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KEY WORDS: ADRENOCORTICAL TUMOURS , ENDOCRINE DYSFUNCTION, VIRILIZATION

AN ANALYTICAL STUDY OF ADRENOCORTICAL TUMOURS IN CHILDREN

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ABSTRACT

AIM – TO REVIEW AND ANALYSE A SERIES OF 10 CASES OF ADRENOCORTICAL TUMOURS IN A SINGLE CENTRE

METHODS – RECORDS OF CHILDREN TREATED FOR ADRENOCORTICAL TUMOURS IN OUR INSTITUTE BETWEEN 2012 TO 2017 WERE REVIEWED. INFORMATION RECORDED FOR EACH PATIENT INCLUDED AGE, SEX, CLINICAL CHARECTERISTICS , DIAGNOSTIC METHODS,STAGE OF DISEASE, TREATMENT, PATHOLOGIC FINDINGS AND OUTCOME

RESULTS – OFF THE 10 CHILDREN TREATED FOR ADRENOCORTICAL TUMOURS IN THE STUDY PERIOD, 6 HAD LEFT SIDED TUMOURS WHILE 4 HAD RIGHT SIDED TUMOUR .ENDOCRINE DYSFUNCTION WAS NOTED IN ALL CASES OF ADRENOCORTICAL TUMOURS, WITH VIRILIZATION BEING THE MOST COMMON PRESENTATION. TOTAL SURGICAL EXCISION WAS DONE IN ALL CASES.

CONCLUSION – THE MOST IMPORTANT ASPECT OF THERAPY FOR ADRENOCORTICAL TUMOURS IS EARLY DIAGNOSIS AND SURGICAL EXCISION. THERE ARE NO RELIABLE MARKERS TO DETERMINE THE POSSIBILITY OF MALIGNANCY

INTRODUCTION

ADRENOCORTICAL NEOPLASMS ARE RARE IN CHILDREN AND ADOLESCENTS .IT ACCOUNTS FOR LESS THAN 0.2% OF ALL PAEDIATRIC NEOPLASM AND 1.3% OF ALL CARCINOMAS IN CHILDREN LESS THAN 20YEARS OF AGE (1,2).SOLITARY TUMOURS ARE USUALLY UNILATERAL ADENOMAS OR RARELY CARCINOMAS

AIM

TO PRESENT A CLEAR PICTURE OF THE ENTIRE SPECTRUM OF PAEDIATRIC ADRENOCORTICAL TUMOURS BY REVIEWING A SERIES OF 10 CASES OF **ADRENOCORTICAL TUMOURS** IN A SINGLE CENTRE

MATERIALS AND METHODS

THIS IS A RETROSPECTIVE STUDY CONDUCTED AT THE INSTITUTE OF CHILD HEALTH WHERE IN 10 CASES OF ADRENOCORTICAL TUMOURS BETWEEN 2012 TO 2017 WERE REVIEWED AND DETAILS WERE COLLECTED REGARDING THE PATIENT 'S CLINICAL DETAILS ,BIOCHEMICAL AND RADIOLOGICAL INVESTIGATIONS ,OPERATIVE DETAILS AND POST OP FOLLOW UP.

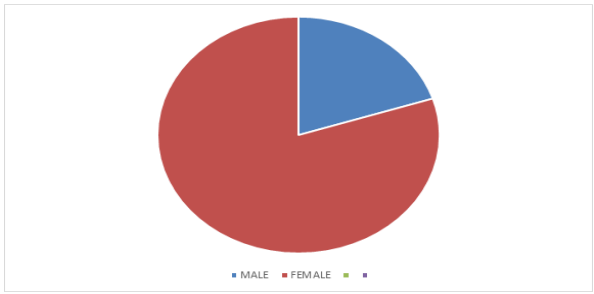
RESULTS

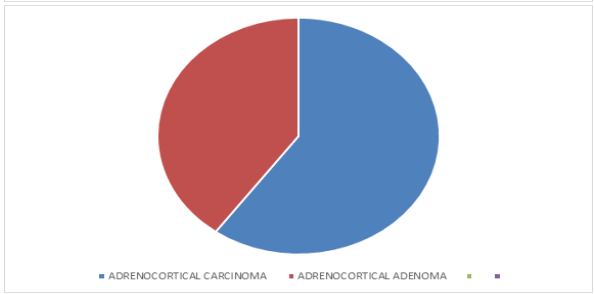
CLINICAL DATA OF THE 10 CHILDREN HAS BEEN SUMMARISED IN TABLE 1.1

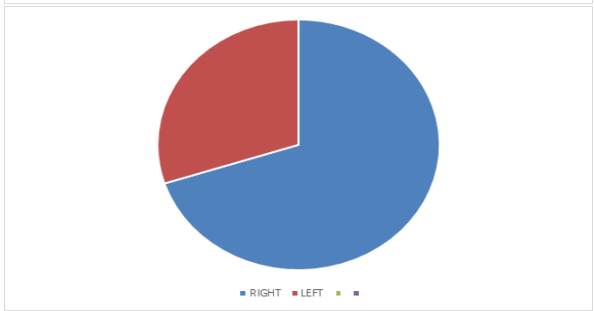
TABLE 1.1

	CASE 1	2	3	4	5	6	7	8	9	10
age	2yrs	4yrs	3yrs	2yrs	6yrs	8yrs	5yrs	3yrs	2yrs	2yrs
sex	M	F	F	F	F	M	F	F	F	F
clinical features	V + CS	V+CS+HTN	V+CS	V	V+CS	V	V+CS+HTN	V+CS	V+CS	V
duration of symtoms	2 months	4 months	4 months	3 months	6months	6 months	5 months	1 yr	7 months	9 months
Sr testosteron e	increased	increased	increased	increased	increased	increased	increased	increased	increased	increased
DHEA	increased	increased	increased	increased	increased	increased	increased	increased	increased	increased
Sr cotisol	increased	increased	increased	Normal	increased	Normal	increased	increased	increased	Normal
usg abdomen	4x 3	3.5 x 2	4 x 4	4.6 x 3.5	3 x3	8 x 6	3 x 2	4.5 x 4	4x 3	5 x 4.5
side	R	L	R	R	L	R	R	R	R	B/L (L followed by R)
liver mets	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil
lung mets	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil
IVC involvemen t	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil
surgery	excision	excision	excision	excision	excision	excision	excision	excision	excision	excision
post op chemo	no	no	no	No	no	no	no	no	no	yes
FOLLOW UP	3yrs	5yrs	3yrs	2yrs	2yrs	2yrs	1yr	4yrs	6 months	2yrs
recurrence	nil	nil	nil	nil	nil	nil	nil	nil	nil	yes

OF THE 10 CHILDREN IN THE SERIES WITH ADRENOCORTICAL TUMOURS 8 WERE FEMALE AND 2 WERE MALE CHILDREN (CHART 1.1) .MEDIAN AGE AT THE TIME OF PRESENTATION WAS 3.7 YEARS .6 OF THEM HAD ADRENOCORICAL CARCINOMA WHILE 4 HAD ADRENOCORTICAL ADENOMA (CHART 1.2) .RIGHT SIDED TUMOUR WAS NOTED IN 7 CASES WHILE IT WAS LEFT SIDED IN 3 CASES (CHART 1.3). CLINICAL EVIDENCE OF HORMONAL DYSFUNCTION WAS NOTED IN ALL CASES WITH VIRILIZATION BEING THE MOST COMMON . CUSHING SYNDROME WAS ALSO NOTED .HYPERTENSION WAS NOTED IN 2 CASES (CHART 1.4). HORMONAL ANALYSIS REVEALED ELEVATED TESTOSTERONE ,CORTISOL AND DHEA LEVELS IN ALL CASES.CECT ABDOMEN WAS DONE TO IDENTIFY RESECTABILITY AND NONE OF THE CASES WERE DEEMED INOPERABLE . ALL OF THEM UNDERWENT ADRENALECTOMY (FIG 1.1 & 1.2) AND WERE PLACED ON STEROID REPLACEMENT POST OPERATIVELY. DURATION OF STEROID THERAPY WAS DETERMINED ACCORDING TO THE SUGGESTIONS FROM A PAEDIATRIC ENDOCRINOLOGIST. LONGEST FOLLOW PERIOD IS 4 YEARS . MEAN FOLLOW UP PERIOD WAS 2.45 YEARS . FOLLOWUP SHOWED A RECURRENCE IN ONE CHILD WHILE ANOTHER CHILD HAD A METACHRONOUS TUMOUR IN THE OPPOSITE ADRENAL GLAND.NO MORTALITY WAS NOTED .POST CHEMOTHERAPY WAS INITIATED ONLY IN ONE CASE IN VIEW OF RECURRENCE







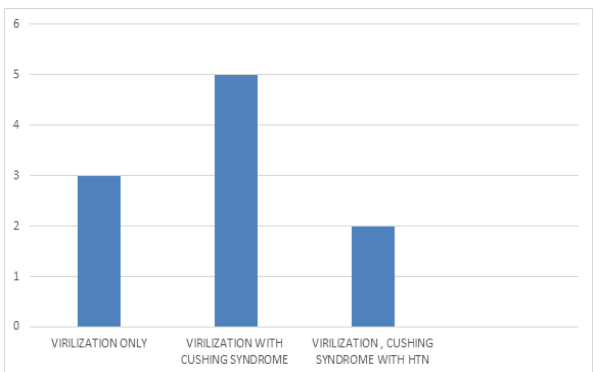
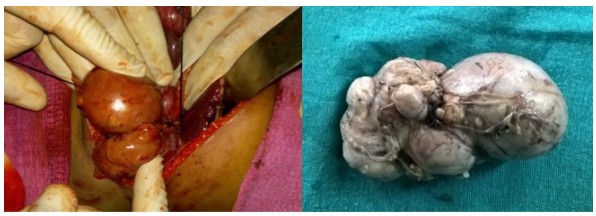


FIG 1 .1 & 1.2



DISCUSSION

ADRENOCORTICAL TUMOURS ARE RARE IN CHILDREN WITH THE FIRST CASE BEING REPORTED IN 1865 (1).APPROXIMATELY 10,000 NEW CASES ARE DIAGNOSED EVERY YEAR IN THE USA IN PATIENTS YOUNGER THAN 20 YEARS) .ANNUAL WORLDWIDE INCIDENCE OF CHILDHOOD ADRENOCORTICAL TUMOUR RANGES FROM 0.3 TO 0.38 PER MILLION CHILDREN BELOW 15 YEARS OF AGE.INCIDENCE OF MOST CHILDHOOD CARCINOMAS INCREASES WITH AGE WHEREAS 65% OF ACT OCCUR IN CHILDREN LESS THAN 5 YEARS OF AGE (3) IT IS BIMODAL IN ITS OCCURRENCE WITH INCIDENCE BEING MORE COMMON IN FEMALES IN CHILDHOOD.HOWEVER AS AGE INCREASES THE INCIDENCE BECOMES MORE OR LESS EQUAL IN MALE AND FEMALE ESPECIALLY DURING ADOLESENCE(4) . CARCINOMAS ARE VERY UNCOMMON AND ACCOUNT FOR ONLY 2 – 12% OF ALL CANCERS IN THIS AGE GROUP (3)

PREDISPOSING GENETIC FACTORS HAVE BEEN NOTED IN APPROXIMATELY 50% OF CHILDREN WITH ADRENOCORTICALTUMOURS .TWO MOST COMMONLY ASSOCIATED GENETIC SYNDROMES ARE LI FRAUMENI SYNDROME AND BECKWITH-WEIDEMANN SYNDROME (3)

MANN ET AL REPORTED A CHILD WITH ADRENICORTICAL TUMOUR ,WHOSE MOTHER HAD INGESTED HYDROXYPROGESTERONE HEXANOATEDURING PREGNANCY TO PREVENT MISCARRIAGE (4).

HORMONE SECRETING TUMOURS AND THE ASSOCIATED ENDOCRINE SYNDROMES REPRENT THE MOST COMMON PRESENTATION .THESE USUALLY PRESENT WITH SIGNS AND SYNPTOMS OF MULTIPLE SYNDROMES.NON FUNCTIONING TUMOURS CONSTITUTE ONLY 10 % OF PAEDIATRIC CASES (4) .

VIRILIZATION WAS THE MOST COMMON PRESENTATION IN THE PAEDIATRIC AGE GROUP AND IS SEEN IN NEARLY 80% OF CASES OF ADRENOCORTICAL TUMOURS. THE COMMON VIRILIZATION FEATURES INCLUDE DEEPENING OF THE VOICE, ACNE, HIRSUTISM, INCREASE OF MUSCLE MASS AND SECRETION AND PROLIFERATION OF THE SEBACEOUS GLANDS WITH CHARACTERISTIC ADULT ODOUR. IN ADDITION TO THESE FEATURES GENDER SPECIFIC CHANGES WERE NOTED. IN FEMALES,

CLITORAL ENLARGEMENT, FACIAL AND PUBIC HAIR , AMENORRHEA AND RARELY TEMPORAL BALDING WERE THE MOST COMMON. SPECIFIC SIGNS IN MALES INCLUDE PENILE ENLARGEMENT AND PRECOCIOUS ISOSEXUAL PSEUDOPUBERTY (4) .

CUSHING.S SYNDROME IS SEEN IN APPROXIMATELY ONE THIRD OF THE PATIENTS WITH ONLY 8% HAVING ISOLATED HYPERCORTISOLISM. ALDOSTERONE-PRODUCING ADENOMA IS EXTREMELY RARE IN CHILDREN (4). FEMINIZATION IS ANOTHER RARE FORM OF PRESENTATION AND ACCOUNTS FOR 2.2% OF THE CASES (4).

BILATERAL TUMORS WERE OBSERVED IN 1.3% (4) AND WERE RARELY ECTOPIC. ECTOPIC ADRENOCORTICAL TUMOURS HAVE BEEN DESCRIBED IN THE SPINAL CANAL (43) AND THORACIC CAVITY (5).

HISTOLOGICAL ANALYSIS OF ADRENOCORTICAL TUMOUR IS TROUBLESOME. EVEN AN EXPERIENCED PATHOLOGIST CAN FIND IT DIFFICULT TO DIFFERENTIATE CARCINOMA FROM ADENOMA.

WEISS ET AL. (4) AND HOUGH ET AL. FORMULATED CLASSIFICATION SYSTEMS BASED ON MACROSCOPIC, MICROSCOPIC AND CLINICAL FEATURES PRESENT AT DIAGNOSIS.

BUGG ET AL. (4) APPLIED A MODIFIED CRITERION OF WEISS AND COLLEAGUES TO ANALYZE A LARGE SERIES OF PEDIATRIC ADRENOCORTICAL TUMOURS

ROUTINE LABORATORY EVALUATION FOR PATIENTS SUSPECTED OF HAVING ADRENOCORTICAL TUMOUR INCLUDES MEASUREMENT OF URINARY 17-KS, 17-OH, AND FREE CORTISOL, AS WELL AS PLASMA CORTISOL, DHEAS, TESTOSTERONE, ANDROSTENEDIONE, 17-HYDROXYPROGESTERONE, ALDOSTERONE, RENIN ACTIVITY, DOC AND OTHER 17-DEOXYSTEROID PRECURSORS (4).

THIS PANEL OF TESTS NOT ONLY HELPS IN THE DIAGNOSIS, BUT ARE ALSO USEFUL MARKERS FOR THE DETECTION OF RECURRENCE

COMPUTED TOMOGRAPHY (CT) SCAN, SONOGRAM AND MAGNETIC RESONANCE IMAGING (MRI) ARE THE IMAGING MODALITIES USED COMMONLY TO ASSESS THESE TUMOURS (6)

ALTHOUGH ULTRASOUND EXAMINATION HAS ITS LIMITATIONS, IT IS AN IMPORTANT MODALITY FOR EVALUATING TUMOR EXTENSION INTO THE INFERIOR VENA CAVA AND RIGHT ATRIUM (6)

MRI HAS SEVERAL ADVANTAGES OVER CT, INCLUDING LACK OF IONIZING RADIATION, CAPABILITY OF IMAGING MULTIPLE PLANES AND IMPROVED TISSUE CONTRAST DIFFERENTIATION. MOREOVER, RECENT STUDIES HAVE INDICATED THAT MRI MAY HELP DIFFERENTIATE BETWEEN BENIGN AND MALIGNANT LESIONS.(6)

SURGERY

SURGERY IS THE SINGLE MOST IMPORTANT PROCEDURE IN THE SUCCESSFUL TREATMENT OF ADRENOCORTICAL TUMOURS (7).

BECAUSE TUMOR FRIABILITY, RUPTURE OF THE CAPSULE AND TUMOR SPILLAGE ARE FREQUENT (OCCURRING IN APPROXIMATELY 20% OF CASES DURING THE INITIAL PROCEDURE AND IN 43% AFTER LOCAL RECURRENCE) (7) SURGERY REQUIRES CAREFUL AND PRECISE PERIOPERATIVE PLANNING. ALL PATIENTS WITH A FUNCTIONING TUMOR ARE ASSUMED TO HAVE SUPPRESSION OF THE CONTRALATERAL ADRENAL GLAND, SO STEROID REPLACEMENT THERAPY IS ESSENTIAL. SPECIAL ATTENTION TO ELECTROLYTE BALANCE, HYPERTENSION, SURGICAL WOUND CARE AND INFECTIOUS COMPLICATIONS IS IMPERATIVE (7).

CHEMOTHERAPY

THE ROLE OF CHEMOTHERAPY IN THE MANAGEMENT OF CHILDHOOD ACT HAS NOT BEEN ESTABLISHED. MITOTANE IS A DRUG WHICH HAS SHOWN PROMISE BUT SINCE 1990, A MULTI-INSTITUTIONAL STUDY TO DETERMINE THE EFFICACY AND TOXICITY OF MITOTANE AS AN ADJUVANT THERAPY FOR NEWLY DIAGNOSED CHILDREN AT HIGH RISK OF RELAPSE . AS PER REPORTS MITOTANE HAS NOT MODIFIED THE RATE OF RELAPSE IN THIS GROUP OF PATIENTS.NEWER REGIMENS HAVE BEEN TRIED LIKE THE ITALIAN PROTOCOL WHICH INCLUDES EDP/M (ETOPOSIDE ,DOXORUBICIN,CISPLATIN/MITOTANE) . ANOTHER NEWER REGIMEN INCLUDES STRETAZOCIN AND MITOTANE (7)

RADIOTHERAPY

THESE ARE GENERALLY RADIORESISTANT TUMOURS. HOWEVER A STUDY DONE BY FASSNACHT ET AL HAS DEMOSTRATED REDUCED RECURRENCE IN CHILD WITH ADRENOCORTICAL CARCINOMA . IT CAN BE CONSIDERED FOR TUMOURS WITH GREATER DIMENSIONS, BLOOD VESSELS INVASION (V1), AND A KI-67 INDEX ≥ 20%, WHICH ARE ASSOCIATED WITH A HIGH RECURRENCE RISK (7).

NEWER MODALITIES

IGF ANTAGONISTS - FIGITUMUMAB AND OSI-906 ARE NOW BIENG CONTEMPLATED IN THE TREATMENT OF ADRENOCORTICAL CARCINOMA POST SURGERY(7)

OTHER NEWER MODALITIES INCLUDE

MTOR ANTAGONISTS. SIROLIMUS , EVEROLIMUS (RAD001),TEMSIROLIMUS (CCI- 779 (7)).

TYROSINE KINASE INHIBITORS TARGETING VEGFR - SORAFENIB AND SUNITINIB(7)

MDR-1 MODULATORS D VERAPAMIL, VALSPODAR (PSC833), TARIQUIDOR (7)

GENE THERAPY AND IMMUNOTHERAPY (7)

CONCLUSION

AN EARLY DIAGNOSIS IS FUNDAMENTAL FOR THE PROGNOSIS AND FOR AN IMPROVEMENT OF THE SURVIVAL RATE OF PATIENTS AFFECTED BY ACC.

THE AGGRESSIVENESS OF THIS TUMOR STILL REQUIRES EFFORTS IN THE IDENTIFICATION OF PROGNOSTIC AND THERAPEUTICS MARKERS

THERE IS A NEED TO EVALUATE THE NEED FOR LYMPH NODE BIOPSY IN CASES OF ADRENOCORTICAL TUMOURS DUE TO THE INABILITY OF HISTOLOPATHOLOGICAL EXAMINATION TO DIFFERENTIATE BETWEEN ADENOMA AND CARCINOMA AND THE ONLY WAY TO CONFIRM MALIGNANCY IS BY DOCUMENTING REGIONAL SPREAD OR RECURRENCE .

MITOTANE THERAPY MAY NOT BE EFFECTIVE IN THE MANAGEMENT OF RECURRENCE IN VIEW OF ITS POOR RESPONSE.

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