for high blood pressure (BP). Despite extensive research focusing on HT, surprisingly there are no longitudinal studies assessing the long-term effects of HS. **Aims:** This study aimed (1) to evaluate the timing of onset for changes in CVR health during long-term sodium loading and (2) to assess whether salt restriction can prevent these effects.
Methods: C57BL/6 mice were randomized to HS, moderate (NS) or low (LS) salt diet and followed longitudinally for 50 weeks (wks). BP, urinary albumin/creatinine ratio (AC), plasma aldosterone (PA) and renin activity (PRA) were assessed monthly. At the end of the study, renal artery resistance and left ventricular (LV) parameters were measured by ultrasound and echocardiogram. Renal AT1 expression (Western Blot) and activity (IHQ) were quantified.
Results: At the beginning of the study, there were no differences in BP and AC between the three dietary groups. Relative to wk 1, BP (mmHg) in the HS group was higher in wk 21 (131±1.7 vs. 115±3.0, p= 0.05). Sodium restriction delayed this increase: SBP was higher in wk 41 in the NS group compared to the wk 1 (128±3.4 vs. 115±6.4, p= 0.05) but did not reach significance in the LS group until the end of the study. Similarly, relative to wk 1, AC (μg/mg) only in the HS group reached significantly higher levels in wk 17 (44±4.2, p<0.05). Again, sodium restriction delayed the occurrence of renal damage. AC reached significance in wks 25 and 41 for NS and LS (35±1.1 and 42±2.6 respectively, p<0.05 vs. baseline). Interestingly, the changes in AC always preceded the changes in BP, irrespective of diet. PA and PRA were appropriately activated by dietary salt restriction and suppressed by aging. The aging-induced suppression appeared stronger for PA than for PRA in the HS group only. Long-term sodium loading (HS) induced increased renal resistance, which was prevented in the LS but not in the NS group. Relative to HS, the LV mass index and cardiac output were lower in the NS and LS groups (p<0.05). LV volume indices and ejection fraction did not differ between groups. Renal AT1 protein expression and activation status (IHQ) were decreased in the sodium restricted group. **Conclusions:** Our study showed that long-term exposure to HS induced a progressive increase in BP and AC in mice. Importantly, these changes were delayed by long-term reduction in sodium intake. Interestingly, changes in AC preceded those in BP, irrespective of diet. Cardiac parameters suggest a sodium-induced eccentric cardiac hypertrophy in the older age, which was prevented by sodium restriction. One possible mechanism behind these effects is the overactivation of the AT1 receptor pathway.

Tumor Biology

ENDOCRINE NEOPLASIA CASE REPORTS II

MENIN Gene Mutation: Unity Amidst Diversity

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MENIN Gene Mutation: Unity amidst Diversity

Introduction

The MEN 1 syndrome is an enigmatic disorder, manifesting a wide spectrum of disorders, in members of a family, harbouring the same gene mutation. We present one such family, with a MENIN gene mutation with marked diversity in the clinical presentation

Clinical cases

1992: RB (Age: 13) presented with accelerated puberty, galactorrhoea and a lactotroph adenoma. Treated with Bromocriptine, followed by hypophysectomy and radiotherapy. He was on hormone replacement for hypopituitarism.

1996: He gained 21 kg of weight and had recurrent episodes of convulsions with unconsciousness.He had hypoglycaemia (13mg/dl; N >70), with hyperinsulinemia (58uIU/ml; N<25). MRI abdomen showed a mass (3.4 x 3.0 cm) over the tail of the pancreas for which a distal pancreatectomy was done (HPE: Neuroendocrine tumour).

2013: He had pain in the lower limbs with hypercalcemia (11.4mg%; N: 8.5-10.5) and hyperparathyroidism (329 pg/ml; N: 10-61) (MIBG Scan: parathyroid adenomas treated by bilateral inferior parathyroidectomy).

2016: He had hypoglycaemia with hyperinsulinemia with multifocal pancreatic NETs. These were enucleated at surgery.

2017: He developed Zollinger Ellison syndrome with raised basal gastrin levels (Gastrin: >200ng/ml; N<180) and multiple duodenal ulcers (Treatment: Pantoprazole). He simultaneously had recurrent hyperparathyroidism and underwent a total parathyroidectomy with allograft. The allograft initially showed evidence of hyperparathyroidism followed by hypoparathyroidism.

His father VB (Age: 56) was seen by us in 1996 for skin lesions and a malignant thymic carcinoid, to which he succumbed to, shortly after the surgery. His aunt, SB (Age: 18), has a lactotroph adenoma with severe insulin resistance characterised by obesity, acanthosis nigricans and hyperandrogenism.

2009: His paternal uncle PB (Age: 54) had a pituitary macroadenoma. He underwent a hypophysectomy and was lost to follow up.

2018: PB had massive haemoptysis. A bronchoscopy showed nodules in the right lung which on biopsy revealed a NET. The whole body scan showed a hilar and mediastinal mass along with metastatic disease to the adrenals, liver, spine, skull and rectum. The histopathology examination revealed a malignant carcinoid

Clinical lesson

Whole exome sequencing of the two of the affected members showed mutations of the MENIN gene at exon 2 c.G2492T:p.G831V; g. chr10. This common mutation in the family was associated with a wide spectrum of diverse clinical manifestations which include the
classic disease, malignant carcinoids of the lung and acromegaloid variant of Type A insulin resistance with hyperandrogenism. These observations suggest the unity amidst diversity in the enigmatic syndrome that encompasses MEN1.