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 endocrinienes, 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 endocrinienes 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 fibrodisplasia, 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.
Hospitlizations were important, accounting for over a quarter of all examinations. Consultations were restricted to simple clinical monitoring and targeted radiography.

### 3.3. Gonadal effects

Gonadal phenomena concerned all 12 female patients, and one of the two males. Age at onset of ovarian activity ranged between fetal life and 6 years. The mean was 2 years and 8 months, with a median of 1 year and 6 months. The male equivalent occurred at the age of 11 years. In girls, the symptoms of precocious puberty that prompted medical consultation were breast development, usually bilateral, sometimes asymmetric, with elevation and areolar hyperpigmentation (Fig. 1), and vulvar development, accompanied by episodes of vaginal bleeding. The initial evaluation included determination of estradiol, gonadotropins, androgens and tumor markers and a LHRH test, pelvic ultrasound, and bone age assessment. Monitoring of gonadal impairment included regular study of estradiol and pelvic ultrasound, accompanied by a thorough clinical examination. During follow-up, ovarian cyst was found in 82% of cases (n = 11). The number of episodes of estrogen excess in a single patient ranged between one and six single episodes, the average being 2.5 (n = 12). The duration of episode of estrogen excess was highly variable from one patient to another, but also for the same patient, ranging from 1 month to 4 years: 50% of episodes were less than 3 months long, 25% lasted between 3 and 6 months, 19% between 6 months and 1 year, and 6% more than 1 year (n = 32). The only male patient with gonadal impairment underwent unilateral orchiectomy for suspected malignant pathology, revealing Leydig cell hyperplasia.

Concerning medical care, 55% received no specific treatment. Three patients were treated with testolactone and one with anastrozole. Levels of estradiol, testosterone and androstenedione-D4 were monitored in treated patients. Out of the four cases treated, we observed clinical and biological efficacy in two during 2 years of treatment, one case of relative effectiveness (anastrozole) during 3 years of treatment, and finally one case of total inefficacy over 4 years. One patient underwent unilateral ovariectomy. The efficacy of treatment of precocious puberty was judged on clinical data as the improvement of Tanner scale and the disappearance of genital signs. The normalization of estradiol was a major criterion, and androgens were performed to differentiate the effect of aromatase inhibiting treatment and normalization of ovarian function. Size and bone age were used throughout. The final size was between

Fig. 1. Characteristic mammary development in a girl of 5 years.
1 m48 and 1 m62, with an average of 1 m52 (n = 5), for an average size target of 1 m62 (n = 5), which corresponds to a defect of 10 cm. Finally, data concerning central puberty were available on 7 patients. Two boys had normal puberty. Out of 5 girls, two had menarche at 10 years and 3 to 12 years. Two of them have had irregular cycles with breakthrough bleeding, requiring the prescription of a progestin treatment. One patient carried a pregnancy to term at the age of 18.

3.4. Bone involvement

Bone involvement was seen in 10 patients and was polyostotic in 80% of cases (Table 1). Age at discovery was between 2 years and 8 years 6 months, with an average of 5 years 6 months; the latest was at 18 years. The number of lesions, excluding the skull, ranged between two and nine, with an average of four. Involvement of the long bones mainly affected the lower member (nine cases) in particular the femur (eight cases) and to a lesser extent the tibia (four cases); the upper limbs were involved in only two patients. The discovery of bone involvement was made in 50% of cases during routine screening as part of follow-up, in 30% in the context of the occurrence of a pathological fracture, and in 20% of cases on imaging examinations performed before the onset of musculoskeletal pain. Screening methods included bone scintigraphy with technetium 99 in eight patients and whole body radiography in seven. Targeted radiographs were routine, particularly during onset of pain or in the follow-up of known lesions. Three patients had the three types of examination (Fig. 2). The major complication of bone disease was pathological fracture, which affected 40% of patients and only involved the long bones. Four fractures of the femur and two of the forearm were identified. Age at onset of fracture episodes ranged between only 5 and 7 years. Surgical treatment of four patients was curative in the context of fractures, and preventative for threatening lesions in one patient. Medical care consisting in administration of bisphosphonate pamidronate 1 mg/kg/day for 3 days, repeated every 6 months, was performed in only one patient over 4 years, and showed efficacy in terms of pain and bone mass by densitometry. Rehabilitation with exercise was also necessary for three patients. Management was often complex, requiring many hospitalizations with long-term follow-up and could last for several months. Care involving the skull was always multifocal. It concerned three patients or 30% of those with bone involvement, particularly of the mandible, the maxilla and the sphenoid. The lesions appeared between the ages of 6 and 7 years, always later than in long bones. Complications included two cases of mandibular dysmorphism, one of compression of the optic nerve with sphenoidal level functional impairment, which was the subject of surgical intervention, two cases of exophthalmia and one of moderate deafness related to damage to the petrous bone. These patients were all followed regularly by ENT and ophthalmology, with audiogram and visual field assessment.

3.5. Other disorders

Skin lesions affected 12 patients or 86% of the cohort (Fig. 3). At least one café-au-lait spot was present in eight patients before the age of 6 years; 55% of patients had one spot, 36% had two and 9% three (n = 11). Areas affected were the lower limbs (27%), upper limbs (20%), trunk (33%) and cervical region (20%).

Endocrine involvement was diagnosed in 28% of the cohort. Evaluation of pituitary and thyroid hormones was performed each year throughout the follow-up of patients. Two cases of hyperthyroidism were identified, requiring surgery. One was a 6-year-old patient who presented a toxic thyroid adenoma requiring lobectomy. The second was a 2-year-old patient with a toxic multinodular goiter and was treated first with carbimazole and then thyroidectomy. Two cases of spontaneous resolution of hyperprolactinemia were also identified, in patients aged 2 years and 7 years.

Fig. 2. Appearance of fibrous dysplasia lesions of the upper end of the right femur in a girl of 5 years, views and lateral radiograph (A) and coronal CT (B).

Fig. 3. Laterocervical café-au-lait spots in a girl 10 years of age.
4. Discussion

4.1. Natural history and diagnostic difficulties

As with all rare diseases, the incidence of MAS is difficult to determine. In this cohort, the incidence was 0.28 cases per year per million inhabitants. Considering mortality due to the disease to be negligible, the prevalence was estimated at about 2.2 cases per 100,000 inhabitants. This figure is higher than the Orphanet data indicating 0.55 cases per 100,000 [9]. However, the diagnostic definition directly affects the calculation of incidence and prevalence. The diagnosis was made when the child was about 5 years old, and the first symptom was observed at about 4 years. In our cohort, it was mostly precocious puberty and lesser bone involvement with the discovery of fracture. The age at onset of bone lesions was early, usually under 6 years, and there was a tendency to stabilize in adulthood. A peak in fracture incidence occurred between 6 and 10 years [10]. With the exception of Cushing’s syndrome, peripheral adrenal effects had a median onset at 3 months of life, and affected 4% of patients [11]. Other endocrine effects, including acromegaly, appeared later, in young adulthood, and were therefore not considered here [12].

4.2. Clinical features

Gonadal activity is characterized in girls by the development of recurrent ovarian cysts secreted mostly in a unilateral fashion, which can persist into adulthood [13,14]. The course is fluctuating and usually begins early in life, before age 4 years or from fetal life [15]. In boys, testicular change is also common, but only 21% will develop clinical precocious puberty. Unilateral or bilateral testicular hypertrophy due to Leydig cell hyperplasia occur, and nodules or testicular microlithiasis are also found [16].

The cohort data on bone disease notably revealed the predominance of polyostotic involvement and the preferential involvement of the long bones (metaphyseal and diaphyseal mostly), particularly the proximal femur [17]. These lesions were subject to change, with possible worsening of pre-existing lesions and the appearance of new ones [8]. Half of the bone lesions were discovered during routine screening, which highlights its importance. Symptoms include pain, deformity and a risk of pathological fractures related to osteopathy due to diffuse demineralization of the injured areas [17]. Concerning the skull there may be complications such as compression of cranial nerves, including the optic nerve and the auditory nerve, potentially causing visual or hearing loss, exophthalmia and facial asymmetry [18].

Café-au-lait skin spots correspond to areas of light brown hyperpigmentation that are not raised and vary, in size from a few millimeters to 20 cm, and in shape; they may be congenital or rapidly progressive following appearance in childhood [19]. Other features include endocrinopathies related to hormonal hypersecretion [12]. Hyperthyroidism was initially estimated to occur in more than one-third of cases [20]. However, a recent series of 36 patients found that 31% had thyroid abnormalities, particularly a morphologically notable type of nodular goiter. Only 10% of patients present hyperthyroidism [21]. The pituitary is affected in acromegaly and hyperprolactinemia. It is most often concomitant and is seen in approximately 20% of patients, mostly in young adulthood [8,22].

4.3. Management and therapeutics

Recommendations drafted by HAS (France) in 2012 have summarized the main lines of care in fibrous dysplasia of bone and McCune–Albright syndrome [23].

The main principles are:

- confirm the diagnosis and search for related attacks;
- announce and explain the disease to the patient and inform about the existence of a patient organization;
- define the multidisciplinary management strategy to monitor the disease activity, reduce pain, prevent the complications, risks, loss of function in daily activities and to optimize the quality of life [23].

The management of precocious puberty in MAS aims to eliminate the systemic effects of sex steroids produced by the gonads. To warrant active treatment, these effects must be physically and psychologically substantial, or threaten the stature objective. Speed of change, pubertal stage, and bone age are the principal criteria [23]. With gonads operating autonomously, treatment of precocious puberty using GnRH agonists is ineffective [24]. Surgical gonadectomy, or ovarian cystectomy in females, is no longer performed, and has been supplanted by anti-steroids associated with aromatase inhibitors, which is now a reference treatment in MAS [8,24,25]. Testolactone is administered progressively to 40 mg/kg/day and anastrozole at a dose of 1 mg/day [8]. Regression of symptoms could be caused by the effectiveness of treatment or the end of the episode. Efficacy in the cohort was variable, but we cannot draw conclusions due to low statistical power, and the findings are observational.

Concerning bone disease, it is recommended to perform a bone scan for the purpose of mapping the lesions. X-rays are required for all pathological areas. The scanner is recommended for lesions of the skull and MRI for the skull base [23]. Orthopedic or surgical treatment in cases of bone involvement are necessary for preventive purposes due to threatening lesions or pathological fractures. Surgery is also indicated for a small number of patients with pain or other therapeutic failure, threatening or actual nerve compression, or unsightly deformity resulting in functional impairment [18,26]. Bisphosphonates (pamidronate 1 mg/kg/day 3 days per 6 months) have demonstrated effectiveness in pain, motor function, fracture rate and bone mineral density [23,27]. It must be associated with calcium and vitamin D supplementations.

The number of examinations related to each specialty was analyzed to elucidate the medical care experienced by patients. The frequency of examinations varied widely from one patient to another and also in the same patient depending on the progression of the disease or the need to undergo therapy. The average rate of examinations does not reflect the extreme inter-individual
variability in the frequency of examinations that can range from monthly monitoring to hospital stays of up to several months.

Among pediatric signs and symptoms, café-au-lait spots, precocious puberty and fibrous dysplasia suggest MAS [11,23,28]. Search for the GNAS mutation (bone biopsy mainly) is justified when there is strong clinical evidence for the diagnosis [23].

4.4. Disability

The concept of disability refers to a disadvantage or handicap resulting from a medical condition [29]. There is nothing in the literature about disability due to MAS, but there are links between disability, monitoring and long-term complications of the disease. While short-term complications are limited to the risks inherent in the occurrence of ovarian cysts and pathological fractures, long-term complications are more numerous and diverse. If not treated, the defect size at early puberty is estimated at 10 cm in this cohort, and facial dysmorphic disorders may be a social handicap [30]. Visual and auditory nerve compression due to cranial lesions such as fibrous dysplasia may lead to sensory disabilities [31]. Bone brittleness and deformities, limbs of unequal length and sclerosis may also lead to motor and social disabilities. Finally, the drudgery of follow-up and prolonged hospitalization during childhood can lead to educational disadvantages and emotional disability. The concept of quality of life in these patients deserves our attention.

5. Conclusion

The main interest of this study was to report 20 years of pediatric clinical experience of MAS at a regional referral medical center using a longitudinal approach, with 14 cases described for an average follow-up of 6 years. Annual examinations to pediatric endocrinology are essential to ensure the coordination of multidisciplinary care. Each visit is an opportunity to explore the development and aggravation of lesions, in the framework of minimal clinical and laboratory evaluation, to reduce the costs of care. Global disability and quality of life also deserve to be specifically studied more widely. Finally, improving the efficiency of molecular diagnosis, as well as the study of environmental and genetic factors, temporality and penetrance are important in the diagnosis and monitoring of patients.

Disclosure of interest

The authors declare that they have no competing interest.

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