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Brain and skull base MRI findings in patients with Ollier-Maffucci disease: A series of 12 patient-cases

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ABSTRACT

Objectives: To estimate the prevalence rate of silent cranial and intracranial lesions in a series of Ollier-Maffucci patients.
Patients and methods: Cerebral MRI was routinely performed in Ollier-Maffucci patients followed-up in our tertiary centers. Patients with previous history of skull base or intracranial tumors were excluded from the study. Clinical and radiological datas were retrospectively collected. The occurrence rate and nature of abnormal cerebral MRIs were determined.
Results: Twelve patients were included. A glioma-looking lesion was found in one patient (8%), while skull base lesions were evidenced in 3 others (25%). A regular MRI follow-up was recommended for each patient, with a time interval varying between 1 year and 3 years depending on the likelihood of tumoral evolutivity, as infered from the MRI findings.
Conclusion: All in all, the high rate of intracranial and skull base lesions with a malignant potential warrants to include cerebral MRI in the routine follow-up of Ollier-Maffucci patients.

1. Introduction

Ollier-Maffucci (OM) disease is an extremely rare entity, with an estimated prevalence of less than 1/100 000. It is characterized by multiple enchondromas affecting mainly the limbs, with additionnal soft tissue hemangioma in the Maffucci variant. Those patients are prone to developp other kind of tumors, including juvenile granulosa tumors, cholangiocarcinomas, pituitary adenomas, acute myeloid leukemia and gliomas. Several authors have indeed reported cases of glioma in OM patients, with an especially high occurrence rate of multicentric gliomas and brain stem gliomas (see [1] and references therein for a recent exhaustive review of the literature).

Given the increased risk of glioma and skull base chondrosarcoma in this patient's population, cerebral MRI was routinely offered to the patients followed-up for an OM disease in our institutions. We retrospectively analyzed the datas, with the aim to estimate the rate of abnormal cerebral imaging in these patients and to draw guidelines regarding the imaging follow-up.

2. Patients and methods

We retrospectively analyzed cerebral MRI findings in a series of patients followed-up for an OM disease. Inclusion criteria were: no previous history of intracranial or skull base tumor, cerebral MRI as

Abbreviations: OM, Ollier-Maffucci; AFUAS, Abnormal Findings of Unknown Aetiology and Significance; DLGG, diffuse low-grade glioma

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Table 1
Clinical and radiological datas of the 12 patients. AFUAS = Abnormal Findings of Unknown Aetiology and Significance.

	Sex	Age at MRI	Rsup Limb	Lsup Limb	Rinf Limb	Linf Limb	Maffucci	Other tumors	Glioma-looking lesion	Skull base lesion	ALUAS
1	F	13	NA	NA	NA	NA	no	NA	no	no	no
2	M	65	NA	NA	NA	NA	no	NA	no	no	no
3	M	15	−	−	+ +	+	no	no	no	no	no
4	M	20	−	+	−	+	no	no	no	no	yes
5	F	63	+	−	+	+	no	no	no	no	no
6	M	15	+	−	−	−	no	no	no	no	no
7	F	33	+ +	+ +	+ +	+ +	yes	no	yes	no	yes
8	F	53	−	+ +	−	+ +	yes	adrenal adenoma	no	yes	yes
9	F	46	+	+ +	+	+ +	no	juvenile granulosa tumor	no	no	no
10	F	28	+	−	+ +	−	no	no	no	yes	no
11	F	35	−	+	−	−	no	no	no	yes	no
12	F	34	−	−	+ +	−	no	no	no	no	yes

part of the check-up. MRI consisted in Flair, T2 and 3D-T1without any gadolinium injection. All MRI were reviewed by a senior neuroradiologist. All patients were seen in clinics by a senior neurosurgeon after MRI completion, to discuss about further management. All patients gave written informed consent to participate to this retrospective study, which was approved by the local ethics committee of Pôle Neurosciences of Lariboisière Hospital.

The level of Ollier-Maffucci disease was scored for each limb: 0 = no chondroma, 1 = few chondroma without any deformity, 2 = many chondroma and/or deformity.

Statistical analysis made use of the non-parametric Mann-Whitney-Wilcoxon test, with the presence of glioma-looking or skull base lesion as categorical variables, and the degree of severity of limbs chondroma (between 1 and 8) and age as continuous variables. The tests were implemented under Rstudio (version 1.0.143).

3. Results

Twelve patients were included in the study (4 males, 8 females). Median age at time of MRI was 33.5 years (mean 35, range 13–65). Patients had different levels of Ollier-Maffucci gravity, as summarized in Table 1. On MRI, one patient presented a lesion suggestive of a left insular low-grade glioma (see Fig. 1). Close imaging monitoring was offered to this patient, but she was eventually lost to follow-up. Skull base lesions − that were indicative of either chondroma or low-grade chondrosarcoma − were discovered in three patients (see Figs. 2–4). Additionnally, parenchymatous Abnormal Findings of Unknown Aetiology and Significance (AFUAS) were seen in three patients, including areas of white matter flair hypersignal in three patients (see Figs. 5–7) and a pattern of leucoencephalopathy in a third patient. In this latter patient, imaging follow-up at two years did not reveal any evolutivity. Although the size of this series is too small to make any definitive conclusions, the degree of Ollier-Maffucci gravity as well as age did not correlate with the presence of a glioma-looking lesion or a skull base lesion on cerebral MRI (p-value = 0.2; 1; 0.6; 1 respectively).

4. Discussion

Recent advances in glioma management converge to the conclusion that the earlier the treatment (and especially the surgery [2]), the better the survival. Up to the point that among other avenues of research, MRI screening in healthy volunteers is currently investigated [3–5]. It has been shown indeed that diffuse low-grade glioma grow silently for many years before symptoms onset [6], and it might be during this silent phase that we missed the action. In this perspective, surgical series of diffuse low-grade glioma of incidental discovery have yielded promising results, both for survival [7,8] and functional status [9,10]. Moreover, the sooner the detection, the smaller the glioma, and the higher the chances of supra-complete resection, which could be currently the only mean to potentially cure the patients [11,12]. Our findings confirm that the presumed rate of glioma in OM patients might be close to 5% (1 likely glioma out of the 12 patients in the present series, ie 8%). Taken together, these datas fully support to include cerebral MRI at regular time intervalls during the management of OM patients.

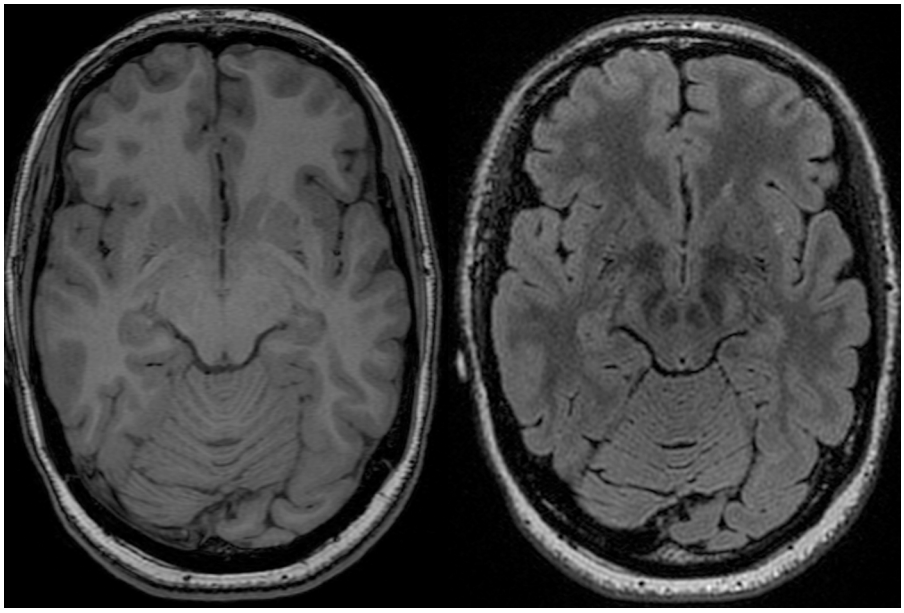

Fig. 1. MRI 3D-T1 and flair axial sequences of patient-case 6. The pattern is suggestive of a small left insular diffuse low-grade glioma.

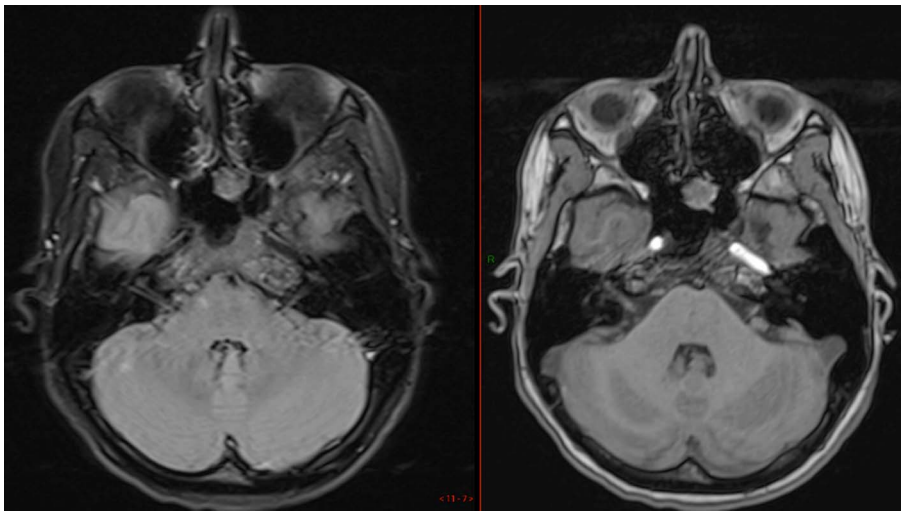

Fig. 2. Flair and T1 axial sequences of patient-case 9, showing lesions located at the left petroclival junction and at the sphenoid-nasal septum junction.

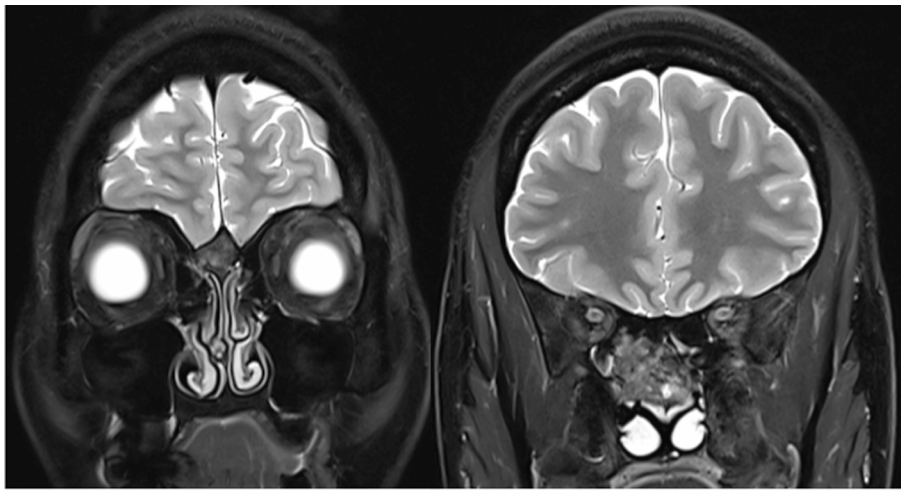

Fig. 3. T2 coronal slices of patient-case 10, evidencing lesions of the crista gali and sphenoid-nasal septum junction.

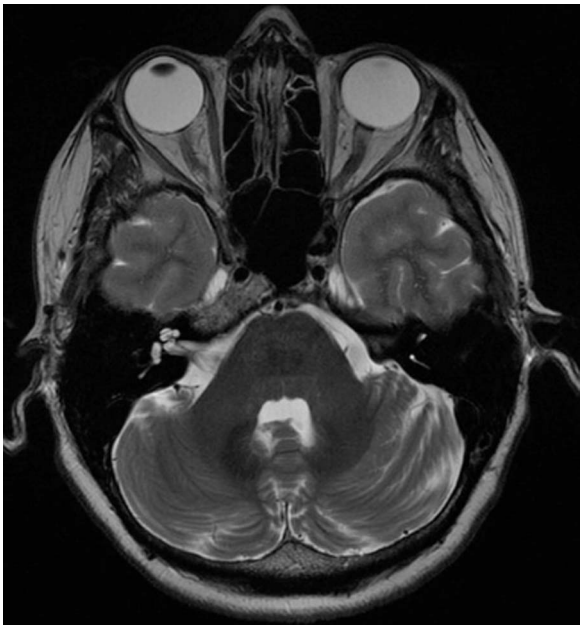

Fig. 4. T2 axial slice of patient-case 7, showing a lesion of the right petrous bone.

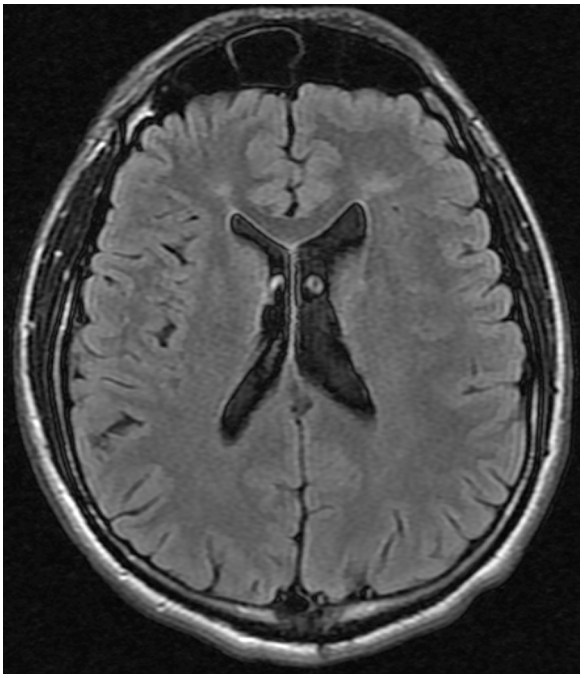

Fig. 5. Bilateral anterior periventricular flair hypersignal of patient-case 4.

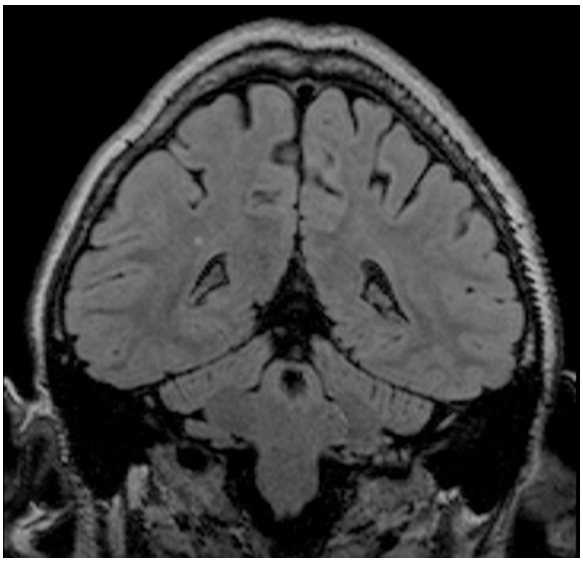

Fig. 6. Right parietal white matter hypersignal of patient-case 7.

In the present study, it was proposed to the patient with a suspected left insular DLGG to redo an MRI one year later, anticipating that an evidence of growth would have triggered surgery recommendation. Unfortunately, this patient was lost to follow-up. A two-years follow-up was recommended to patients with inconclusive MRI lesions. For young OM patients with normal MRI, we recommended to check again every 3 years. The rationale is that if the glioma has just been missed, its average size 3 years later should be about 12 mm [13], which would still be highly favorable for surgical treatment. In summary, this study also shed lights to the issues that would be encountered in the broader perspective of glioma screening in healthy volunteers [14].

Our study also revealed a high rate of skull base lesions. As no biopsy was performed, we cannot decide about the exact histopathological diagnosis of these lesions, in particular between chondroma or low-grade chondrosarcoma. Given the reported association between chondrosarcoma and OM disease, it seems appropriate to offer a radiological follow-up for these patients. Hence, a yearly monitoring was offered to the three patients with a skull base lesion.

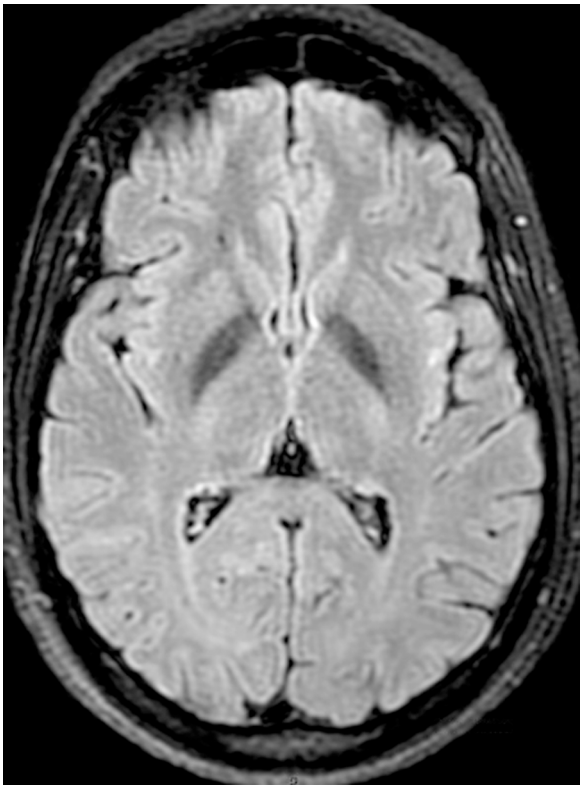

Fig. 7. Bilateral insular white matter flair hypersignals in patient-case 12.

On a pathophysiological point of view, the clinical observation of a high rate of glioma (and skull base chondrosarcoma) occurrence in OM patients has been recently biologically grounded by the discovery of the somatic IDH mosaicism in these patients. Indeed, the same IDH132 mutations (IDH132C in 65% of cases and IDH132H in 15% of cases) was systematically found in metachronous cartilaginous samples of each patient. Hence, it is believed that in about 5% of OM patients (and more frequently in those patients with the IDH132H mutation), the mosaicism, for some reason, also involves some precursors of the glial cells, constituting the seed of the gliomagenesis. However, in this hypothesis of IDH mutation mosaicism, the exact timing of the mutation onset during the embryogenesis remains to be determined, so that only cells of cartilaginous and glial tissues would be electively affected (or only cells of cartilaginous tissues and bone marrow in the case of OM patients with acute myeloid leukemia). To further support this theory, it would be very important to determine whether a small fraction of glial precursors cells also harbour the IDH mutation far from the glioma area. If yes, this would also suggest that IDH mutation by itself is a necessary but not sufficient condition to initiate gliomagenesis. It has been indeed suggested that additional events (p53 alterations and/or ATRX loss for example) are required to initiate tumor proliferation in those patients. An alternative hypothesis would be that an unknown biological mechanism occurs at an early stage of embryogenesis, that will predispose to a high risk of IDH mutation in the subsequent developpemental processes of embryogenesis. This theory would better explain the highly variable clinical patterns (both regarding endochondromatosis and the association with other tumors) in OM patients. But in this scenario, it would be more difficult to explain why it seems to be always the same IDH mutation that occurs in the different lesions of a given patient.

5. Conclusion

Our datas argue in favor of regular cerebral MRI in the follow-up of OM patients. Although abnormal findings evidenced in the present series are not necessarily tumoral, the increased risk of gliomas and skull base chondrosarcomas in this patients population fully justifies a carefull watch & wait attitude, with MRI at regular time intervals, in order to detect as early as possible any evolutivity that would trigger active treatment.

Acknowlegdments

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