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RESEARCH ARTICLE

FAMILIAL HYPERALDOSTERONISM: ABOUT A REVEALING SIBLING OF TWO AND SYSTEMATIC REVIEW

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Abstract

Introduction: Bilateral primary aldosteronism may be caused by genetic forms, including familial hyperaldosteronism (FH) types I to IV. The management of this particular condition refers to medical treatment in spite of surgical procedures. In this article, we report on the family case of a sibling through 2 index patients followed in our department.

Case Report: 59-year-old patient followed in our training for a secondary hypertension due to a confirmed left conn adrenal adenoma family history of a similar case in the sister with confirmed adrenal Conn adenoma causing hypertension diagnosed in the early forties in all the siblings and some other family members with a history of cerebral strokes. Our department postponed the surgical management planned for the sister in favour of a medical approach, which will be decided on the basis of the response to dexamethasone treatment in our two patients, in the absence of possibilities for genetic typing tests.

Discussion and Conclusion: There are 4 types of familial hyperaldosteronism, whose characteristics and genotype/phenotype correlation are very diverse. Type 1, as we suspected in our family, is characterised by a prevalence of stroke and a satisfactory response to corticosteroid therapy, particularly dexamethasone, as both a diagnostic and therapeutic test. Management has long depended on the attitudes of the medical teams, but the scientific societies of endocrinology have now issued well-coded diagrams and guidelines for screening and treatment of these cases, increasingly favouring a medical approach rather than the invasive, and often bilateral, surgery previously practised.

Introduction:-

Primary hyperaldosteronism is a common and often unrecognised cause of secondary hypertension, characterised by excessive and autonomic aldosterone secretion. Excess aldosterone can also induce hypokalemia and lead to an increased risk of cardiovascular and cerebrovascular events and kidney damages.

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Bilateral primary aldosteronism may be caused by genetic forms, including familial hyperaldosteronism (FH) types I to IV. The management of this particular condition refers to medical treatment in spite of surgical procedures.

In this article, we report on the family case of a sibling through 2 index patients followed in our department.

Case report:

59-year-old patient with a history of prediabetes for 2 years, renal lithiasis removed twice, abstinent smoker, family history of a similar case in the sister with confirmed adrenal Conn adenoma also followed in our department, hypertension was also diagnosed in the early forties in all the siblings (1 brother and 2 other sisters) as well as the parents, aunt and 2 maternal uncles, all of whom died of cerebral stroke.

This patient was followed in our training for a secondary hypertension due to a conn adenoma biologically confirmed by a mildly elevated aldosterone/renin ratio of 65 pmol/mui, and radiologically with a typical aspect of hypodense left adrenal nodule measuring 26 mm with 6 HU of SD.

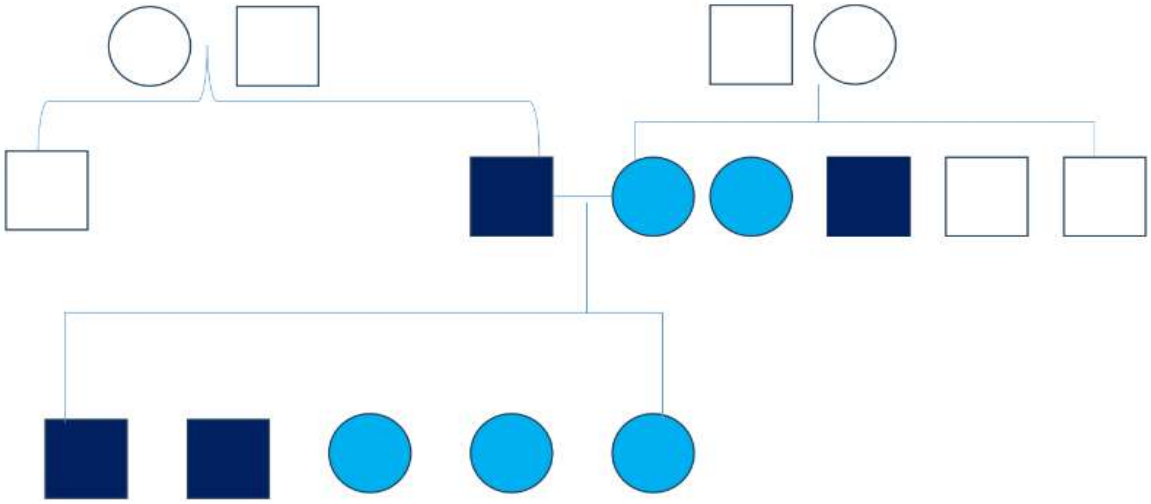

Figure N° 1:- Family pedigree : our patient affected female affected mâle.

Our first patient, had been treated with aldosterone antagonists and developed induced gynecomastia as a side effect, which led to cessation of treatment.

Given the prevalence of stroke in our family, FHA type 1 was suspected.

In view of the new recommendations from scientific societies, our department postponed the surgical management planned for the sister in favour of a medical approach, which will be decided on the basis of the response to dexamethasone treatment in our two patients, in the absence of possibilities for genetic typing tests for familial hyperaldosteronism.

Discussion:-

Aldosterone, the major circulating mineralocorticoid, participates in blood volume and serum potassium homeostasis. Primary aldosteronism is a disorder characterised by hypertension and hypokalemia due to autonomous aldosterone secretion from the adrenocortical zona glomerulosa. Improved screening techniques, particularly application of the plasma aldosterone:plasma renin activity ratio, have led to a suggestion that primary aldosteronism may be more common than previously appreciated among adults with hypertension.

In 1953, Litynski (1), reported the first case of an adrenocortical adenoma associated with hypertension and hypokalemia. Three years later, Conn (2) reported a similar case and described the full characterization of the syndrome of primary aldosteronism PA, which usually affect a single adrenal gland, except for familial cases due to germline mutations which, by definition, involve both adrenal glands and therefore cannot be cured by unilateral adrenalectomy (3). The familial occurrence of PA has been known for decades, since the discovery of PA in 1966 by Sutherland et al.(4). Notably, they reported that in some pedigrees of PA patients, the syndrome could be corrected

by glucocorticoids, leading them to define the condition as glucocorticoid-remediable aldosteronism, a condition now redefined as familial hyperaldosteronism (HF) type 1 (HF-1) (5).

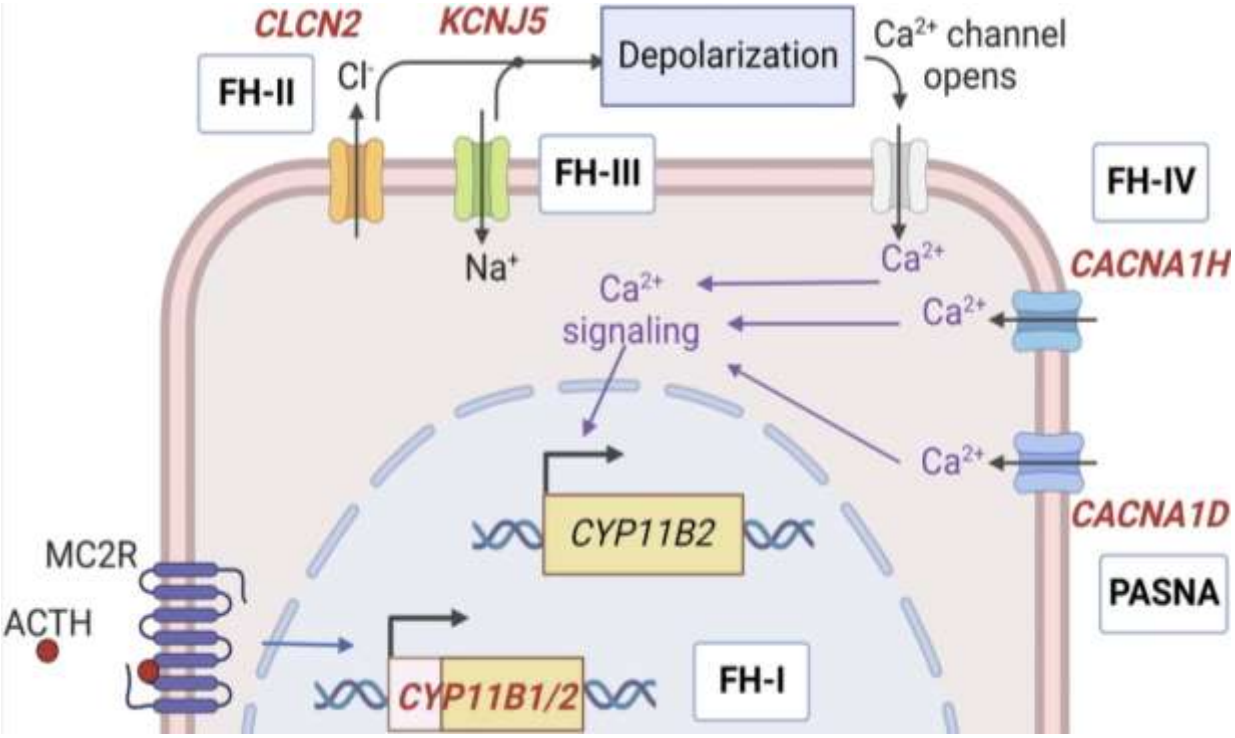

Figure N°2:- Schematic overview of the different pathophysiological mechanisms of familial primary hyperaldosteronism (5).

FH-I, referred to as glucocorticoid remediable aldosteronism, is characterised by early and severe hypertension, and is due to the formation of a chimeric gene between the adjacent CYP11B2 and CYP11B1 genes (encoding aldosterone synthase and 11β-hydroxylase respectively). This type is often associated with a family history of stroke before the age of 40, as described in our family cases.

Whereas FH-II is clinically and biochemically indistinguishable from sporadic forms of PA and is only diagnosed on the basis of at least two affected family members. No causative gene has yet been identified, and no genetic test is available.

Severe, early-onset hypertension in children and young adults, resistant to treatment and associated with severe hypokalemia, is a feature of FH-III. Mild forms similar to FH-II have been described. In this type, gain-of-function in the KCNJ5 gene are implicated. Lately, a new autosomal dominant form of familial PA, called FH-IV, has been described, associated with mutations in the CACNA1H gene, in patients suffering from hypertension and PA before the age of 10. Moreover in rare cases, PA can be associated with complex neurological disorders involving seizures and cerebral paralysis (primary aldosteronism, seizures and neurological abnormalities [PASNA]) due to de novo germline mutations in the CACNA1D gene (6,7).

Subforms	Gene	Phenotype	Therapy
FH-I (OMIM #103900)	*CYP11B1/CYP11B2* (cytogenetic location 8q24.3)	Primary aldosteronism, dexamethasone-responsive; high levels of hybrid steroids (18-hydroxycortisol, 18-oxocortisol); increased prevalence of intracranial aneurysms and haemorrhagic stroke	Dexamethasone (first choice in adults), MRA (second choice in adults, first choice in children)
FH-II (OMIM #605635)	*CLCN2* (cytogenetic location 3q27.1)	Primary aldosteronism	MRA
FH-III (OMIM #613677)	*KCNJ5* (cytogenetic location 11q24.3)	Severe to mild primary aldosteronism; hybrid steroids (18-hydroxycortisol, 18-oxocortisol), in some cases massive adrenal hyperplasia	MRA (first choice), bilateral adrenalectomy (second choice in MRAs not effective)
FH-IV (OMIM #617027)	*CACNA1H* (cytogenetic location 16p13.3)	Primary aldosteronism	MRA
PASNA syndrome (OMIM #615474)	*CACNA1D* (cytogenetic location 3p21.1)	Primary aldosteronism variably associated with seizures, neurological abnormalities, heart defects, hypoglycaemia, and hyperinsulinaemia	MRA, calcium channel blockers

Figure N°3:- Table summarising the different types of familial hyperaldosteronism (5).

A systematic literature search was previously carried out to manage these cases due to the rarity of the condition, and most recommendations were based on expert opinion and small series of patients. For this reason, and in order to unify management, new recommendations have been included in the European Reference Network on Rare Endocrine Conditions clinical practice guideline.

Regarding screening recommendations support testing for PA in any patient with early onset (<40 years old) hypertension, and helps to clarify the indications for comprehensive management in the diagram below (5).

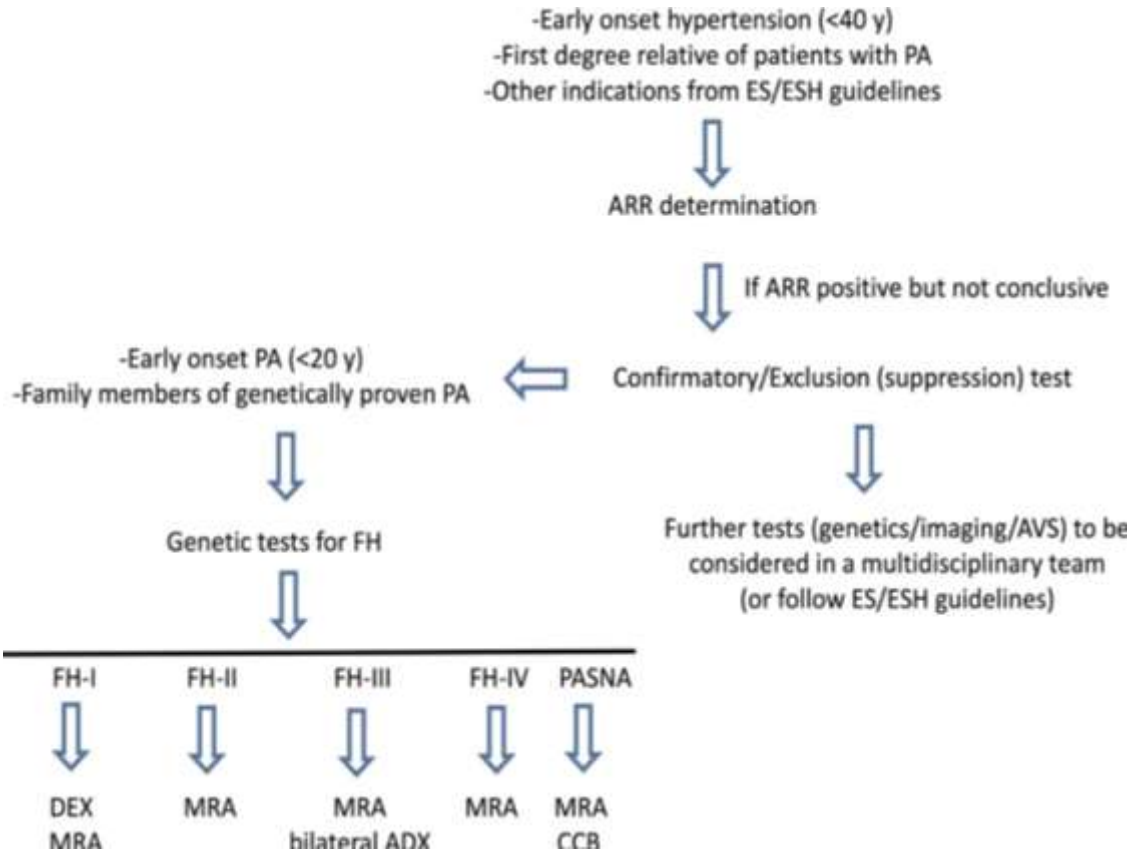

Figure N°4:- Proposed diagnostic diagram for patients with suspected FH (6).

Conclusion:-

Over the last decade, enormous progress has been made in understanding the molecular basis of PA, especially in familial forms, and this has opened the way to personalised treatment. The new recommendations from scientific societies are extremely useful and eagerly awaited, in order to establish a standardised approach to diagnosis and management.

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