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McCune–Albright syndrome, natural history and multidisciplinary management in a series of 14 pediatric cases

Syndrome de McCune-Albright, histoire naturelle et prise en charge multidisciplinaire dans une série de 14 cas pédiatriques

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Abstract

Background. – McCune–Albright syndrome is a rare disorder characterized by endocrine disorders, *café-au-lait* spots and fibrous dysplasia of bone that occurs early in life. *Methods.* – A series of 14 pediatric cases were followed between 1994 and 2013 by the competence center for rare endocrine diseases and constitutional bone diseases at CHU de Nancy (France). The diagnosis is based on the presence of at least two symptoms. *Results.* – The mean follow-up was 6 years (1–17 years). The sex ratio was six girls per boy. The incidence was 0.28 cases/million population/year. Mean age at diagnosis was 6 years. A mutation in the *GNAS* gene was found in 33% of patients tested. Gonadal involvement (13/14 cases), including early peripheral puberty and ovarian cysts in girls (82%) occurred on average at 4 years of age. Bone involvement (10/14 cases) appeared on average at 5 years of age and was most often multiple (80%) with fracture risk, and the skull, with a neurosensory risk. *Conclusion.* – Clinical definition and methods of screening and monitoring can be improved to allow for an earlier intervention. It must be multidisciplinary and take into account the disability and quality of life of the patient.

Keywords: McCune–Albright syndrome; Pediatrics; Natural history; Management; Disability

Résumé

Contexte. – Le syndrome de McCune-Albright est une maladie rare caractérisée par des anomalies endocriniennes, des taches café-au-lait sur la peau et une dysplasie fibreuse des os survenant tôt dans la vie. *Méthodes.* – Une série de 14 cas pédiatriques a été suivie entre 1994 et 2013 par le centre de compétence des maladies endocriniennes rares et des maladies osseuses constitutionnelles du CHU de Nancy (France) avec un diagnostic fondé sur la présence d'au moins deux des signes cliniques. *Résultats.* – La période moyenne d'observation a été de 6 ans (1–17 ans). Le sex-ratio était de six filles pour un garçon. L'incidence était de 0,28 cas/million d'habitants/an. L'âge moyen au moment du diagnostic était de 6 ans. Une mutation dans le gène *GNAS* a été retrouvée chez 33 % des patients testés. L'atteinte gonadique (13/14 cas), comprenant puberté précoce périphérique et kystes ovariens chez les filles (82 %), a eu lieu en moyenne à 4 ans. L'atteinte osseuse (10/14 cas) est apparue en moyenne à 5 ans et était le plus souvent multiple (80 %), périphérique avec le risque de fracture, et touchant le crâne, avec un risque neurosensoriel. *Conclusion.* – La définition et les méthodes de dépistage et de surveillance clinique peuvent être améliorées pour permettre une prise en charge plus rapide. Celle-ci doit être multidisciplinaire et tenir compte du handicap et de la qualité de vie du patient.

Mots clés : Syndrome de McCune-Albright ; Pédiatrie ; Histoire naturelle ; Prise en charge ; Handicap

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1. Introduction

McCune–Albright syndrome (MAS) was first described in 1936 and 1937, in a presentation of six children with a condition corresponding to a clinical triad of bone lesions of fibrodysplasia, areas of skin hyperpigmentation and ipsilateral endocrine disorders involving precocious puberty in girls [1,2]. The origin of MAS is sporadic activation of the heterozygous *GNAS* gene that affects mainly codon 201 by the appearance of a missense mutation, causing a mosaic disease affecting the concerned tissues [3]. *GNAS* gene mutation involves independent activation of protein Gs and the signaling cascade mediated by protein kinase A [4]. The mutation can be sought by PCR or sequencing methods in leukocytes in peripheral blood or in a tissue sample obtained after appropriate extraction [5,6]. Epidemiological results reveal a rare disease with an estimated prevalence in the range of 1/100,000 to 1/1000,000 [7]. The diagnosis of MAS was originally clinical, based on the triad described. However, other clinical definitions have now been put forward, including the presence of bone involvement accompanying any characteristic endocrine or skin disorder [7,8].

We carried out a retrospective study at a competence medical center for rare endocrine diseases in Nancy (France) over a period of 20 years between 1994 and 2013, attempting to describe the clinical, hormonal, morphological and genetic features of MAS, and looking at follow-up and coordinated patient care.

2. Methods

2.1. Records and ethics

All records of the medical center for rare endocrine diseases, CHU de Nancy (Vandœuvre-lès-Nancy, France), that mentioned a diagnosis or suspicion of McCune–Albright syndrome during the 20-years period between 1994 and 2013, were studied. The selection of cases was made possible by cross-referencing three files ("Photos," "Genetics," and "Consultation"). Authorization was obtained from the National Commission on Informatics and Liberties (CNIL). The consent of the patient (or her or his legal representative) was obtained.

2.2. Criteria for inclusion

Inclusion criteria were the presence of at least two clinical signs of the triad with or without mutation of the *GNAS* gene, or one clinical sign of the triad with a mutation in GNAS. Of the 28 cases recovered, two showed no signs of the triad. One patient had puberty of central origin, one had typical MAS on medical center monitoring that ended in 1990. However, 11 patients had a single sign of the triad with no mutation. A cohort of 14 patients was therefore selected.

2.3. Genetic investigation

The search for somatic mutation of the *GNAS* gene was performed at the molecular biology laboratories, University Hospital of Montpellier (six cases), and the University Hospital of Caen (eight cases). The study was carried out using PCR by the Sanger method in the presence of a PNA probe. Mutations sought were C.601C> T, C.601C> A C.601C> G, C.602G> A. Tissue was analyzed, as appropriate: blood or affected tissues (bone, gonadal and thyroid) after appropriate extraction.

3. Results

3.1. Diagnosis

The 14 patients were 12 girls and 2 boys, giving a sex ratio of 6:1 (Table 1). Considering the 13 cases living in the area over the 20-year period, the regional incidence in Lorraine (France) was 0.28 cases per year per million inhabitants. The age at diagnosis of MAS was between 6 months and 22 years, with a mean of 6 years and a median of 4 years. The age when the first symptom was reported ranged between fetal life and 11 years, with a mean of 3 years and 6 months ($n = 13$). The first symptom reported was often gonadal (79% of cases), and less commonly bone disease. No skin or endocrine phenomenon was recorded as diagnostic of MAS ($n = 14$). Principal practitioners involved were a pediatrician (six patients), GP (five patients), and a pediatric orthopedic surgeon (three patients). Half of the patients experienced a delay in diagnosis of more than one year. Half had the complete clinical triad, the other half two signs of the triad. No patient was included because of the presence of only one clinical criterion and the mutation (Table 1).

The search for the mutation of the *GNAS* gene was performed on blood samples in 12 out of 14 cases (Table 1). Out of the 12 patients tested, two samples were positive (17% of cases). The search for mutations in tissue samples was performed on six patients. The sites were the gonads (two samples ovaries and one testis), bone (two samples) and thyroid (two samples). The sampling was performed in the context of therapeutic surgery. A mutation was found in one third of patients tested and 43% of samples ($n = 7$). The four patients who tested positive for all materials exhibited all three of the triad.

3.2. Patient monitoring

Out of the 14 patients, three were seen for reviews or short-term follow-up and 11 for prolonged follow-up. The duration of follow-up at the competence medical center ranged between 1 and 17 years, with a mean of 6 years (Table 1). A monitoring consultation involved: clinical and hormonal assessment and pelvic ultrasound in girls; height and weight; pubertal stage; presence of *café-au-lait* spots and musculoskeletal functional signs. The frequency of examinations at the competence medical center was between 0.3 and 3.4 per year with a mean of one visit per year. Seven patients currently continue regular monitoring, four were referred for follow-up post-adult transition, two were re-directed to the general practitioner in the context of joint monitoring and one patient was lost to follow-up. Monitoring of orthopedic patients was performed iteratively in 7 out of 14 cases. The frequency of orthopedic examinations ranged between 0.5 and 1.1 per year, with a mean of one.