to the mechanical presence of teratoma in the fetal pelvis, (ii) iatrogenic injury to urethra and (iii) pressure necrosis of the mid-urethra that is compressed between pubic symphysis and the tumor. Intactness of proximal and distal parts of the urethra rules out the possibility of interference with urethral embryogenesis. Absence of concomitant injury to rectum and absence of intraoperative difficulties as recorded by experienced surgeons makes iatrogenic injury unlikely. If pressure necrosis is the cause, then why is it not occurring in boys? Therefore, Athena surmises that it could be due to unrecognized iatrogenic intraoperative injury to specific branches of the middle rectal artery. Branches of this artery supplies middle one third of vagina and the adjoining mid-urethra in females. Athena’s guess is supported by the fact that one of the patients in Shalaby’s series developed concomitant rectosigmoid stricture and mid-vaginal stenosis following SCT excision. The proximal urethra is usually supplied by the inferior vesical artery and the distal urethra by internal pudendal artery. Intactness of these arteries perhaps explains as to why the proximal and distal one third of the urethra is preserved in “Vanishing mid-urethra syndrome”. Rich collaterals between inferior vesical artery and bulbary artery probably protect the male urethra even if the middle rectal artery is damaged during surgical excision of SCT.
Table 1: Sacrococcygeal Teratoma - The great masquerader

| Author (year) † | Initial diagnosis * | Final diagnosis * | Reason for misdiagnosis |
|-----------------|---------------------|------------------|-------------------------|
| Mullen (2013)   | Hemangioma          | SCT              | Rich vascularity of SCT was mistaken for hemangioma in 2 cases |
| Jan (2012)      | MMC                 | SCT - Type IV    | Cystic presacral masses in 5 children were mistaken for MMC |
| Jan (2012)      | Gluteal Abscess     | SCT - Type III   | Lateralized cystic SCT in right gluteus mistaken for abscess; Lateral SCT are rare |
| Jan (2012)      | Vertebral disc prolapse | SCT         | Presented with paraplegia due to spinal metastasis |
| Jan (2012)      | Fecal fistula       | SCT - Type IV    | ? |
| Jan (2012)      | Perianal fistula    | SCT - Type IV    | Recurrent multiple fistulae due to incomplete excision of SCT (cf: Pye 1987) |
| Jan (2012)      | SFT                  | SCT              | Presented with urinary incontinence which is unusual for fetus-in-fetu |
| Jan (2012)      | Inguinal lymphadenitis | SCT - Type IV  | Inguinal metastasis of hidden presacral SCT |
| Nasir (2012)    | SCT                 | Plexiform Neurofibroma | Genitourinary plexiform neurofibroma is unusual for a 9-year-old girl |
| Paradis (2012)  | SFT                  | Currarino syndrome | Prenatal imaging diagnosed SCT but not the other components of Currarino Triad |
| Al-Salem (2011) | SFT                  | Infante Fibrosarcoma | Sacrum is an unusual site for fibrosarcoma |
| Sonmez (2009)   | SFT - Type I        | Malignant Triton Tumor | Triton Tumor is unusual in newborn; Family history of neurofibroma provides the diagnostic clue |
| Khalil (2009)   | Abscess             | SCT              | Cystic SCT mistaken for abscess |
| Sugitani (2009) | Meningomyelocele    | SFT - Type I     | Cystic SFT mimicked MMC |
| Watanabe (2008) | SFT                 | Cystic Neuroblastoma | Cystic neuroblastoma of sacrum is extremely rare |
| York (2006)     | SFT - Type III      | Lymphangioma     | Abdomino-perineal multiseptate cystic mass |
| Tanaka (2005)   | SFT - Type III      | Neuroblastoma    | Sacrum is unusual site for neuroblastoma |
| Garel (2005)    | Cloaca              | SFT - Type IV    | Cystic Presacral SCT mimicked cloaca in prenatal USG. Absence of T1 hyper signal of meconium in prenatal MRI was diagnostic |
| Cable (1997)    | SFT                 | Chordoma         | Chordoma is unusual tumor in children |
| Evans (1994)    | Meningomyelocele    | SFT              | Sacral cystic mass in prenatal USG and elevated AFP is common to both MMC and SCT |
| Hayashi (1993)  | SFT                 | Klippel-Trenaunay-Weber syndrome | Prenatal USG was mistaken. Even maternal serum HCG was elevated |
| Pye (1987)      | Fistula-in-ano     | SFT (? Type II)  | Chronic infection of cystic SCT with spontaneous rupture |

SCT - Sacrococcygeal Teratoma, MMC - Meningomyelocele, AFP - Alpha Fetoprotein, MRI - Magnetic Resonance Imaging, USG – Ultrasonography
* Type of SCT is according to Altman Classification; † For citations see reference list

SCT is fraught with several serious complications. Huge tumor distorting the anatomy, extensive pelvic dissections and tumor infiltration or encasement of pelvic nerves leads to numerous complications such as bowel and bladder dysfunction, sexual inadequacy, gait alteration, distorted gluteal mound, wound dehiscence and death due to excessive intraoperative blood loss or malignant recurrences. In the last decade (2003 - 2013) several authors [19 - 35] reported their long-term results with SCT excision (Table 2). Mean follow-up in some of the series was as long as 25 years. But these impressive studies are far from bringing the good news. Although mortality is less than 10% in most of the reports, continence and cosmesis are of great concern. Approximately one third of patients suffer long-term incontinence of stool and urine. In some of the studies [22, 25] fecal and urinary incontinence is as high as 64% and 50% respectively. Athena wonders as to what proportion of post-surgical female urinary incontinence can be attributed to missed diagnosis of “vanishing mid-urethra”.

---

Journal of Neonatal Surgery Vol. 2(2); 2013
Table 2

Long-term results of Sacrococcygeal Teratoma - Summary of Reports published between 2003 - 2013

| Author (Year)    | Country | Study Period | n (M: F) | Mean (Range) Follow-up in Months | Complications ‡ |
|------------------|---------|--------------|----------|----------------------------------|-----------------|
| Sinha (2013)     | India   | 1998 - 2012  | 10 (3:7) | 25 (1 - 72)                      | 1 (10%) Local Recurrence 0 (0%)                       |
| Kouranloo (2013) | Iran    | 1986 - 2000  | 26 (6:20)| ? (3 - 156)                      | 8 (31%) 2 (8%) 1 (4%)                               |
| Osman (2012)     | Egypt   | 2001 - 2011  | 45       | (3 - 120)                        | 4 (10%) 5 (12%) 0 (0%) 2 (5%)                      |
| Hager (2012)     | Austria | 1968 - 2011  | 24 (3:21)| ? (?)                            | 6 (25%) 1 (4%) 7 (20%) 9 (64%)                     |
| Barakat (2011)   | Egypt   | 2004 - 2010  | 22 (6:16)| 40 (?)                          | 4 (18%) 1 (5%) 7 (32%) 5 (23%)                     |
| Ho (2011)        | Australia| 1996 - 2008  | 17       | 32 (?)                           | 1 (6%) 2 (12%) 1 (6%)                               |
| Berger (2011)    | Germany | 1998 - 2009  | 24 (5:19)| ? (?)                            | 12 (50%) 0                               |
| Manzoni (2011)   | Italy   | 1985 - 2009  | 14       | 121 (?)                          | (79%) (36%) (14%)                                   |
| Khalil (2009)    | UK      | 1987 - 2006  | 12 (3:9) | 127 (12 - 204)                   | 2 (17%) 2 (17%) 1 (8%) 3 (25%)                     |
| Draper (2009)    | Canada  | 1970 - 2006  | 46       | 200 (?)                          | 2 (5%) 1 (7%) 7 (50%) 0 (0%)                       |
| Chirdan (2009)   | Nigeria | 1990 - 2008  | 38 (7:31)| 72 (1 - 96)                      | 8 (21%) 3 (14%) 3 (14%) 2 (10%)                   |
| Hashish (2009)   | Egypt   | 1998 - 2008  | 35 (11:24)| (3 - 96)                        | 8 (25%) 4 (12%) 2 (6%) 5 (16%)                     |
| Tailor (2009)    | UK      | 1993 - 2006  | 9        | 30 (6 - 132 mo)                  | ? 3 (38%) ? ?                                    |
| Cozzi (2008)     | Italy   | 1968 - 1988  | 18 (6:12)| 300 (204 - 456)                  | 6 (33%) 5 (38%) 8 (62%) 3 (23%)                  |
| Derikx (2007)    | Netherlands | 1980 - 2003  | 148      | 116 (24 - 276)                   | 31 (41%) 4 (3%) 23 (31%) 35 (38%)                |
| Bittmann (2006)  | Switzerland | 1972 - 2002  | 25 (6:19)| 212 (0 - 396)                    | 9 (60%) 2 (8%) 1 (7%) 5 (33%) 1 (10%)            |
| Gabra (2006)     | UK      | 1977 - 2001  | 33 (5:28)| 96 (24 - 168)                    | 4 (50%) 3 (15%) 7 (35%) 6 (30%)                   |
| Abubakar (2005)  | Nigeria | 1985 - 2003  | 21 (4:17)| 6 (?)                           | 9 (43%) 2 (10%)                               |

* Bowel Dysfunction includes major wound dehiscence, wound infections, scar hypertrophy and deformed gluteal mound
† Bladder Dysfunction includes urinary incontinence, emphysema, urinary retention and ureteral strictures
§ Unsightly scar includes major wound dehiscence, wound infections, scar hypertrophy and deformed gluteal mound
‡ The denominator of percentage calculation is the number of children for whom adequate data are available and not the total number of patients reported in the study.

For citations see the reference list.

n - Number of patients; M: F - Male: Female ratio
One study from Ghana [36] reports a wound dehiscence rate as high as 90%. To Athena's dismay most of the studies do not even mention sexual inadequacy and gait related problems. Bittmann et al [33] recorded obstetric difficulty due to rigid pelvic-outlet in one of their patients (10%). Zaccara et al [37] did gait analysis of SCT patients using Vicon 3-D motion analysis system. Although children exhibited an apparently normal gait following SCT excision, kinesiometric analysis showed significant reduction in hip extension, range of ankle movements and knee power. Paradoxical increase in ankle power was also noticed. Precise definitions and rigorous postoperative evaluation are missing in all most all the studies. Athena fears that a more stringent follow-up protocol may increase the complication rates in excess of 50%.

Approximately 3 to 31% of SCT have a tendency to recur after excision. Derikx et al [38] and De Backer et al [39] studied the factors responsible for tumor recurrence in a cohort of 173 and 70 children respectively. Incomplete excision [38], failure to excise coccyx [39] and malignant or immature histology have emerged as risk factors of tumor recurrence [38, 39]. Microscopic residue of mature or immature teratoma at the resection margin was rarely associated with local recurrences; however, presence of yolk sac tumor (YST) component was an exception to this rule [39]. In case of cystic teratomas spillage of solid components rather than the cyst fluid was responsible for recurrences [39]. According to Derikx et al [38] tumor size, Altman type and age at diagnosis are not associated with recurrence. In this context, Athena is reminded of a previous paper wherein Bilik et al [40] have showed that a large tumor may possibly have imperceptibly tiny foci of malignant cells; missing these tiny foci during histological sectioning may erroneously label the tumor as benign. In huge tumors it is impractical to histologically sample and study every millimeter of the lesion. In the background of this contention Athena deems it wise to consider large tumor size as a risk factor of local recurrence even though Derikx's data do not support that notion. Is it not true that wisdom is beyond the realms of statistics and evidences?

Early detection of recurrence is often facilitated by serial estimation of tumor markers during follow-up. The role of alpha fetoprotein (AFP) and human chorionic gonadotropin (HCG) in the follow-up of SCT is well known. Pauniaho et al [41] studied the role of various tumor markers in a cohort of 32 children with 1 to 15 years of follow-up. Six of the children had 8 recurrences. AFP was useful in detecting malignant recurrences while CA-125 was useful in early detection of recurrences of mature and immature tumors. Athena would recommend complementing AFP with CA-125 in post-surgical follow-up of SCT.

Rich vascularity and huge tumor size often cause fetal circulatory failure and hydrops. Recently several parameters, based on prenatal sonography, have been developed to prognosticate the fetal outcome in SCT. Sy et al [42] proposed a ratio between the volume of the tumor and the fetal head. In case of cystic SCT, only the volume of solid component was taken into consideration. There were no deaths when the tumor-head ratio (THR) was less than 1; alarmingly the mortality was 61% when the THR was more than 1. Rodriguez et al [43] suggested a ratio of tumor volume and fetal weight. The tumor-fetal ratio (TFR) was predictive of fetal outcome before 24 weeks of gestation. TFR < 0.12 had a significantly better outcome than TFR > 0.12. The sensitivity and specificity of this prediction were 100% and 83% respectively. Despite the limitation of small sample size in these studies, Athena believes these parameters be of use in offering evidence based prenatal counseling.

REFERENCES

1. Mullen M, Rabban J, Frieden IJ. Sacrococcygeal teratoma masquerading as congenital hemangioma. Pediatr Dermatol. 2013; 30: 112 - 116.
2. Jan IA, Hazratullah, Ishaque N, Haq A, Gondal M, Sharif A, Ahmad S. Unusual presentation of Sacrococcygeal teratomas in pediatric patients. Saudi J Health Sci 2012; 1: 30 - 34.
3. Nasir AA, Abdur-Rahman LO, Ibrahim KO, Adegoke MA, Afolabi JK, Adeniran JO. Genitourinary plexiform neurofibroma mimicking sacrococcygeal teratoma. J Surg Tech Case Rep. 2012; 4: 50 - 52.
4. Paradies G, Zullino F, Orofino A, Leggio S. Unusual presentation of sacrococcygeal teratomas and associated malformations in children. Clinical
experience and review of the literature. Ann Ital Chir. 2012. pii:S0003469X1201929X. [Epub ahead of print]

5. Al-Salem AH. Congenital-infantile fibrosarcoma masquerading as sacrococcygeal teratoma. J Pediatr Surg. 2011; 46: 2177 - 2180.

6. Sonmez K, Turkylilmaz Z, Karabulut R, Kapsiz A, Eser EP, Memis L, Basaklar AC. A Triton tumor mimicking sacrococcygeal teratoma. J Pediatr Surg. 2009; 44: e5 - e8.

7. Khalil BA, Aziz A, Kapur P, Humphrey G, Morabito A, Bruce J. Long-term outcomes of surgery for malignant sacrococcygeal teratoma: 20-year experience of a regional UK centre. Pediatr Surg Int. 2009; 25: 247 - 250.

8. Sugitani M, Morokuma S, Hidaka N, Kinoshita Y, Taguchi T, Teukimori K, Wake N. Three-dimensional power Doppler sonography in the diagnosis of a cystic sacrococcygeal teratoma mimicking a meningomyelocele: A case report. J Clin Ultrasound. 2009; 37: 410 - 413.

9. Watanabe M, Komuro H, Kaneko M, Hori T, Tatekawa Y, Kudo S, Urita Y, Inoue S, Minami M, Sugano M. A rare case of presacral cystic neuroblastoma in an infant. J Pediatr Surg. 2008; 43: 1376 - 1379.

10. York DG, Wolfe H, von Allmen D. Fetal abdominoperineal lymphangioma: differential diagnosis and management. Prenat Diagn. 2006; 26: 692 - 695.

11. Tanaka K, Kanai M, Yosiizawa J, Yamazaki Y. A case of neonatal neuroblastoma mimicking Altman type III sacrococcygeal teratoma. J Pediatr Surg. 2005; 40: 578 - 580.

12. Garel C, Mizouni L, Menez F, Luton D, Guibourdenche D, Aigrain Y, Sebag G. Prenatal diagnosis of a cystic type IV sacrococcygeal teratoma mimicking a cloacal anomaly: contribution of MR. Prenat Diagn. 2005; 25: 216 - 219.

13. Cable DG, Moir C. Pediatric Sacrococcygeal Chordomas: A Rare Tumor to be Differentiated From Sacrococcygeal Teratoma. J Pediatr Surg1997; 32: 759 - 761.

14. Evans MJ, Danielian PJ, Gray ES. Sacrococcygeal teratoma: a case of mistaken identity. Pediatr Radiol. 1994; 24: 52 - 53.

15. Hayashi M, Kurishita M, Sodemodo T, Kozu H, Kumasaka T, Saiki S. Prenatal ultrasonic appearance of the Klippel-Trenaunay-Weber syndrome mimicking sacrococcygeal teratoma with an elevated level of maternal serum hCG. Prenat Diagn. 1993; 13: 1162 - 1163.

16. Pye G, Blundell JW. Sacrococcygeal teratoma masquerading as fistula-in-ano. J R Soc Med. 1987; 80: 251 - 252.

17. Shalaby MS, O’Toole S, Driver C, Bradnock T, Lam J, Carachi R. Urogenital anomalies in girls with sacrococcygeal teratoma: a commonly missed association. J Pediatr Surg. 2012; 47: 371 - 374.

18. Nieuwenhuijs JL, De Jong TPVM. Two cases of unusual urethral complications after resection of sacrococcygeal teratoma. J Pediatr Surg 2003; 38: E57 (pages 14 - 15)

19. Sinha S, Sarin YK, Deshpande VP. Neonatal sacrococcygeal teratoma: our experience with 10 cases. J Neonat Surg. 2013; 2: Article number 4.

20. Kouranloo J, Sadeghian N, Mirshemirani AR. Benign sacrococcygeal teratoma: A fifteen-year retrospective study. Acta Medica Iranica 2006; 44: 33 - 36.

21. Osman MA, Ibrahim IA. Sacrococcygeal teratoma: 10-year experience in upper Egypt. Ann Pediatr Surg 2012; 8: 45 - 48.

22. Hager T, Sergi C, Hager J. Sacrococcygeal Teratoma – a single center study of 43 years (1968–2011) including follow-up data and histopathological re-evaluation of specimens. Eur Surg 2012; 44: 255 - 266.

23. Barakat MI, Abdelaal SM, Saleh AM. Sacrococcygeal teratoma in infants and children. Acta Neurochir. 2011; 153: 1781 - 1786.

24. Ho KO, Soundappan SV, Walker K, Badawi N. Sacrococcygeal teratoma: the 13-year experience of a tertiary paediatric centre. J Paediatr Child Health. 2011; 47: 287 - 291.

25. Berger M, Heinrich M, Lacher M, Hubertus J, Stehr M, von Schweinitz D. Postoperative bladder and rectal function in children with sacrococcygeal teratoma. Pediatr Blood Cancer. 2011; 56: 397 - 402.

26. Manzoni C, Canali R, Narciso A, Nanni L, Pintus C. Sacrococcygeal teratoma: single center experience and functional long-term follow-up. Clin Ter. 2011; 162: 99 - 106. [English abstract of Italian article]

27. Draper H, Chitayat D, Ein SH, Langer JC. Long-term functional results following resection of neonatal sacrococcygeal teratoma. Pediatr Surg Int. 2009; 25: 243 - 246.

28. Chirdan LB, Uba AF, Pam SD, Edino ST, Mandong BM, Chirdan OO. Sacrococcygeal teratoma: clinical characteristics and long-term outcome in Nigerian children. Ann Afr Med. 2009; 8: 105 - 109.

29. Hashish AA, Fayad H, El-attar AA, Radwan MM, Ismael K, Ashour MHM, Elhalaby E. Sacrococcygeal Teratoma: Management and Outcomes. Ann Pediatr Surg 2009; 5: 119 - 125.

30. Tailor J, Roy PG, Hitchcock R, Grant H, Johnson P, Joseph VT, Lakho K. Long-term functional outcome of sacrococcygeal teratoma in a UK regional center (1993 to 2006). J Pediatr Hematol Oncol. 2009; 31: 183 - 186.

31. Cozzi F, Schiavetti A, Zani A, Spagnoletti G, Cozzi DA. The functional sequelae of sacrococcygeal teratoma: a longitudinal and cross-sectional follow-up study. J Pediatr Surg. 2008; 43: 658 - 661.

32. Derixon JP, De Backer A, van de Schoot L, et al. Long-term functional sequelae of sacrococcygeal teratoma: a national study in The Netherlands. J Pediatr Surg. 2007; 42: 1122 - 1126.

33. Bittmann S, Bittmann V. Surgical experience and cosmetic outcomes in children with sacrococcygeal teratoma. Curr Surg. 2006; 63: 51 - 54.

34. Gabra HO, Jesusdason EC, McDowell HP, Pizer BL, Losty PD. Sacrococcygeal teratoma--a 25-year experience in a UK regional center. J Pediatr Surg. 2006; 41: 1513 - 1516.

35. Abubakar AM, Nggada HA, Chinja YJ. Sacrococcygeal teratoma in Northeastern Nigeria: 18-years experience. Pediatr Surg Int. 2005; 21: 645 - 648.

36. Amoah M, Boateng N, Abantanga FA. Sacrococcygeal teratoma: a 4-year experience at Komfo Anokye
Teaching Hospital. Postgrad Med J Ghana 2012; 1: 15 - 19.

37. Zaccara A, Iacobelli BD, Adorisio O, et al. Gait analysis in patients operated on for sacrococcygeal teratoma. J Pediatr Surg. 2004; 39: 947 - 952.

38. Derikx JP, De Backer A, van de Schoot L, et al. Factors associated with recurrence and metastasis in sacrococcygeal teratoma. Br J Surg. 2006; 93: 1543 - 1548.

39. De Backer A, Madern GC, Hakvoort-Cammel FG, Haentjens P, Oosterhuis JW, Hazebroek FW. Study of the factors associated with recurrence in children with sacrococcygeal teratoma. J Pediatr Surg. 2006; 41: 173 - 181.

40. Biilk R, Shandling B, Pope M, Thorner P, Weitzman S, Ein SH. Malignant benign neonatal sacrococcygeal teratoma. J Pediatr Surg. 1993; 28: 1158 - 1160.

41. Pauniaho SL, Tatti O, Lahdenne P, et al. Tumor markers AFP, CA 125, and CA 19-9 in the long-term follow-up of sacrococcygeal teratomas in infancy and childhood. Tumour Biol. 2010; 31: 261 - 265.

42. Sy ED, Filly RA, Cheong ML, et al. Prognostic role of tumor-head volume ratio in fetal sacrococcygeal teratoma. Fetal Diagn Ther. 2009; 26: 75 - 80.

43. Rodriguez MA, Cass DL, Lazar DA, et al. Tumor volume to fetal weight ratio as an early prognostic classification for fetal sacrococcygeal teratoma. J Pediatr Surg. 2011; 46: 1182 - 1185.

**Contributed By:**

V. Raveenthiran

Department of Pediatric Surgery, SRM Medical College & Hospital SRM University, Chennai, India.

E mail: vrthiran@yahoo.co.in

© Raveenthiran V, 2013

Submitted on: 24-03-2013
Accepted on: 26-03-2013
Published on: 01-04-2013

**Conflict of interest:** The author is an Editor of the journal. But he did not take part in the evaluation or decision making of this manuscript. The manuscript has been independently handled by two other editors.

**Source of Support:** Nil