U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Dean L. McCune-Albright Syndrome. 2012 Mar 8 [Updated 2017 Mar 6]. In: Pratt VM, McLeod HL, Rubinstein WS, et al., editors. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012-.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

McCune-Albright Syndrome

Laura Dean, MD[1]

Created: March 8, 2012; Updated: March 6, 2017.

Characteristics

McCune-Albright Syndrome (MAS) is a rare genetic disorder originally characterized as the triad of polyostotic fibrous dysplasia of bone, precocious puberty, and café-au-lait skin pigmentation (1-3). With time other associated endocrinopathies have been recognized, including hyperthyroidism, growth hormone excess, FGF23-mediated phosphate wasting, and hypercortisolism (4, 5).

MAS is caused by an activating mutation in the *GNAS* gene, which encodes the alpha subunit of the stimulatory G protein involved in G-protein signaling (6, 7). A missense mutation, typically Arg201Cys or Arg201His (NM_001077488.3:c.604C>T, rs11554273), impairs the intrinsic GTPase activity of the Gsα protein, resulting in the constitutive activation of the Gsα-cAMP signaling pathway in the cells that contain the mutation.

The mutation arises early in embryogenesis and is distributed in a mosaic pattern. The clinical phenotype is therefore highly variable, depending upon the location and timing of the mutation during embryologic development. Skin manifestations are common and are usually present at or shortly after birth. The café-au-lait spots typically have irregular margins giving them a "coast of Maine" appearance, and usually show an association with the midline of the body.

In MAS, fibrous dysplasia of bone typically occurs at several sites (polyostotic), and commonly presents with fracture, deformity and/or bone pain (8). Radiographs show characteristic expansile lesions with a "ground glass" appearance. Craniofacial fibrous dysplasia can be severe in individuals who have pituitary disorders leading to hypersecretion of growth hormone. Treatment can be challenging and should begin as soon as possible.

In girls, precocious puberty is a common initial manifestation, with recurrent ovarian cysts leading to episodes of vaginal bleeding and breast development. Precocious puberty is less common in boys, presenting with penile enlargement, pubic and axillary hair, acne, body odor, and sexual behavior. However, in both girls and boys, there is a high frequency of gonadal pathology (ovarian abnormalities in girls, and testicular abnormalities in boys) (9).

Diagnosis

The NIH Genetic Testing Registry, GTR, displays genetic tests that are currently available for the *GNAS* gene and the McCune-Albright Syndrome.

Author Affiliation: 1 NCBI; Email: mgs@ncbi.nlm.nih.gov.

Currently, the diagnosis of McCune-Albright syndrome is made clinically in most cases. This is due to the mosaic nature of the disease whereby a negative genetic test result (e.g., in blood) does not exclude the presence of the mutation in other tissues. However, newer techniques such as digital PCR may improve the sensitivity of genetic testing in individuals who have clinical signs of McCune-Albright syndrome (10, 11).

Management

Treatment is individualized based on each patient's clinical presentation. Letrozole (12) and/or tamoxifen (13) may be effective for treatment of precocious puberty in girls. Medications and/or surgery may be used for treatment of hyperthyroidism (14, 15), growth hormone excess (16, 17), and hypercortisolism (18). Management of fibrous dysplasia of bone is palliative, with surgery as needed for fracture and deformity (19, 20). Bisphosphonates are effective for treatment of fibrous dysplasia-related pain, but have not been shown to have any long-term effect on the course of the disease (21, 22).

Genetic Counseling

McCune-Albright syndrome is caused by a new (de novo) mutation that occurs after conception, at an early stage of development. Individuals with McCune-Albright syndrome have not been observed to pass the syndrome on to their children.

Acknowledgments

The author would like to thank Albert Beckers MD, PhD, and Adrian F. Daly MB BCh, PhD, Department of Endocrinology, Centre Hospitalier Universitaire de Liège, University of Liège, Belgium, for reviewing this summary.

Version History

To view an earlier version (8 March 2012), please click here.

References

1. Albright F, B.A., Hampton AO, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas, of pigmentation, and endocrine dysfunction, with precocious puberty in females: report of 5 cases. N Engl J Med. 1937;216:727–746.
2. McCune D. Osteitis fibrosa cystica: the case of a nine-year-old girl who also exhibits precocious puberty, multiple pigmentation of the skin and hyperthyroidism. Am J Dis Child. 1936;52:743–744.
3. Boyce, A.M. and M.T. Collins, Fibrous Dysplasia/McCune-Albright Syndrome, in GeneReviews(R), R.A. Pagon, et al., Editors. 1993: Seattle (WA).
4. Dumitrescu C.E., Collins M.T. McCune-Albright syndrome. Orphanet J Rare Dis. 2008;3:12. PubMed PMID: 18489744.
5. Collins MT. S.F., Eugster E, McCune-Albright syndrome and the extraskeletal manifestations of fibrous dysplasia. Orphanet J Rare Dis. 2012;7 Suppl 1:S4. PubMed PMID: 22640971.
6. Weinstein L.S., Shenker A., Gejman P.V., Merino M.J., et al. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. The New England journal of medicine. 1991;325(24):1688–95. PubMed PMID: 1944469.
7. Schwindinger W.F., Francomano C.A., Levine M.A. Identification of a mutation in the gene encoding the alpha subunit of the stimulatory G protein of adenylyl cyclase in McCune-Albright syndrome. Proc Natl Acad Sci U S A. 1992;89(11):5152–6. PubMed PMID: 1594625.

8. Collins M, R.M., Bianco P., Fibrous dysplasia. In: Rosen C (ed.) Primer on the metabolic bone diseases and disorders of mineral metabolism, 2008. **1**(American Society of Bone and Mineral Research, Washington, D.C.): p. 423-428.
9. Boyce A.M., Chong W.H., Shawker T.H., Pinto P.A., et al. Characterization and management of testicular pathology in McCune-Albright syndrome. J Clin Endocrinol Metab. 2012;97(9):E1782–90. PubMed PMID: 22745241.
10. Vasilev V., Daly A.F., Thiry A., Petrossians P., et al. McCune-Albright syndrome: a detailed pathological and genetic analysis of disease effects in an adult patient. J Clin Endocrinol Metab. 2014;99(10):E2029–38. PubMed PMID: 25062453.
11. Rostomyan L., Beckers A. Screening for genetic causes of growth hormone hypersecretion. Growth Horm IGF Res. 2016;30-31:52–57. PubMed PMID: 27756606.
12. Feuillan P., Calis K., Hill S., Shawker T., et al. Letrozole treatment of precocious puberty in girls with the McCune-Albright syndrome: a pilot study. The Journal of clinical endocrinology and metabolism. 2007;92(6):2100–6. PubMed PMID: 17405850.
13. Eugster E.A., Rubin S.D., Reiter E.O., Plourde P., et al. Tamoxifen treatment for precocious puberty in McCune-Albright syndrome: a multicenter trial. J Pediatr. 2003;143(1):60–6. PubMed PMID: 12915825.
14. Mastorakos G. M.N., Doufas AG, Koutras DA, Hyperthyroidism in McCune-Albright syndrome with a review of thyroid abnormalities sixty years after the first report. Thyroid. 1997;7(3):433–9. PubMed PMID: 9226216.
15. Celi F.S., Coppotelli G., Chidakel A., Kelly M., et al. The role of type 1 and type 2 5'-deiodinase in the pathophysiology of the 3,5,3'-triiodothyronine toxicosis of McCune-Albright syndrome. J Clin Endocrinol Metab. 2008;93(6):2383–9. PubMed PMID: 18349068.
16. Akintoye S.O., Chebli C., Booher S., Feuillan P., et al. Characterization of gsp-mediated growth hormone excess in the context of McCune-Albright syndrome. J Clin Endocrinol Metab. 2002;87(11):5104–12. PubMed PMID: 12414879.
17. Akintoye S.O., Kelly M.H., Brillante B., Cherman N., et al. Pegvisomant for the treatment of gsp-mediated growth hormone excess in patients with McCune-Albright syndrome. J Clin Endocrinol Metab. 2006;91(8):2960–6. PubMed PMID: 16720661.
18. Brown R.J., Kelly M.H., Collins M.T. Cushing syndrome in the McCune-Albright syndrome. J Clin Endocrinol Metab. 2010;95(4):1508–15. PubMed PMID: 20157193.
19. Stanton RP. I.E., Springfield D, Lindaman L, Wientroub S, Leet A., The surgical management of fibrous dysplasia of bone. Orphanet J Rare Dis. 2012;7 Suppl 1:S1. PubMed PMID: 22640754.
20. Lee J, F.E., Chen Y, Kim H, Lustig L, Akintoye S, Collins M, Kaban L., Clinical guidelines for the management of craniofacial fibrous dysplasia. 2012. **7**(Suppl 1): p. S2.
21. Plotkin H., Rauch F., Zeitlin L., Munns C., et al. Effect of pamidronate treatment in children with polyostotic fibrous dysplasia of bone. J Clin Endocrinol Metab. 2003;88(10):4569–75. PubMed PMID: 14557424.
22. Collins M.T., Kushner H., Reynolds J.C., Chebli C., et al. An instrument to measure skeletal burden and predict functional outcome in fibrous dysplasia of bone. J Bone Miner Res. 2005;20(2):219–26. PubMed PMID: 15647815.

License