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Review

McCune Albright syndrome

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Identity

Note

McCune Albright syndrome is characterized by the triad of polyostotic fibrous dysplasia, pigmentary skin lesions and endocrinopathy.

Inheritance

MAS is not inherited. It is a sporadic genetic disorder, caused by a mutation in the GNAS gene encoding the alpha subunit of the stimulatory G protein (GSalpha), cyclic AMP protein kinase dependent cellular signaling pathway involving G protein coupled receptors. An arginine or occasionally serine, leucine or glycine to histidine transposition at residue 201 attenuates GTpase activity. This results in constitutive activation of adenylyl cyclase.

The somatic mutation occurs in early embryogenesis, resulting in widespread tissue distribution of abnormalities. The post zygotic mutation is responsible for the mosaic pattern of tissue distribution and the extreme variability of clinical changes, varying from multi system disease to almost unrecognized disorders with single organ involvement.

Increased adenylate cyclase activity in bone from clinical fibrous dysplastic lesions is caused by expression of Cfos proto-oncogene in bone. Recent identification of increased fibroblast growth factor (FGF23) activity in fibrous dysplastic lesions has linked the bony abnormalities to a recognized marker of bone metabolism.

Clinics

Phenotype and clinics

The phenotype of MAS is extremely varied, ranging from multisystem disease, to minimal single organs being affected.

Fibrous dysplasia is the characteristic lesion seen in MAS, the bone lesion being of marrow stromal cells of osteogenic lineage, with increasing cyclic AMP up regulating osteogenic cells to osteoblasts within the fibrous dysplastic cells, compared to normal woven bone. Cartilaginous islands with woven bone and immature mesenchymal cells are found in the lesions, with resultant increased bone fragility in affected areas. Lesions may be polyostotic, panostotic or monostotic, with increased risk for long bone fractures, shepherd's crook deformity of proximal long bones and spinal compression fractures. Osteomalacia complicates 50% of fibrous dysplasia bone lesions, due to increased FGF23 activity resulting in phosphaturia.

Café au lait marks with a coast of Maine appearance follow a dermatomal distribution along the lines of Blaschko. The activating GSalpha mutation in skin involves tyrosinase gene activation in affected melanocytes. Similar pigmentation is seen in oral mucosa.

Endocrinopathies

The endocrine events most commonly seen are gonadotrophin independent precocious puberty, thyrotoxicosis and Cushing syndrome.

Gonadotrophin independent precocious puberty in girls is seen in at least 30%, presenting with premature thelarche. Progress is often intermittent and characterized by suppressed gonadotrophins and elevated oestrogen levels, confirming the ovarian source of the disorder. Ovarian cysts are commonly seen. Continuous oestrogen production may result in long term continuing menstrual abnormalities and infertility.

Male precocious puberty is less common, seen in 15%. Macro-orchidism without precocity is more common and may be unilateral or bilateral, often with excess Sertoli cell hyperactivity. Testicular microlithiasis is present in 62% compared with a normal population microlithiasis rate of 5%.

Thyroid disease has been described in association with nodular and diffuse goitres, single toxic adenoma and hyperthyroidism with T3 toxicosis, with an overall prevalence of 30%. Thyroid cancer has only rarely been described. Clinical difficulty in detection of hyperthyroidism in the presence of a hyperdynamic circulation due to polyostotic fibrous dysplasia is significant, with biochemical evaluation prior to surgery suggested to reduce the risk of thyroid storm.
Acromegaly is reported in up to 21% of affected patients, the pattern of disease varying from the common isolated form and often being co-secretory without adenoma formation. GS alpha mutations in these lesions have been demonstrated on the maternal allele.
Cushing syndrome Macro nodular adrenocortical hyperplasia is the typical feature, with various outcomes reported, from spontaneous resolution to a severe neonatal presentation.
Upper gastrointestinal polyps are now identified in association with MAS, with the typical hamartomatous appearance similar to Peutz Jegher syndrome polyps. These may be in association with oral melanotic pigmentation or independent of pigmentary changes. Overlap in clinical features between disorders associated with multiple endocrine disease such as Carney complex and Peutz Jegher syndrome is evident.
Phosphaturia with associated hypophosphataemia may require oral phosphate and calcitriol. No outcome data has been reported. Surgical removal of FD lesions has been observed to decrease phosphate wasting.

Neoplastic risk

Café au lait skin lesions are benign
Fibrous dysplastic lesions can undergo malignant sarcomatous transformation, most commonly in cranio-facial bones. Other rare sarcomas include angiosarcoma, liposclerosing myxoma and chondrosarcoma. Of those patients who have developed sarcoma within FD lesions, 46% had received prior radiation treatment in the affected field (for acromegaly).NB Increased sensitivity of FD lesions to metaplasia after radiation has cause for concern for treatment planning strategies
Thyroid cancer has only rarely been reported.
Testicular Sertoli and Leydig cell tumours have both been described, but are rare.
Ovarian hyperfunction is associated with ovarian cysts but are benign. Long term excess oestrogen secretion might increase the risk for breast cancer, particularly in the presence of growth hormone excess.
Growth hormone excess with acromegaly is benign but care is required with treatment planning strategies in view of excess radiation risk in an area affected with fibrous dysplasia.

Treatment

Fibrous dysplasia can be treated with bisphosphonates. These drugs are well tolerated and reduce bone pain and bone turnover. Overall impact on the course of the disease is unclear, with minimal reduction in long term fracture risk and variable reports of possible reduction in lesional size in adults. Bisphosphonate use in children has not been shown to arrest uncontrolled expansion of dysplastic lesions in long bones or to change histomorphology in treated children or adolescents. Dental extractions and restorations do not exacerbate FD lesions. Surgical interventions using a combined approach, involving medullary rodding and bisphosphonate have been shown to improve surgical outcomes.Optic canal decompression in fibrous dysplasia of the sphenoid should be confined to surgical intervention for uncontrolled compression of visual or other nerve pathways.
Precocious puberty in girls. Treatment is complex with escape from effect of aromatase inhibitors. Selective oestrogen receptor modulators have been reported to be effective but with similar escape phenomena. Secondary activation of the hypothalamic pituitary ovarian axis in response to persistent oestrogen exposure may require addition of GRNH analogue. Surgery for removal of a cystic ovary or laparoscopic cystectomy has been occasionally effective. Oophorectomy is not recommended as fertility is potentially normal.
Precocious puberty in boys. Aromatase inhibitors or androgen blockade have been utilized with variable outcome. GNRH analogues may be required for secondary activation of the hypothalamic pituitary axis.
Acromegaly. Management is difficult due to lack of a discrete lesion, limited access due to sphenoid wing fibrous dysplasia and radiation risk to dysplastic areas. Somatostatin and dopamine agonists have been used with variable outcomes.

Prognosis

Morbidity is most commonly related to complications of polyostotic fibrous dysplasia and the need for orthopaedic intervention.
Multiple lower limb fractures and bilateral hip shepherd's crook deformity frequently result in limited locomotion in adulthood, for severely affected individuals. Endocrinopathies are amenable to intervention, but management strategies are limited by effectiveness of medical interventions and radiation related risk. Excess mortality risk is related to malignancy risk and occasionally to high output cardiac failure or cardiomyopathy.

Genes involved and proteins

GNAS

Alias
gsp oncogene

Location
20q13

Note

Mutations of gsp are readily identified in lesional tissue from affected individuals with enhanced detection by multiple rounds of nested PCR and by including a peptide nucleic acid (PNA) in the PCR to block amplification of wild type GNAS targets.

Peripheral Blood gsp detection is similarly enhanced, using PNA clamping.

Protein expression: The GNAS locus is under complex imprinting control. GNAS encodes GS alpha expressed from maternal and paternal alleles in most tissues, with preferential expression of the maternal allele in kidney, thyroid and pituitary somatotrophs. Transcripts upstream from Exon 1 are expressed only from the paternal allele.

Other transcripts 38 kb upstream from exon 1 encode 2 proteins, XLalphas and ALEX and a transcript 52 kb upstream of exon 1, encode distinct proteins that may affect signal transduction. The latter is expressed exclusively from the maternal allele, encoding a neurosecretory protein, NESP55.

Gsalpha expression from the maternal allele will result in pathophysiological abnormality in tissues where that allele is expressed, but paternally expressed GNAS alleles may also result in endocrine dysfunction. Imprinting suppressing expression of paternal GNAS allele in some patients may result in a more severe phenotype.

Mutations occurring later in embryogenesis are likely to give rise to fewer mutant cells and a milder phenotype.

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