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Comprehensive Multidisciplinary Insights into Fibrous Dysplasia and McCune - Albright Syndrome.

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Abstract: ***McCune - Albright syndrome, documented since 1937, is clinically characterized by a classic triad of café au lait macules, endocrinopathies and fibrous bone dysplasia, due to somatic activating mutations in the GNAS gene that produces a Gαs protein coding responsible for cyclic AMP (cAMP) regulation, resulting in cellular mosaicism, with mutated and normal cells in affected tissues. Due to the multiple actions of the Gαs protein, the damage in FD/MAS can be multisystemic, so a multidisciplinary approach is needed for its approach and management, involving pediatricians, dermatologists, radiologists, nuclear medicine, traumatologists, geneticists, endocrinologists and internists, the latter being of utmost importance at the time of transition of these patients from children to adults. The following is a review of the literature, following an extensive literature search on the multidisciplinary approach to FD/MAS.***

Keywords: Fibrous Dysplasia, McCune - Albright Syndrome, GNAS Gene, Endocrinopathies

1. Introduction

The association between fibrous bone dysplasia (FD) with café au lait macules and peripheral precocious puberty (PPP) was described for the first time in 1937 by Donovan James McCune and Fuller Albright [1], since then, the understanding of this pathology has had multiple significant evolutions especially with the advance of molecular genetics that has allowed the specific identification of the GNAS gene mutation as the main etiology of the disease [2, 3].

McCune - Albright Syndrome (MAS) is results from somatic mutations in the GNAS gene, which encodes the alpha subunit of the Gs protein, responsible for the regulation of cyclic AMP (cAMP), resulting in cellular mosaicism, with mutated and normal cells in the affected tissues [4, 6, 7].

The classic triad of MAS is given by fibrous bone dysplasia, café au lait macules and hyperfunctioning endocrinopathies, presenting a broad clinical spectrum [7, 8, 9].

Genetic evolution has led to the knowledge and management of this disease by multiple clinical specialties [3, 10]. From an initial approach by the pediatric and dermatology teams, who are often the ones who perform the initial care of patients who consult for the sudden appearance of a café - au - lait spot, continuing with an management of associated endocrinopathies and monoarticular or polyarticular fibrous dysplasias.; identified by scintigraphy performed by nuclear medicine and radiology, as well as the pediatric - adult transition with the important participation of internists [11, 12].

This study highlights the critical need for a multidisciplinary diagnostic and therapeutic approach to optimize patient outcomes in FD/MAS

2. Methodology and Authors' Considerations

Our study entails a literature review of Mccune - Albright syndrome, to document the multidisciplinary approach of the different specialties (Orthopedics, Dermatology, Endocrinology, Nuclear Medicine, Radiology, Pediatrics, Internal Medicine, Genetics) involved in the identification of this pathology, without leaving aside the pathophysiological, clinical and diagnostic description of the disease.

All the above is preceded by a review in databases such as PubMed, Medline, Embase, ResearchGate.

Fibrous Dysplasia/McCune - Albright Syndrome

Molecular Genetics

The activating somatic pathogenic variant of the GNAS gene, which encodes the alpha subunit of the G protein (Gαs), is characterized by affecting the skin, skeleton and endocrine organs; however, due to the widespread localization of the Gαs protein, it can generate multiorgan involvement [11, 12, 13]

Under normal conditions, the signaling cascade of the Gαs protein begins with the binding of a ligand to the receptor, which produces the activation of the α subunit, which exchanges guanosine diphosphate (GDP) for guanosine triphosphate (GTP), then the alpha subunit, which remains activated, activates adenylyl cyclase that produces adenosine monophosphate (cAMP) from adenosine triphosphate (ATP),

then cAMP activates protein kinase A to generate the cellular response (see Figure 1) [12].

Exons 1 - 13 of GNAS encode Gsα. FD/MAS results from mutations in exon 8, where arginine 201 is converted to histidine (R201H) or cysteine, and from mutations in exon 9, where glutamine replaces arginine (see Figure 2) [14]; all leading to overactivation of the protein (Gαs), with the pathophysiological consequences of FD/MAS [14].

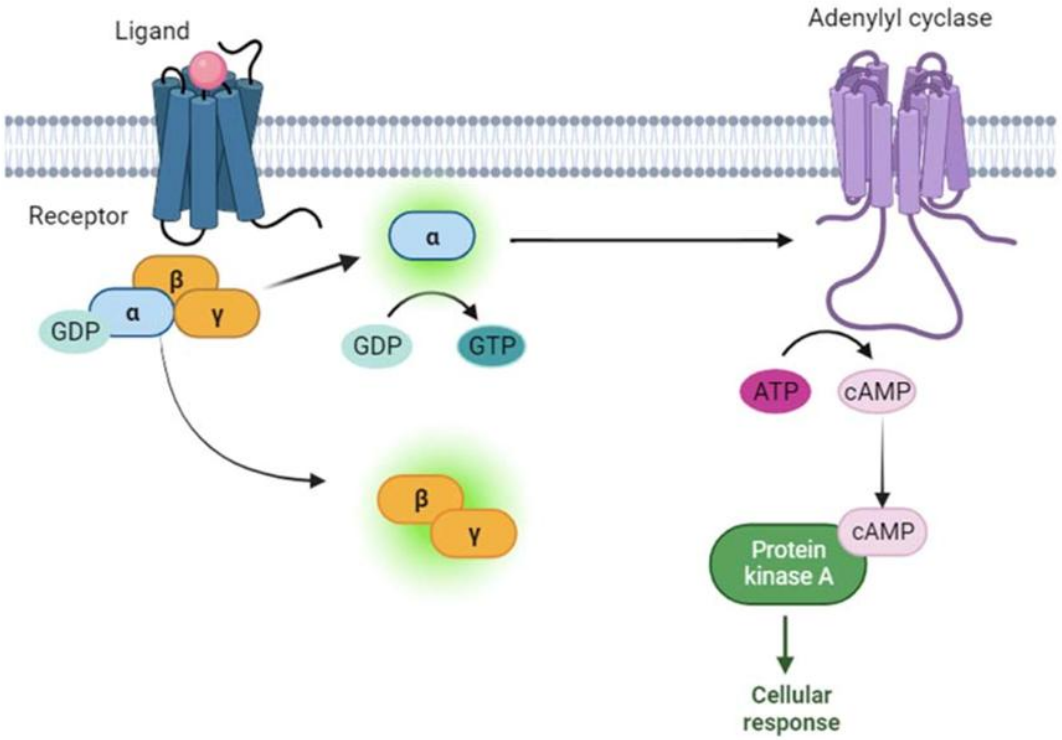

Figure 1: Activation of protein kinase A (from activation of protein Gαs).
Source: Vado Y, Manero - Azua A, Pereda A, Perez de Nanclares G. Choosing the Best Tissue and Technique to Detect Mosaicism in Fibrous Dysplasia/McCune - Albright Syndrome (FD/MAS). Genes (Basel).2024 Jan 18; 15 (1):

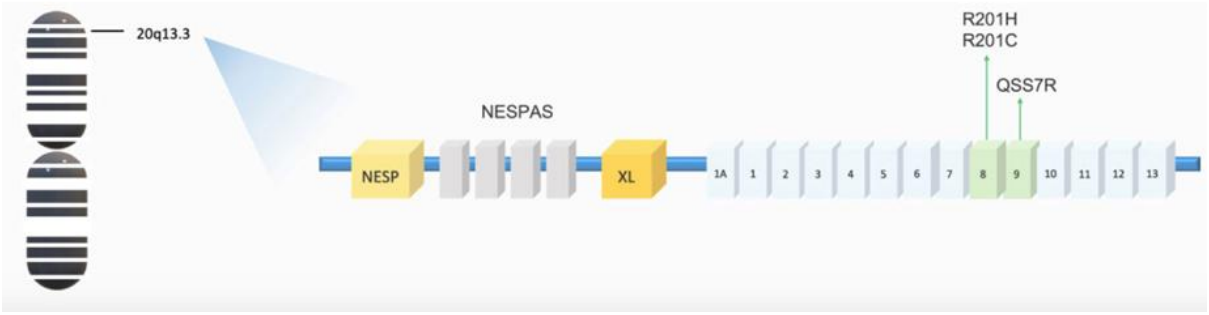

Figure 2: Diagram of the GNAS complex locus.
Source: Mascioli I, Iapadre G, Ingrosso D, Donato GD, Giannini C, Salpietro V, Chiarelli F, Farello G. Brain and eye involvement in McCune - Albright Syndrome: clinical and translational insights. Front Endocrinol (Lausanne).2023 May

Clinical features

The authors propose an organ - by - organ classification of the clinical features of DF/MAS, considering the findings in 3 specific organs (skin, skeletal system, endocrine system).

Skin: The presence of hyperpigmented cutaneous macules, which are called café - au - lait macules, with irregular and jagged edges that resemble the "coast of Maine" with a distribution that respects the midline of the body and follows the Blaschko lines, which reflect migration patterns of embryonic cells ([6, 11, 15]. See figure 3.

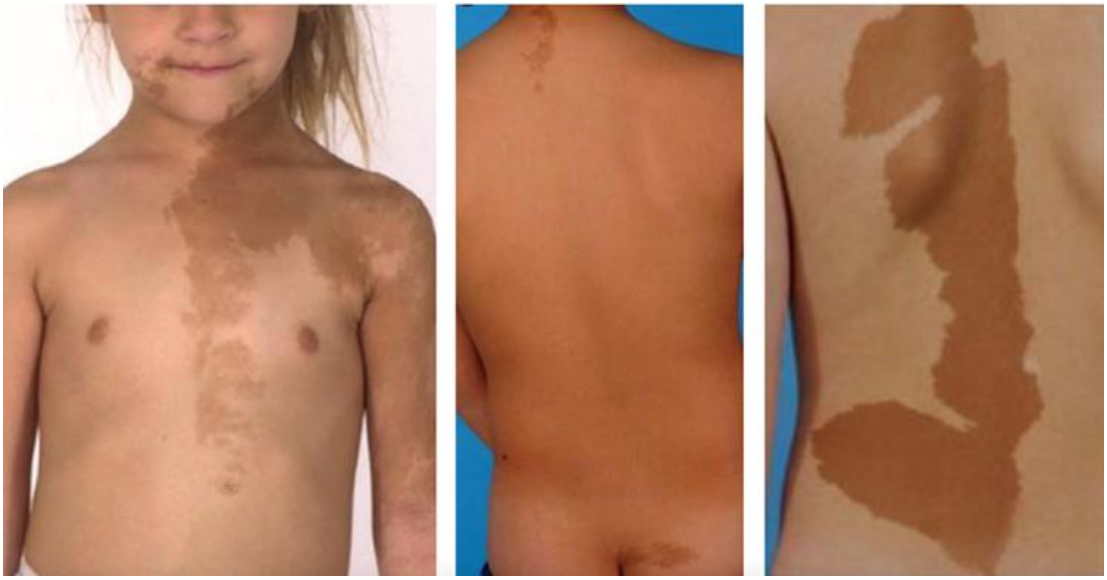

Figure 3: Café - au - lait macules, characteristic of FD/MAS.
Source: Collins, M. T. · Singer, F. R. · Eugster, E, McCune - Albright syndrome and the extraskeletal manifestations of fibrous dysplasia, Orphanet Journal of Rare Diseases.2012; 7: S4

Skeletal system: Fibrous dysplasia (FD) is characterized by proliferation of fibrous tissue, affecting both bone and bone marrow, producing a greater risk of bone deformity, fractures, pain and loss of function.

It can be monostotic (involvement of a single bone) or polyostotic (involvement of >1 bone), appearing in any part of the skeleton [6, 15] (see figure 4).

Bone lesions usually appear during the first years of life, continuing their appearance during childhood, most of them are significant and the average detection is at the age of 10 years, the appearance of FD after the age of 15 years is rare, in adulthood they usually become less active [6]. It is emphasized that before 5 years of age, if bone lesions are not observed in the scintigraphy, FD is not ruled out [11, 16].

Children typically present lameness, pain, pathological fractures, facial asymmetry or progressive facial deformity, loss of vision due to compromise of the optic nerves by alterations in the intracranial bone morphology, mild to severe scoliosis, generally progressive, aneurysmal bone cysts and even transformation to malignancy [6, 11, 12].

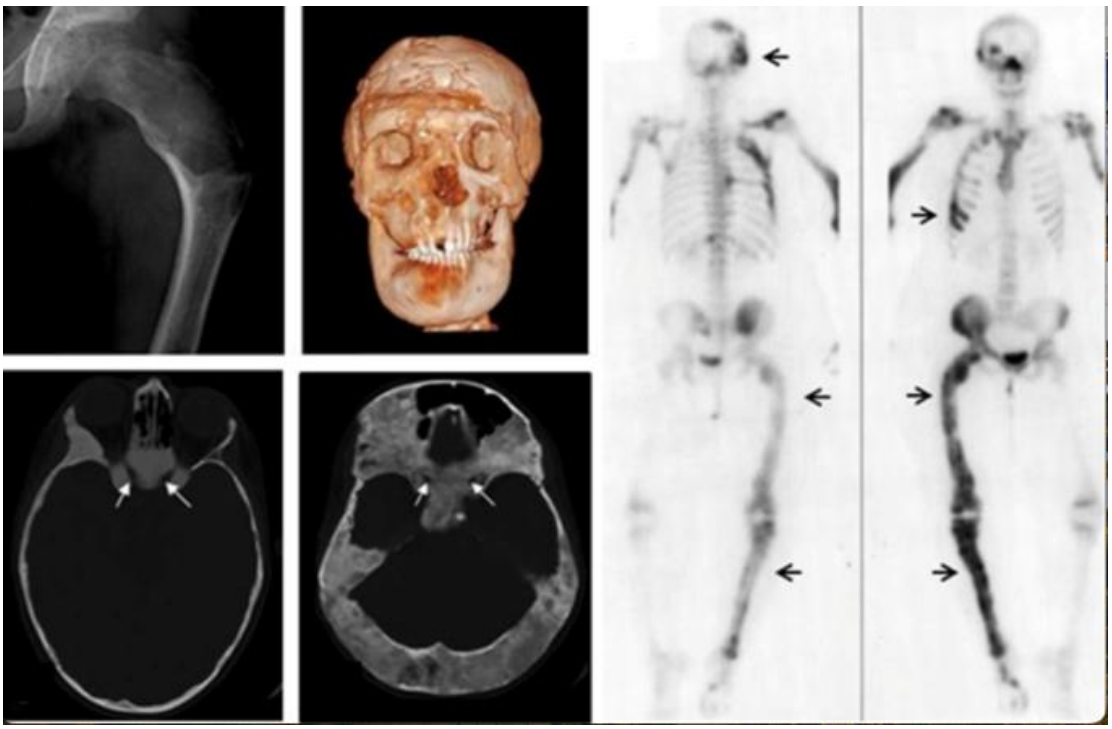

Figure 4: Fibrous dysplasia of multiple skeletal points, with images (radiographic, tomographic and gammographic).
Source: Szymczuk V, Florenzano P, de Castro LF, et al. Fibrous Dysplasia / McCune - Albright Syndrome.2015 Feb 26 [Updated 2024 Feb 8]. In: Adam MP, Feldman J, Mirzaa GM, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 - 2024.

Endocrinopathies: Findings may include:

Peripheral precocious puberty (Gonadotropin Independent): Over 85% of affected girls with FD/MAS present with PPP, which manifests with estrogen - producing ovarian cysts (E2), resulting in the development of secondary sexual characteristics (breast growth, vaginal maturation), accelerated growth, vaginal bleeding, all independent of FSH and LH levels [6, 12].

Testicular: In children it is less common (10 - 15%), and results from the autonomous production of testosterone, which leads to pubertal development, increased growth velocity, appearance of pubic hair, acne, inappropriate sexual desire, many times the evolution leads to unilateral or bilateral macroorchidism [6, 18].

Thyroid lesions, with or without non - autoimmune hyperthyroidism: approximately 30% of FD/MAS experience hyperthyroidism, mediated by accelerated conversion of T4 to T3 at the peripheral level, which can cause further progression of bone age, and cases of malignant transformation of the thyroid gland have even been reported [6, 18].

Excess of growth hormone: Hyperproduction of GH occurs in 15% of patients, and 80% of these patients present associated hyperprolactinemia, manifesting clinically with acromegalic phenotype, which should be treated for the possibility of cranial enlargement leading to macrocephaly with ocular and auditory complications [19].

Phosphate loss mediated by fibroblast growth factor 23 (FGF23), with or without hypophosphatemia: FGF23 is found increased in FD/MAS, which leads to its phosphaturic potential to cause renal tubulopathy with some degree of phosphate loss (20), the hypophosphatemia presented many times is mild, however when frank hypophosphatemia is found it is linked to patients with more severe FD and it has even been documented that it can become more severe in periods of skeletal growth.
Affected individuals may develop rickets/osteomalacia and increased fractures [6, 21].

Neonatal hypercortisolism: During the neonatal period a state of hypercortisolism has been documented leading to the development of Cushing's syndrome, so DF/MAS becomes an important diagnostic impression in patients with increased cortisol in this age group [12, 22].

3. Diagnosis

The clinical diagnosis of FD/MAS is established in patients presenting with two or more typical features of FD/MAS. In individuals presenting only monostotic fibrous dysplasia, confirmation of pathogenic variant activators of the GNAS gene is required to confirm the diagnosis, with specific analysis of exons 8 and 9 in the affected tissue having the highest diagnostic sensitivity in PCR sequencing [6, 12].

It is important to know that the detection of variants depends on the level of mosaicism in the tissue and the sensitivity of the technique used [6, 15].

The required laboratory and imaging tests are linked to the DF/MAS target organs, see Table 2, and are performed periodically depending on the physical examination findings and the medical consideration of a possible diagnosis of DF/MAS [6].

Differential diagnosis Table 2 summarizes the differential diagnoses to be considered with FD/MAS.

Table 1

Laboratories	Images
Spontaneous growth hormone Insulin - like factor type 1 (IGF1) Prolactin	Craniofacial X – rays X - rays of long bones Complete spine x – rays Left wrist x - ray (Bone age)
Thyroid hormones: (Thyroid stimulating hormone (TSH), Total thyroxine (T4t), Free thyroxine (T4f), Triiodothyronine (T3).	Gynecological ultrasounds Testicular Ultrasound Thyroid Ultrasound
Phosphocalcic profile: (Vitamin D, Phosphorus, Alkaline phosphatase, Parathyroid hormone (PTH), Total calcium, ionic calcium, 24h urine phosphorus).	CT scans (Brain, Thoracic, Abdominal)
Gonadal profile (Leutenizing Hormone, Follicle Stimulating Hormone, Estradiol (girls), Testosterone in boys, Testosterone in girls, Testosterone in boys)	Gammagraphy oseas
Cortisol ACTH	Magnetic resonance imaging.

Source: Authors

Table 2

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/FD/MAS	Distinguishing from FD/MAS
HRAS *NRAS*	Cutaneous-skeletal hypophosphatemia syndrome (CSHS) [1]	Not inherited [2]	• FGF23-mediated hypophosphatemia • Hyperpigmented macules that follow developmental lines of Blaschko • Skeletal features (e.g., skeletal deformities, dysplastic bone lesions, scoliosis, craniofacial involvement ranging from calvarial thinning & maxillary hypoplasia to severe osteolysis w/large calvarial defects)	• Epidermal & congenital melanocytic nevi • Neurologic abnormalities • Endocrinopathies are not a common feature, but central precocious puberty, thyroid nodules, & pheochromocytoma have been reported. • Ophthalmologic disorders (colobomas, limbal dermoids, strabismus, corneal opacities)
NF1	Neurofibromatosis 1 (NF1)	AD	• ≥6 café au lait macules that are generally smooth bordered ("coast of California") as opposed to the irregularly bordered ("coast of Maine") lesions seen in FD/MAS • Skeletal features (e.g., kyphoscoliosis, sphenoid dysplasia, cortical thinning of long bones, & bowing & dysplasia, particularly of the tibia, which may result in pseudarthroses)	• Tumors of the nervous system (e.g., neurofibromas & optic gliomas) • Pigmented iris hamartomas • Axillary freckling
SH3BP2 [3]	Cherubism	AD	Fibro-osseous skeletal lesions (See Table 4.)	• Symmetric fibro-osseous lesions are generally limited to the maxilla & mandible. • No extraskeletal manifestations

AD = autosomal dominant; FD/MAS = fibrous dysplasia / McCune-Albright syndrome; MOI = mode of inheritance
1. Ovejero et al [2016], de Castro et al [2020]
2. CSHS is a mosaic disorder resulting from postzygotic somatic activating pathogenic variants in *HRAS* or *NRAS* [Lim et al 2014].
3. In approximately 80% of affected individuals, cherubism arises from a heterozygous pathogenic variant in *SH3BP2*.

Source: Szymczuk V, Florenzano P, de Castro LF, et al. Fibrous Dysplasia / McCune - Albright Syndrome.2015 Feb 26 [Updated 2024 Feb 8]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 - 2024.

Multidisciplinary Management

As evidenced in the literature on the subject, we emphasize that the participation of multiple specialties is essential in order to make an adequate diagnosis and therapeutic management of DF/MAS, a condition that affects individuals across all stages of life and poses a significant diagnostic challenge for primary care practitioners; in this study we highlight the general approach to make diagnostic impressions about DF/MAS and we hope in a new chapter to talk about all the therapeutic alternatives that this pathological condition deserves.

4. Conclusion

Fibrous Dysplasia/McCune - Albright Syndrome (FD/MAS) demands a multidisciplinary approach for effective diagnosis and management. This review underscores the need for collaborative efforts across medical specialties to address its complex pathophysiology and optimize patient care.

5. Future Considerations

The objective of our review focused specifically on the documentation of the multidisciplinary approach to DF/MAS with a pathophysiological, clinical and diagnostic description of the disease. We highlight that it deserves a separate chapter on organ - to - organ treatments and associated complications, which will be explored in future studies

Acknowledgements

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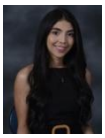

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