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Fluorescent in situ hybridization (FISH)—a quick screening tool for female children with palpable gonads for excluding androgen insensitivity syndrome

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Abstract

Background: The incidence of inguinal hernia in the pediatric population is 0.8–4.4% with a male to female ratio of 5:1.The reported incidence of sliding hernia containing an ovary in female infants and children is 15–20%.The complete androgen insensitivity syndrome occurs in 1–2% of girls with an inguinal hernia. Thus, the incidence of CAIS in females with hernias and palpable gonads is 4/1,000,000.

Results: This is a retrospective analysis of 694 children that had undergone inguinal hernia repair in last 11 years. Out of these, 123 were females, 36 cases had palpable gonads at the time of presentation. FISH analysis was done in 29 cases (80%). None of the cases showed the presence of the Y chromosome. An abnormal chromosomal pattern was seen in one case on complete karyotyping.

Conclusion: The reported incidence of CAIS in girls with inguinal hernia is low, thus subjecting every girl child with inguinal hernia to undergo karyotyping is distressing for the parents. FISH analysis is an effective screening modality to rule out CAIS in girls with an inguinal hernia. Thus, it is recommended to screen only high-risk cases with palpable gonads at presentation.

Background

The incidence of inguinal hernias in the pediatric population ranges from 0.8 to 4.4%, [1] with a male-to-female ratio of 5:1. Female infants and children undergoing inguinal herniotomy have a reported incidence of sliding hernias containing an ovary in 15–20% of these repairs [2]. The association between complete androgen insensitivity syndrome (CAIS) and inguinal hernia in girls has been appreciated since 1953 when Morris first compiled a series of cases from the literature and coined the term testicular feminization syndrome [3]. Complete androgen insensitivity may occur in 1–2% of girls with inguinal hernias [4]. Thus, the incidence of CAIS in females with inguinal hernias and palpable gonads is 4/1,000,000. Pediatric surgeons often find it difficult to raise the issue of complete androgen insensitivity syndrome preoperatively with the parents because of the major social consequences of this rare diagnosis. In 1997, Viner et al. advocated that all girls with suspected inguinal hernia must undergo karyotype analysis, a recommendation that many surgeons find distressing for the parents [5]. We evaluated the role of fluorescent in-situ hybridization (FISH) analysis as an effective screening test to rule out complete androgen insensitivity syndrome in girls with inguinal hernia. FISH is a molecular cytogenetic technique in which a fluorescent labeled DNA or RNA sequence is used as a probe to identify or quantify the naturally occurring counterpart of the sequence in a biological sample.

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Material and methods

The present study was a single center retrospective study including all the female children operated for inguinal hernia during the period 2009 to 2019. Records of 123 female children operated for unilateral or bilateral inguinal hernia were retrieved from the hospital information system and analyzed. Their demographic profile, age at presentation, age at the time of surgery, clinical profile, laterality, records of investigations including FISH and ultrasound abdomen to rule out CAIS or any other disorder of sexual differentiation, were recorded in a pre-designed performa.

In our practice, before elective hernia repair in cases of female inguinal hernia with palpable gonads we counsel the parents about the rare association of CAIS. We have not chosen karyotyping as the preferred screening modality since it takes about 2–3 weeks to get a complete analysis**.** In our setup, a pelvic ultrasound also does not give a satisfactory and convincing evaluation of internal genitalia in an infant, and is difficult to assess the prolapsed gonad. Another limitation of ultrasound is that it is operator dependent. We have chosen the FISH analysis for Y chromosome as it gives quicker results and gives the all-important information about the presence or absence of the Y-cell line. This test is advised in all such cases if the parents consent for the same, otherwise the parents are counseled for regular follow-up till puberty.

Inclusion criteria

All cases of females, presenting with inguinal hernia from neonatal to 12 years of age which were operated in the last 11 years were included in the present study.

Exclusion criteria

Incomplete information in the records

Results

In total, 694 children had undergone hernia repair during the above stated period, 123 were girls (17.7%) and 571 (82.3%) were boys (1:4.6). Among these 123 girls, 6 (4.9%) were neonates, 38 (30.9%) cases were less than 1 year of age and 79 (64.2%) cases were more than 1 year of age. (Figure 1) 24 cases had bilateral hernia and 99 cases presented with hernia only on one side. Thirty-eight cases had hernia on left side and 61 cases had hernia on right side (1:1.6).

Out of 24 cases of bilateral hernia, in 10 cases a gonad were palpable on one side. In 9 cases, FISH showed XX chromosomal pattern and absence of Y chromosome. In one case, the child had dysmorphic facies hence a complete karyotyping was done, which showed 94% cells XX and 6% cells XO configuration, suggestive of low-grade Turner syndrome mosaicism.

Out of a total 99 cases of unilateral inguinal hernia, a gonad was palpable at the time of presentation in 26 (26.2%) cases. Of these 26 cases, FISH test was done in 19 cases (73%). FISH analysis showed absence of Y chromosome in all these cases. Thus out of total 123 cases of inguinal hernia in girls 36 (29.2%) cases had palpable gonads at the time of presentation. FISH analysis was done in 29 cases (80%) (Table 1). None of the cases showed presence of Y chromosome.

Discussion

This retrospective analysis confirms the data reported in the literature, with inguinal hernia being more common in males, our ratio being 4.6 males:1 female. Hernias are more common on the right side. Twenty-nine % of the girls presented with palpable gonads at the time of presentation. The reported prevalence of complete androgen insensitivity syndrome is between 2 and

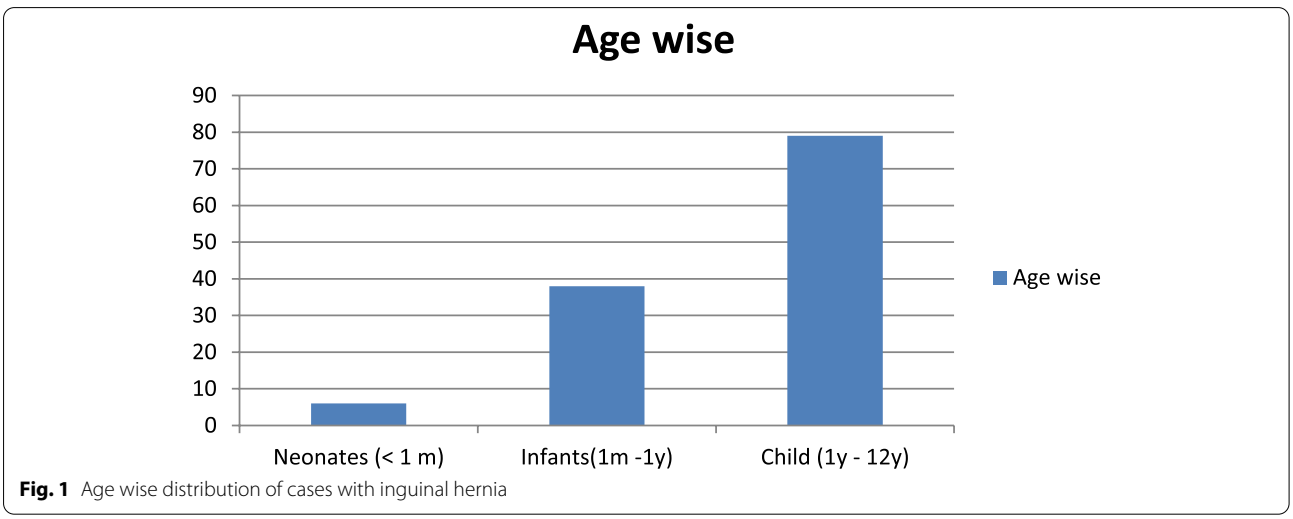

Fig. 1 Age wise distribution of cases with inguinal hernia

Table 1 Distribution of cases based on laterality and their results

Laterality	No. of cases	Gonads palpable	FISH done	CAIS detected
Unilateral	99	26 (26.2%)	19 (73%)	None
Bilateral	24	10 (41.6%)	10 (100%)	None, 1 case of Turner syndrome
Total	123	36 (29.2%)	29 (80%)	Nil

5 per 100,000 live births [6]. About 70–80% of cases of complete androgen insensitivity syndrome present with unilateral or bilateral inguinal hernia in childhood [7]. Complete androgen insensitivity syndrome may present in adolescence with primary amenorrhea during puberty with normal breast development and pubertal growth spurts at the appropriate age.

In our series, we did a FISH test in almost all cases of female hernias with palpable gonads; there was no case in which Y chromosome was detected. This is comparable to previous studies [8], though in that study all females with inguinal hernia were screened using buccal mucosa smear to look for Y chromosome pattern. In another study, Timo et al. [9] found one case of CAIS out of the 109 cases screened. In another study [5], three cases of CAIS were seen out of 270 cases screened. They measured the vaginal length in all females as a screening tool and confirmed the diagnosis using karyotyping**.** Despite being an inexpensive and innocuous screening test, it has got low sensitivity. Considering the low incidence of disorders of sexual differentiation subjecting every case of female inguinal hernia to chromosomal analysis may not appear to be justifiable as it may increase undue anxiety amongst the parents. On the other hand, failure to exclude complete androgen insensitivity syndrome will result in these children presenting in puberty with primary amenorrhea with its associated anatomical and psychological complications. It could be argued that these psychological effects might have been reduced by the knowledge earlier in their childhood that they would occur. In addition, vaginal reconstruction could have been planned before the onset of sexual activity. Many surgeons screen for CAIS by rectal examination or pelvic ultrasound but neither of these is conclusive to exclude this disorder [10].

Thus, genetic analysis is the only way in which we can effectively screen this disorder in girls with inguinal hernia. The fluorescent in situ hybridization technique is a quicker and efficient alternative when compared to karyotyping. It takes about 4 days to get the FISH result whereas it takes around 2–3 weeks for complete karyotyping. Thus, all girls with an inguinal hernia with palpable gonads should undergo a FISH analysis prior to elective hernia repair. It is not justifiable to lose an opportunity to diagnose this disorder which has got long-term consequences. Most of the earlier studies screened all the girls that presented with inguinal hernia, we limited our screening to only those girls that presented with palpable gonads.

Limitations of the study

The incidence of CAIS in females with hernias and palpable gonads is 4 in 1,000,000 cases. Hence, we need to screen a large number of cases to eventually test the sensitivity of FISH at detecting CAIS in females with hernias and palpable gonads. More studies in direction are required to establish this. Another limitation of this study is that FISH is an expensive test and has limited availability.

Conclusion

The reported incidence of CAIS in girls with inguinal hernia is low, thus subjecting every girl child with inguinal hernia to undergo karyotyping is distressing for the parents. FISH analysis is an effective screening modality to rule out CAIS in girls with an inguinal hernia. Thus, it is recommended to screen only high risk cases with palpable gonads at presentation.

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Authors' contributions

MA has made substantial contribution to the conception and design of work and drafted the work. NZ reviewed the work and final draft was approved by AK. The manuscript has been read and approved by all the authors and each author believes that the manuscript represents honest work.

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Availability of data and materials

Data sharing is not applicable to this article as no data sets were generated or analyzed.

Declarations

Ethics approval and consent to participate

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parent has given his consent for his images and other clinical information to be reported in the journal. The patient's parent understands that his names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed. This manuscript has got ethical approval by the hospital committee.

Consent for publication

Written informed consent was obtained from the patient for publication of this case and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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