

Efficacy of Fine Needle Aspiration Cytology in the Diagnosis of Thyroid Lesions in Children and Adolescents

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ABSTRACT

Introduction: Thyroid disorders are one of the most common endocrine disorders worldwide. Though prevalence of thyroid disease in children and adolescents is low, the incidence of malignancy is more in this subgroup, as compared to adults.

Objective: To evaluate the efficacy of fine needle aspiration cytology (FNAC) in the diagnosis of thyroid lesions in children and adolescents.

Material and Methods: A prospective descriptive analytical study conducted over a duration of three years from January 2010 to December 2012. FNAC was performed on 58 children and adolescents in the age group ranging from 1-year-old to 21-year-old. Ultrasound (US) findings were available in 36 (62.06%) cases. Histopathology subsequent to surgery was obtained in 14 (24.13%) cases.

Statistical Analysis: The qualitative data were expressed as proportions, percentages and 95% CI. Quantitative data

was expressed as mean \pm SD. Data was analysed using SPSS software version 16 and STAT CAL of Epi info.

Results: Five cytological categories and the respective proportion of cases in each category were the following: 1. Benign – 48 (95% CI 38.13, 57.86), 2. Indeterminate – (95% CI – 0.11, 6.11), 3. Suspicious – 1 (95% CI – 1.61, 3.6), 4. Malignant – 6 (95% CI – 0.22, 12.02) and 5. Inadequate – 3 (95% CI – 0.11, 6.11). Statistical analysis was done by SPSS version 16 software. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were found to be 100%, 70%, 57.14%, 100% and 100% respectively.

Conclusion: Sensitivity, specificity and accuracy of FNAC in children and adolescents is similar to that in adults. Because it helps reduce the number of diagnostic surgeries, implementing FNAC as a initial diagnostic tool can go a long way in clinical decision making in this sub group of patients with thyroid disease.

Key Words: Children, Adolescents, Thyroid, Fine needle aspiration cytology

INTRODUCTION

Thyroid disorders are one of the **most common** endocrine disorders found worldwide. According to a recent update of thyroid disorders in India, the incidence is 42 millions [1]. Prevalence of thyroid nodules in children is less as compared to adults, ranging from 0.05% to 1.8%, as quoted in various studies [2]. This prevalence increases to 13% in teenagers [3]. However the malignancy rate is more in children, with some studies quoting a prevalence ranging from 9.2 to 50% [4-8]. In addition, the clinical presentation and biologic behavior of thyroid malignancies diverge from their adult counterpart with respect to large tumor size and high probability of lymph node metastasis [9]. Albeit this fact, benign disease make up the bulk of thyroid disorders, majority of whom respond to medical line of management with follow up in chosen few cases. Hence it is of the essence to know the accurate diagnosis before deciding on the binary mode of medical versus surgical management.

Since the introduction of FNAC in 1960, in Scandinavia, it has been effectively used for evaluation of palpable lesions. The advent US and US guided FNAC have paved way for diagnosis of deep seated lesions with increased precision. Among all these, the role of FNAC in diagnosis of thyroid lesions cannot be overemphasized, due to the ease of accessibility of thyroid gland, amenability to medical line of management and the fact that biopsy is not practiced in this region. Many studies have published a high accuracy rate of FNAC in thyroid lesions in adults, [10-12] its reliability in children and adolescents has not been studied extensively. The available data is sparse and depicts conflicting results [13-17].

MATERIAL AND METHODS

This was a prospective study over a duration of 3 years from January 2010 upto December 2012. The study population included 58 children and adolescents (Age=Equal to or below 21 years). The demography including age, sex and clinical characteristics were recorded. After obtaining the informed

consent from the guardian in cases below 18 years and from the patients above 18 years, FNAC was done by non-aspiration technique using a 24 gauge needle and 10 ml syringe. No sedation was used, except in one case in which the child was 1-year-old and hence local spray sedative was used and found to be effective. Three to four passes were made. In case of more than one nodule, FNAC was done from the largest nodule. If fluid was aspirated, the entire fluid was removed and FNAC done from the residual swelling. Sediment smears were performed on the aspirated fluid. Half of the slides were fixed in 90% ethanol for hematoxylin and eosin (H & E) and Papanicolaou stain. Remaining half were air dried for May Grunwald Giemsa stain. The FNAC procedure as well as reporting was done by a single cytopathologist. All the cases were categorised into one of the five groups:

1. Benign - The cases which included colloid goiter, colloid goiter with cystic change, colloid cyst, adenomatous goiter, thyroglossal cyst, lymphocytic thyroiditis, Hashimoto's thyroiditis, granulomatous thyroiditis and acute suppurative thyroiditis.
2. Indeterminate - The cases which included follicular and hurthle cell neoplasm.
3. Suspicious for malignancy - Those cases which showed high cellularity with increased micro follicles, nuclear features like nucleomegaly, nuclear grooving and scanty colloid.
4. Malignant - The cases which included papillary carcinoma, medullary carcinoma and anaplastic carcinoma.
5. Inadequate - The cases in which the smears showed < six follicular cell clusters spread on two separate smears.

Surgery was done in 14 cases (24.13%). The specimens received were formalin fixed, paraffin embedded and stained with H& E staining technique. Ultrasound was available in 36 cases. The nodule characteristics like echogenecity, echo texture, margin regularities, vascularity, were recorded.

No complications other than mild pain was recorded during the entire study.

STATISTICAL ANALYSIS

All qualitative data was expressed as proportions, percentages and 95% CI. Quantitative data was expressed as mean \pm SD. Data was analyzed using SPSS software version 16 and STAT CAL of Epi info.

RESULTS

A total of 58 children and adolescents ranging from one and 21 years of age group underwent FNAC.

Demography: The mean age \pm SD of the study population was 17.41 \pm 4.07. The youngest child was one year of age who was diagnosed to have thyroglossal cyst. The distribution

of thyroid lesions in prepubertal, pubertal and adolescents was 9%, 26% and 65% respectively [Table/Fig-1]. There was no significant difference among different age groups and prevalence of thyroid diseases. (Chi-square test for trend, p value > 0.05) Females were more commonly affected as compared to males, with a female to male ratio of 5.4:1.

Cytology: Cytologically the total 58 cases were divided into different diagnostic categories [Table/Fig-2].

Benign lesions: The proportion of benign lesions were 48 (95% CI 38.13, 57.86) The most common benign lesion was colloid goiter (56.89%), followed by thyroiditis (20.68%), and thyroglossal cyst (5.17%). Lymphocytic thyroiditis was the most common of inflammatory process accounting for 8(13.79%) of total 12 thyroiditis (20.68%) cases, followed by 2 cases (3.44%) of Hashimoto's thyroiditis and 1 case (1.72%) each of granulomatous thyroiditis and acute suppurative thyroiditis. There was one case of granulomatous thyroiditis in a 17-year-old male child. AFB stain was negative and the disease was self limiting with patient recovering one week after steroid treatment. There was one case of acute suppurative thyroiditis in a 7-year-old female child which responded to antibiotic treatment.

Indeterminate category: Out of total 58 cases, three (95% CI – 0.11,6.11) were diagnosed as follicular neoplasm and belonged to the indeterminate category.

Suspicious category: There was only one case (95% CI – 1.61, 3.6) diagnosed in this category.

Malignant category: This included three- (95% CI – 0.11,6.11), i.e., papillary carcinoma two cases (3.44%) and medullary carcinoma one case (1.72%).

Thyroid lesions at cytology	Prepubertal (1 to 10 years)		Pubertal (11 to 17 years)		Adolescents (18 to 21 Years)	
	Females (3)	Males (2)	Females (10)	Males (5)	Females (36)	Males (2)
Benign	3	2	7	5	29	2
Malignant	-	-	3	-	3	-
Suspicious	-	-	-	-	3	-
Inadequate	-	-	-	-	1	-
Total	5 (9%)		15 (26%)		38 (65%)	

[Table/Fig-1]: Depicts distribution thyroid lesions in prepubertal, pubertal

Cyodiagnostic category	No. of cases (%)
Benign	48 (83%)
Indeterminate	3(5%)
Suspicious	1(2%)
Malignant	3 (5%)
Inadequate	3 (5%)
Total	58(100%)

[Table/Fig-2]: Cytologic diagnostic categories in 58 cases

Histopathology	Cytology		
	No. of cases	Consistent	Non consistent
Benign Goiter Thyroglossal duct cyst	7 (50%) 6 1	7	0
Indeterminate Follicular neoplasm	3	1	2
Malignant Papillary carcinoma Medullary carcinoma	6 (42.85%) 2 1	2 1	0 0
Suspicious	1 (7.14%)	0	1
Total	14 (100%)	11	3

[Table/Fig-3]: Cytodiagnostic categories in function of histopathology

Inadequate: There were three cases (95% CI – 0.11,6.11) in which material was inadequate for reporting. A repeat of FNAC in two cases revealed colloid goiter with cystic change and Hashimoto's thyroiditis in one case.

Histopathology was available in 14 cases who underwent surgery [Table/Fig-3].

Ultrasound findings: Out of 36 cases in which ultrasound findings were available, 31 cases were categorised as benign and 5 as malignant. At cytology, out of 31 cases deemed as benign on USG, 30 cases turned out to be benign and 1 as malignant. Out of 5 cases deemed as malignant at FNAC, 1 case proved to be benign and rest 4 as malignant.

Suspicious category was considered as malignant for statistical calculations. Cases diagnosed as suspicious or malignant on cytology which subsequently turned out to be malignant on histopathology were considered to be "true positives". Cases deemed as benign on both cytology and histopathology composed "true negatives". Cases with malignant cytology and benign histopathology (include follicular adenoma), comprised "false positives". Cases with benign cytology but malignant histopathology encompassed "false negatives". Considering this we had three false positive cases. In all the three cases the follicular patterned lesion was the cause of misinterpretation. There was no false negative case. Considering these criterias sensitivity, specificity and accuracy were 100%, 70%, and 100% respectively. Positive predictive value and negative predictive value were 57.14% and 100% respectively.

DISCUSSION

Thyroid disorders are one of the commonest endocrine disorder. The prevalence of thyroid nodules in adults range from 4% to as high as 67% including those detected by autopsy, ultrasonography and high risk groups like women and elderly individuals [18]. The rate of malignancy is low accounting for about 5% [19]. In children

and adolescents the prevalence of thyroid nodules is less, the quoted rate being 0.05 to 1.8% [2]. The proportion of this group at risk of malignancy has been found to be 9.2% to 50% [4-8]. This group needs to be identified because they need surgery, others requiring surgery may be those with disfiguring goiters or obstructive symptoms. Many of the benign thyroid diseases with classical clinical and hormonal setting are easy to diagnose and FNAC serves to only confirm the diagnoses. However many a times the clinical and hormonal profile do not match. In a resource poor set up of rural India, the hormonal profile and antibody titers are not available or unaffordable. The diagnosis in such places rest on simple, easy and cost effective test.

Over time, FNAC has been proved to be simple and cost effective technique in the diagnosis of thyroid lesions in adult population, with a high sensitivity and specificity reaching up to 89% and 100% respectively [20]. American Thyroid Association and National Comprehensive Cancer Network has proposed the use of FNAC in initial diagnostic work up over scintigraphy and ultrasonography due to its high accuracy and cost effectiveness [21]. However the role of FNAC in thyroid lesions in children and adolescents is controversial with a wide range of sensitivity and specificity.

Willgerodt et al., in a study of 169 children and adolescents with thyroid nodules, performed 188 FNAC with a high inadequacy rate of 13.8%. Out of 13 malignant tumors diagnosed at histopathology, at FNAC two were inadequate and four were misinterpreted as benign. The overall accuracy of 77.2% in their study, inferior to that reported in the literature for adults, prompted the authors to suggest a more aggressive diagnostic approach in children and adolescents [13]. Degnan et al., reported the results of FNAC in children studied over a duration of 10 years. The three false negative cases and sensitivity of 60% was insufficient for the authors to advocate the use of FNAC as a sole predictor of malignancy. The authors noted that overall accuracy of FNAC was similar to that of scintigraphy and US [14]. In contrast to this data, Kaur et al in a study of 77 cases published an overall diagnostic accuracy of 98.6%, sensitivity, specificity, positive predictive value and negative predictive value of 100%, 98.6%, 80% and 100% respectively. There was only one false positive case which turned out to be Hashimoto's thyroiditis at histology which is an inherent pitfall of missing the target at FNAC [15]. Amrikachi et al., in a study on 218 children and adolescent patients reported a high sensitivity of 100% [16]. Al sheikh et al., too obtained a good accuracy of 87% in a study involving 47 cases. The reported rate of inadequacy ranges from 5.9% to 28% [17]. The high diagnostic accuracy of FNAC helps surgeon in selecting patients for surgery, as a result there have been reduction in the number of thyroid surgeries by 25% to 50% [22]. Corrias et al., compared US, scintigraphy and FNAC in

evaluation of thyroid nodules in childhood. They reported the sensitivity, specificity and accuracy of FNAC to be 95%, 86.3% and 90.4% respectively, which was significantly higher than other two diagnostic modalities. They ascertained that FNAC alone contributes significantly for detection of malignancy in childhood [23]. In our study we report a high sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 100%, 70%, 57.14%, 100% and 100% respectively. The inadequacy rate in our study is low i.e., 5.17%.

Patient's age has no impact on the nature of thyroid lesions as to benign or malignant [24]. However the prevalence of thyroid nodules increases with puberty which is explained by the hormonal changes that occur. In our study also there was a significant increase in the prevalence of thyroid nodules at adolescence. This has been linked to the expression of estrogen receptor and IGF-1 level [25]. Sensitivity of thyroid glands to estrogen further explains the higher proportion of female patients in our study, which is in accordance with previous studies [26]. Several studies have been conducted to justify the role of pre-operative US and scintigraphy in diagnosis of thyroid lesions in adults with conflicting results [27]. Similar studies in children and adolescents are very few in number making their finding unsuitable for choosing treatments for individual patients. Nini et al., in a study of 45 children with thyroid nodules, reviewed USG findings in 31 patients. They noticed that out of 12 nodules which had increased vascularity, the final diagnosis by cytology and histopathology was both benign (9) and malignant (3). Neither US nor radionuclide scan had any role in risk stratification. They further stated that patient age or even nodule size had no bearing in predicting the nature of thyroid nodules [24]. Corris et al., reported that there was no significant difference with respect to the nodule number, size, growth progression or echogenic pattern in benign and malignant groups, emphasizing the need for tissue diagnosis by FNAC or histopathology post-surgically. [23]. In lesions < 1.5 cm, the most reliable diagnostic criteria for cancer in children and adolescents include irregular outline, sub capsular location and increased vascularity [28]. However in lesions >1.5 cm the accuracy of US remains low with hypoechogenicity remaining the only predictor of malignancy. In our study, however hypoechogenicity and increased vascularity was more frequently associated with malignant diagnosis at cytology. In view of limited number of histopathology confirmation in cases with ultrasound findings, the validity of these results in our study remains questionable.

Some characteristics of thyroid malignancies are different in pediatric population and include large tumor volume at initial diagnosis, multicentricity and high probability of cervical lymph node and distant metastasis [9]. The latter characteristic has shown a change in trend due to improvement in the diagnostic modalities. In a recent study comparing groups of thyroid cancer patients, one in 1936 to 1970 and other in 1971 to

1990 showed that those in the later years presented with lower incidence of cervical lymph node metastasis, local invasion and lung metastasis. All these have been attributed to the early diagnosis and hence better survival outcome in the pediatric population [29]. Moreover despite the high recurrence rate in pediatric group as compared to adults, the survival is better, being 99.3% in 5 years and 98.5% in 10 years [30]. Hence proactively diagnosing this malignant subgroup is extremely important and indispensable. In our study none of the cases in malignant group had local or distant metastasis.

The disappointing specificity and positive predictive value in our study may be explained by the inherent limitation of FNAC in the area of follicular patterned lesions. This group encompasses hyperplastic goiter, follicular adenoma, follicular carcinoma and follicular variant of papillary carcinoma. Yang et al., put forth that most definitive finding suggesting a follicular neoplasm include repetitive micro follicle in a bloody background [31]. However macro follicular adenoma or a mixed micro and macro follicular adenoma may be misinterpreted as adenomatous goiter. Similarly a dominant nodule of an adenomatous goiter if aspirated may be over diagnosed as follicular neoplasm. Nevertheless, in such gray zone areas, judicious use of immunocytochemical markers may provide greater precision, though the area needs to be further explored. Though initially thought to be a promising marker in FNAC, Galactin-3 has reduced practical utility in malignancy due to false positivity encountered in non neoplastic lesions [27]. Lately tandem expression of galectin -3 and HBME-1 has been shown to have high sensitivity for detection of thyroid cancers especially follicular lesions at FNAC [32]. Advent of molecular diagnostics has heralded an outburst of new markers, still a desperate quest for a precise marker for thyroid carcinoma at aspirate smears persists and needs further studies.

There are no major reported limitations of FNAC in children and adolescents. In some thyroids with increased vascularity, the hemorrhage may hinder with other investigations that need to be performed on the same day. Mild pain can be balanced by analgesic cream [27].

CONCLUSION

Sensitivity, specificity and accuracy of FNAC in children and adolescents is similar to that in adults. Implementation of FNAC as an initial diagnostic tool can go a long way in clinical decision making in this sub group of patients with thyroid disease as it helps in reducing the number of diagnostic surgeries.

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