Kruger Paul (Orcid ID: 0000-0001-8081-3949)
King Sebastian (Orcid ID: 0000-0001-5396-0265)

Screening for Associated Anomalies in Anorectal Malformations: the Need for a Standardised Approach

Running title: Screening anorectal malformation patients

Paul Kruger MD [1, 2], Warwick J. Teague DPhil FRACS [1, 2, 3], Rija Khanal MD [1, 2], John M. Hutson AO DSc FRACS [2, 3, 4], Sebastian K. King PhD FRACS [1, 2, 3, 5]

[1] Department of Paediatric Surgery, The Royal Children's Hospital, Melbourne, Victoria, Australia

[2] Surgical Research, Murdoch Children's Research Institute, Melbourne, Australia

[3] Department of Paediatrics, University of Melbourne, Victoria, Australia

[4] Department of Urology, The Royal Children's Hospital, Melbourne, Victoria, Australia

[5] Department of Gastroenterology and Clinical Nutrition, The Royal Children's Hospital, Melbourne, Victoria, Australia

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ans.15150

Correspondence to:

Associate Professor Sebastian King

Department of Paediatric Surgery

The Royal Children's Hospital

50 Flemington Road, Parkville, Melbourne, Victoria

Australia 3052

(P) +61 3 9345 5801

(F) +61 3 9345 6668

(E) sebastian.king@rch.org.au

This study was presented at the Pacific Association of Pediatric Surgeons in Hawaii, April 2016.

One table

Abstract: 203 words

Text: 1180 words

Abstract

Background

Anorectal malformations (ARM) are common congenital abnormalities of the terminal hindgut. The high incidence of associated anomalies necessitates systematic screening, which should include renal and spinal ultrasonography, spinal radiography and an echocardiogram. This study aimed to determine the incidence of associated anomalies in ARM, and whether screening protocols were appropriately applied.

Methods

A retrospective review was performed of all ARM patients managed at The Royal Children's Hospital, Melbourne over a 16-year period (2000 – 2015). Data collected included ARM type, presence of associated anomalies, as well as utilisation of renal and spinal ultrasonography, spinal radiography and echocardiography.

Results

A total of 243 patients (male 146/243, 60%) were reviewed. The most frequent ARM types were perineal fistula (83/243, 34%) and rectovestibular fistula (40/243, 16%). Full screening was performed in 153/243 (63%), while 18/243 (7%) received no screening. In fully screened patients, associated anomalies were diagnosed in

143/153 (93%), with cardiovascular, renal and musculoskeletal anomalies being most frequent.

Conclusions

The high incidence of associated anomalies identified in fully screened ARM patients highlights the importance of systematic screening. Clinically significant anomalies may have been overlooked in the more than one-third of ARM patients in whom screening was absent or incomplete. Standardised screening protocols for ARM patients have now been implemented.

Keywords: neonate, anorectal malformation, associated anomaly, screening

Anorectal malformations (ARM) are common congenital abnormalities of the terminal hindgut, with an incidence of 1/2–5000 live births. [1, 2] Malformations occur over a wide spectrum, ranging from a simple anal membrane to cloacal exstrophy. The majority of ARM are associated with other congenital anomalies that may affect multiple organ systems. Renal anomalies are most common, followed by musculoskeletal, cardiovascular and gastrointestinal anomalies. [3] Anorectal malformations that involve the more proximal urinary tract have a higher frequency of associated anomalies. The VACTERL (Vertebral, Anal, Cardiac, Tracheo-Esophageal, Renal and Limb) associations are common. First described in 1973, the VATER association was later expanded to include cardiac and additional limb anomalies. [4-6] Patients are now considered to have the VACTERL association when three or more of these body systems are affected. [7]

When patients are diagnosed with associated anomalies that do not conform to a recognised syndrome or association, these anomalies are often grouped by body system. Anomalies may occur in craniofacial, airway, gastrointestinal (excluding oesophageal atresia), reproductive and neurological systems. Whilst morbidity among patients with ARM is most often related to the complexity of the malformation, mortality is more often related to the associated anomalies (e.g. cardiac malformations, chromosomal syndromes).

The high incidence of associated anomalies necessitates thorough and systematic screening of patients following ARM diagnosis, and clinicians must be vigilant in ensuring screening protocols are followed. This should include careful

physical examination, along with renal ultrasonography, spinal radiography, spinal ultrasonography and an echocardiogram. [8] By analysing the diagnostic work-up of associated anomalies in patients with ARM managed at our tertiary referral centre, we aimed to determine whether screening protocols adequately addressed the incidence of these anomalies.

Methods

A retrospective review of all patients with an ARM managed at our tertiary centre between January 2000 – December 2015 was performed. Patients were identified from the Neonatal Intensive Care Unit patient registry, the operating theatre databases and admissions coded by health information systems. Ethical approval was obtained from the institutional Research Ethics Committee (DA058-2014-01).

All medical records (electronic and/or paper) were reviewed in order to record key demographics, including: (1) ARM type, (2) investigations performed, and, (3) associated anomalies identified. A patient was considered to have undergone full screening if, in addition to their clinical examination, they had undergone vertebral imaging (x-ray, spinal ultrasonography or MRI), renal imaging (ultrasonography) and an echocardiogram. No age limit was placed for the timing of the investigations. Associated anomalies were recorded if detected on investigations, or mentioned in consultation letters and/or discharge summaries. The patient cohorts were analysed for gender, ARM type, investigations performed, and incidence of anomalies. A diagnosis of the VACTERL association was ascribed when three or more appropriate systems were affected. [7]

Study data were collected and managed using REDCap electronic data capture tools hosted at our research institute. [9] The definitive diagnoses were confirmed by the senior author. SPSS software (IBM Corp. Released 2013. IBM

SPSS Statistics for Macintosh, Version 22.0, Version 22.0. Armonk, NY: IBM Corp) was used for subgroup analyses, including Fisher's exact test. Demographic data were described with frequencies and proportions.

Results

A total of 243 ARM patients were included, the majority of which (146/243, 60%) was male. The most frequent types of ARM were perineal fistula (n = 83) and rectovestibular fistula (n = 40). Ten patients had Down syndrome. Fifteen patients were deceased at the time of analysis, with causes of death including inoperable airway malformations, disseminated intravascular coagulation, multi-organ system failure, renal failure, and aspiration pneumonia secondary to cerebral palsy. Inadequate screening was not considered a contributing, nor complicating, factor in any of the identifiable causes of death. The most common type of ARM in the deceased patients was cloacal exstrophy (n = 3).

Screening investigations

In total, 153/243 (63%) patients underwent a full screen, 72/243 (30%) underwent a partial screen, and 18/243 (7%) had no screening whatsoever. Full screening occurred more often in males (100/146, 68% versus 53/97, 54%). There was a trend between screening thoroughness and the complexity of the ARM. (Table 1) When cloacal anomalies were considered as one group, the ARM types most often fully screened were rectal atresia (12/13, 92%) and rectovesical fistula (7/8,

88%), whilst anal stenosis was the most poorly screened (5/25, 20%). The investigation most frequently omitted was the echocardiogram (82/243, 34%).

Fully screened cohort

Of the 153 patients that underwent a full screen, 143/153 (93%) had an associated anomaly. The system most often involved was the cardiovascular system (126/153, 82%), followed by the renal tract (64/153, 42%) and musculoskeletal systems (61/153, 40%). The VACTERL association was present in 85/153 (56%), affecting 52/100 male patients and 33/53 female patients. The greatest incidence of VACTERL within the fully screened patients occurred in patients with either a cloacal anomaly or a rectovaginal fistula.

Discussion

We have described a well-defined cohort of ARM patients, managed at our large tertiary referral centre over a 16-year period. In more than one-third of the patients, the appropriate screening investigations for the commonly associated anomalies were either performed incompletely or not at all. When screening was performed appropriately, more than 90% of the patients were found to have an associated anomaly. The data presented in this study and previous studies strongly suggest that thorough screening for associated anomalies in patients with ARM should be standard practice, regardless of ARM type. Accurate and timely diagnosis of the associated anomalies facilitates informed discussion with the families, ensures appropriate clinical care, and guides long-term management. [8]

Many authors have described the need for, and inadequacy of, screening in ARM patients. [10-13] Despite increased awareness over the last two decades, it appears that clinicians continue to under-investigate affected patients. Consistent with previous reports, we observed a trend towards poorer compliance with screening for associated anomalies in those patients with a presumed less complex ARM type (anal stenosis, perineal fistula). [10, 11] Rollins *et al.* [12] demonstrated a deficiency in their screening of perineal fistula patients. As 35% of these perineal fistula patients were subsequently found to have an associated anomaly, their and our authors' findings highlight the need for increased vigilance in patients with less anatomically severe malformations. These low screening rates may be attributed to the perception that simple lesions are less likely to be associated with other

anomalies. [12] It may be also result from a delay in diagnosis in many of these patients, which then leads to inadequate assessment. [13] Unfortunately, the delay in diagnosis of associated anomalies may also result in lost opportunities for appropriate non-operative interventions. [8]

Within the limits of a retrospective study, we have demonstrated the ongoing issue of inadequate screening for associated anomalies in ARM patients. These inadequacies were most demonstrated in patients with less complex anatomical malformations. The standard of practice should include dedicated spinal x-ray, spinal cord ultrasonography, renal ultrasonography and echocardiogram for all patients. The utilisation of MRI may be necessary to further investigate spinal abnormalities identified on spinal x-ray and/or ultrasonography. As a result of our findings, we have instituted a screening protocol at our tertiary centre for all ARM patients to ensure that patients undergo full evaluations.

Acknowledgements

Associate Professor Sebastian King and Associate Professor Warwick Teague are both generously supported by The Royal Children's Hospital Foundation.

References

[1] Nah SA, Ong CC, Lakshmi NK, *et al*. Anomalies associated with anorectal malformations according to the Krickenbeck anatomic classification. *J Pediatr Surg* 2012;**47**:2273-8.

[2] Herman RS, Teitelbaum DH. Anorectal malformations. *Clin Perinatol* 2012;**39**:403-22.

[3] Levitt MA, Pena A. Anorectal malformations. *Orphanet J Rare Dis* 2007;**2**:33.

[4] Quan L, Smith DW. The VATER association: Vertebral defects, Anal atresia, T-E fistula with esophageal atresia, Radial and Renal dysplasia: a spectrum of associated defects. *J Pediatr* 1973;**82**:104-7.

[5] Tetamy S, Miller JD. Extending the scope of the VATER association: definition of the VATER syndrome. *J Pediatr* 1974;**85**:345-9.

[6] Rittler M, Paz JE, Castilla EE. VACTERL association, epidemiologic definition and delineation. *Am J Med Genet* 1996;**63**:529-36.

[7] Solomon BD. VACTERL/VATER association. *Orphanet J Rare Dis* 2011;**6**:56.

[8] Solomon BD, Baker LA, Bear KA, *et al*. An approach to the identification of anomalies and etiologies in neonates with suspected VACTERL (vertebral defects, anal atresia, tracheo-esophageal fistula with esophageal atresia, cardiac defects, renal and limb anomalies) association. *J Pediatr* 2014;**164**:451-7.

[9] Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap) - a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;**42**:377-81.

[10] Ratan SK, Rattan KN, Pandey RM, *et al*. Associated congenital anomalies in patients with anorectal malformations: a need for developing a uniform practical approach. *J Pediatr Surg* 2004;**39**:1706-11.

[11] Endo M, Hayashi A, Ishihara M, et al. Analysis of 1,992 patients with anorectal malformations over the past two decades in Japan. Steering Committee of Japanese Study Group of Anorectal Anomalies. *J Pediatr Surg* 1999;**34**:435-41.

[12] Rollins MD, Russell K, Schall K, *et al*. Complete VACTERL evaluation is needed in newborns with rectoperineal fistula. *J Pediatr Surg* 2014;**49**:95-8.

[13] Kim HLN, Gow KW, Penner JG, *et al*. Presentation of low anorectal malformations beyond the neonatal period. *Pediatrics* 2000;**105**:e68-70.

Table 1: Number of ARM types in total within the full cohort of patients (n = 243)

Anorectal Malformation Type	**Fully screened (n)**	**Total ARM number (n)**	**Percentage**
Cloaca: < 3cm common channel	2	2	100
Cloaca: > 3cm common channel	2	2	100
Rectal Atresia	12	13	92
Rectovesical / bladder-neck fistula	7	8	88
Rectoprostatic fistula	21	26	81
Rectovaginal fistula	4	5	80
Rectobulbar fistula	6	8	75
Rectovestibular fistula	29	40	73
Cloaca: unknown common channel	2	3	67
Perineal fistula	50	83	60
Cloacal exstrophy	4	7	57
Rectourethral fistula – unknown	1	2	50
Unknown	3	7	43
Other	4	12	33
Anal stenosis	5	25	20