A Cohort Study of CNS Tumors in Multiple Endocrine Neoplasia Type 1

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ABSTRACT

Purpose: Multiple endocrine neoplasia type 1 (MEN1) is thought to increase the risk of meningioma and ependymoma. Thus, we aimed to describe the frequency, incidence, and specific clinical and histological features of central nervous system (CNS) tumors in the MEN1 population (except pituitary tumors).

Experimental Design: The study population included patients harboring CNS tumors diagnosed with MEN1 syndrome after 1990 and followed up in the French MEN1 national cohort. The standardized incidence ratio (SIR) was calculated based on the French Gironde CNS Tumor Registry. Genomic analyses were performed on somatic DNA from seven CNS tumors, including meningiomas and ependymomas from patients with MEN1, and then on 50 sporadic meningiomas and ependymomas.

Results: A total of 29 CNS tumors were found among the 1,498 symptomatic patients (2%; incidence = 47.4/100,000 person-years; SIR = 4.5), including 12 meningiomas (0.8%; incidence = 16.2/100,000; SIR = 2.5), 8 ependymomas (0.5%; incidence = 10.8/100,000; SIR = 17.6), 5 astrocytomas (0.3%; incidence = 6.7/100,000; SIR = 5.8), and 4 schwannomas (0.3%; incidence = 5.4/100,000; SIR = 12.7). Meningiomas in patients with MEN1 were benign, mostly meningothelial, with 11 years earlier onset compared with the sporadic population and an F/M ratio of 1/1. Spinal and cranial ependymomas were mostly classified as World Health Organization grade 2. A biallelic *MEN1* inactivation was observed in 4/5 ependymomas and 1/2 meningiomas from patients with MEN1, whereas *MEN1* deletion in one allele was present in 3/41 and 0/9 sporadic meningiomas and ependymomas, respectively.

Conclusions: The incidence of each CNS tumor was higher in the MEN1 population than in the French general population. Meningiomas and ependymomas should be considered part of the MEN1 syndrome, but somatic molecular data are missing to conclude for astrocytomas and schwannomas.

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an inherited disease that predisposes carriers to primary hyperparathyroidism, duodenal–pancreatic neuroendocrine tumors (DP-NET), pituitary tumors, and adrenal, thymic, and bronchial neuroendocrine tumors (NET). MEN1 is caused by mutations on the *MEN1* gene in the heterozygous state. *MEN1* is located on chromosome 11q13 and encodes for menin (1–3).

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Translational Relevance

The increase in the incidence of pituitary tumors is now well-demonstrated in patients with multiple endocrine neoplasia type 1 (MEN1). In contrast, the association of MEN1 with other central nervous system (CNS) tumors remains uncertain. MEN1 is suspected to increase the risk of developing ependymomas and meningiomas, but data on this subject are scarce. We describe here the epidemiological analysis of 1,498 patients with MEN1 in order to decipher the frequency, incidence, and characteristics of CNS tumors in patients with MEN1 and the impact on patient survival. The study population was extracted from the French *Association Francophone de Chirurgie Endocrinienne* and *Groupe d'étude des Tumeurs Endocrines* cohort of patients with MEN1, which includes individuals diagnosed in 1990 and later. We explored the involvement of *MEN1* in the tumorigenesis of CNS tumors by performing molecular analysis on meningioma and ependymoma tissues from patients with and without MEN1.

The criteria for diagnosis were first established in Gubbio (4) and have been regularly updated since (5, 6).

MEN1 is suspected to increase the risk of ependymomas and meningiomas, but there is little literature on the subject. To our knowledge, no study so far has included a large series of primitive brain tumors in patients with MEN1. Moreover, the impact of these tumors on survival in MEN1 is unknown. Among primitive brain tumors, we retained for the present study meningiomas, ependymomas, schwannomas, and astrocytic and/or oligodendrocytic (MESA) tumors. Pituitary tumors were excluded from the present study. We first aimed to describe the main clinical epidemiological and histological features of these tumors in the MEN1 population. Second, to better understand the role of *MEN1* in the growth of such tumors, we aimed to assess *MEN1* mutations and deletions in MESA tumors from patients with MEN1 compared with those in sporadic tumors.

Materials and Methods

MEN1 cohort with and without CNS tumors

The study population was diagnosed with MEN1 syndrome and followed up in the MEN1 cohort of the *Association Francophone de Chirurgie Endocrinienne* and the *Groupe d'étude des Tumeurs Endocrines* (AFCE-GTE). The MEN1 cohort of the AFCE-GTE network has been previously described, providing different studies on pituitary adenoma, breast cancer, or DP-NET (7–12).

Briefly, the AFCE-GTE French MEN1 cohort, created in February 1991, includes 22 reference clinical centers and the genetics departments responsible for diagnosing MEN1. MEN1 cases are detected both by the network of genetics laboratories in charge of the diagnosis (TENGEN) and by the national reference centers for neuroendocrine tumors where multidisciplinary decisions are made (REseau NAtional de référence pour la prise en charge des Tumeurs neuro ENdocrines; https://www.reseau-gte.org/renaten/). Including criteria are based on international recommendations (See Supplementary Material S1 for additional information; refs. 6, 13). After receiving patients' information about the cohort, copies of clinical, surgical, and pathological reports were obtained and examined after pseudonymization by a single investigator (PG) before inclusion in the cohort. Inclusion and data collection processes followed French

legal rules (Supplementary Material). Genetic testing for *MEN1* was performed by Sanger sequencing, multiplex ligation–dependent probe amplification (MLPA) analysis, or next-generation sequencing (NGS) on leukocyte DNA from patients reviewed in one of the laboratories of the TENGEN network (14).

Data are gathered in a secure database at the Dijon Clinical Investigation Center (*Institut National de la Santé et de la Recherche Médicale*, CIC1432) and monitored regularly. Written and signed informed consent was obtained from patients following the French rules regarding observational cohorts. Explanations regarding the aims of the studies are given, i.e., best knowledge of the natural history of MEN1 disease in order to improve the quality of life. The study was conducted in accordance with the Declaration of Helsinki ethical guidelines. The MEN1 cohort was approved by the Institutional Review Board CPP Sud-Est V (2018-A0192847), the Comité Consultatif sur le Traitement de l'Information en matière de Recherche (Consultative Committee on Treatment of Information in Health Research, file number 12.364), and the national data privacy commission [*Commission Nationale de l'Informatique et des Libertés* (National Committee for Data Protection), authorization number DR 2013-348], including an authorization to contact general practitioners and patients (n°912352).

MEN1, CNS tumor diagnosis, and follow-up

The diagnostic criteria used for MEN1 conformed to the regularly updated recommendations (Supplementary Data S1; refs. 4–6) and were confirmed by genetic testing for *MEN1* (14).

Among this MEN1 cohort, all patients with diagnosed central nervous system (CNS) tumors were selected. MESA tumors were defined by neuropathological results if there had been surgical removal or biopsy of the tumor. Otherwise, the diagnosis was based on MRI observation, including typical radiological features, radiologist conclusions, clinical history, and compatible follow-up. Follow-up starts at the date of birth of the patient. The loss of follow-up rate was 44.3% for this population followed up for a median follow-up of 50 years (interquartile range = 36–63 years).

Epidemiological and clinical data collection from patients with MEN1 with and without MESA

Data were extracted from the AFCE-GTE French cohort of patients with MEN1. Clinical data included age at MESA diagnosis, age at MEN1 diagnosis, gender, clinical history, imaging conclusions, administered therapies, performed surgeries, associated tumors, follow-up duration, survival, and cause of death. The percentage of all MESA tumors and of each type of MESA tumor in the MEN1 population was also ascertained.

Brain and spine MRI examinations were not systematically performed for each patient. However, following recommendations, all patients with MEN1 undergo brain MRI follow-up for pituitary tumors. No systematic MRI central review was performed. All operated and diagnosed tumors are recorded in the data collection.

Genomic analysis on tumor tissues

Genomic analyses were performed on DNA from formalin-fixed paraffin-embedded (FFPE) MESA tumors of patients with MEN1 and sporadic MESA as previously described (Supplementary Tables S1, S2, and S3; refs. 15, 16). *MEN1* somatic mutation was analyzed by Sanger sequencing (if unsuccessful, *MEN1* sequencing was performed by NGS), somatic driver mutation by NGS, *MEN1* deletion in sporadic tumors by MLPA, and *NF2* copy number variation (CNV) by RT-qPCR (15–20).

Seven FFPE meningiomas or ependymomas were available from the MEN1 cohort. A neuropathological central review of these seven tumors was performed. The sporadic tumors included (i) 21 frozen sporadic meningothelial meningiomas (Supplementary Table S1), (ii) 20 frozen non-meningothelial meningiomas (Supplementary Table S2), and (iii) nine FFPE ependymomas (Supplementary Table S3). A neuropathological review was performed, including the assessment of tumor cell percentage.

DNA was extracted using the QIAamp DNA FFPE Tissue Kit (Qiagen, Courtaboeuf, France) for FFPE tissues or using the QIAamp DNA Mini Kit (Qiagen).

For tumors from patients with MEN1, loss of heterozygosity was assessed by Sanger sequencing targeting the exon carrying each MEN1-mutated patient's mutation [MEN1 (NM_130799) primers are available on request]. If unsuccessful, MEN1 sequencing was performed by NGS using a custom QIAseq Targeted DNA panel (Qiagen) on the MiSeqDx system (Illumina; ref. 15).

In parallel, a somatic driver mutation was sought in 10 of the most frequent genes in meningioma tumorigenesis, NF2, AKT1, TRAF7, PIK3CA, KLF4, SMO, SMARCB1, TERT, and CDKN2A/B (20), and added to SUFU and SMARCE1, and in PTEN, which is suspected to predispose to meningioma through Cowden syndrome, as previously described (14). Sequencing of POLR2A, BAP1, and PIK3R1 was not available in this study (17–19).

Sporadic frozen tumors were analyzed (i) for MEN1 somatic mutation by Sanger sequencing, (ii) for MEN1 deletion by MLPA using the P244 MLPA Probe Mix (MRC-Holland), (iii) for a somatic driver mutation by NGS, as described above, and (iv) for CNV of NF2 by RT-qPCR using the HS00918833-CN TaqMan® Copy Number Assays (Roche) on a Viia 7 system (Applied Biosystems; ref. 14). Sporadic FFPE ependymomas were analyzed by NGS for MEN1 and NF2 mutations and CNV as described above. CNV analysis was performed using the Copy Number Variant Detection tool of the CLC Genomics Workbench v20 software (Qiagen).

Statistical analysis

Descriptive results are expressed as percentages for qualitative variables and as means or medians (with SDs or IQRs) for continuous variables according to their distribution. Statistical analyses were performed using Prism v6.0 (GraphPad software). Patient characteristics were compared using the two-tailed Fisher exact test for qualitative variables and the non-paired non-parametric Mann–Whitney test for quantitative values. For all analyses, a P value below 0.05 was considered significant.

Methods used for the calculation of incidence rates

We estimated the incidence rate of CNS tumors (overall and separately according to each type of tumor) in male and female patients with MEN1 by dividing the number of MESA tumors in this population by the number of person-years at risk. This number corresponds to the sum of the number of years that each patient included in the cohort was exposed to that risk, i.e., from the date of birth to the onset of a CNS tumor for patients experiencing this type of tumor or to death or the last follow-up otherwise. This incidence was calculated for the entire MEN1 cohort also by gender and by 5-year age group, with their 95% confidence intervals (95% CI), per 100,000 persons. The population was divided into 18 age groups of 5 years each, from 0 to more than 85 years. In order to allow comparison with other populations, we standardized the incidence rates on gender and age using the European population as the reference (Waterhouse and colleagues, 1976) by multiplying the age-

specific incidence rates estimated in our cohort by the number of persons in each gender and age group of the standard population.

We also estimated the standardized incidence ratio (SIR) using the indirect standardization method. The SIR of CNS tumors in patients with MEN1 was thus calculated as the ratio between the number of observed cases of CNS tumors in the MEN1 cohort and its expected number given the incidence by the same gender and age group in the general population. We used the incidence rates extracted from the French Gironde CNS Tumor Registry from the period 2015 to 2019. All the calculations were made using STATA/IC 15.1 software using the commands "stptime" and "strate, smr()."

Data availability

The data will be made available upon reasonable request. Request for access to data extracted from the French MEN1 cohort database could be directed to the data collection manager, Dr Pierre Goudet (pierre.goudet@u-bourgogne.fr). Data from the Gironde CNS Tumor Registry could be accessible via the dedicated website https://sites.bph.u-bordeaux.fr/REGISTRES-CANCERS-AQUITAINE/Snc/S_Accueil.aspx.

About molecular data, only targeted sequencing at the constitutional or somatic level was performed in this study. All variants found on somatic DNA are reported in Supplementary Tables S1, S2, and S3. All variants found on germline DNA are reported in **Tables 4** and **5**.

Results

From February 1991 to January 2021, the GTE MEN1 cohort included 1,498 symptomatic patients. A total of 29 CNS tumors were found (2%). There were 12 meningiomas (0.8%), 8 ependymomas (0.5%), 5 astrocytic and/or oligodendrocytic tumors (0.3%), and 4 schwannomas including 2 vestibular schwannomas (0.3%).

In the present study, the standardized incidence rate (SIR) of CNS tumors was at 47.4 per 100,000 person-years (56 per 100,000 person-years for males and 42.8 per 100,000 person-years for females; **Table 1**). The standardized incidence rate for meningiomas, ependymomas, schwannomas, and astrocytomas was at 18.9, 20.9, 6.9, and 8 per 100,000 person-years, respectively. The SIR for CNS tumors in the present MEN1 population was at 4.5 (3.2–6.5; **Table 1**).

The presence of CNS tumors in patients with MEN1 was significantly correlated with the presence of adrenal NET (51.7% of patients with MESA vs. 27.2% of patients without MESA; $P < 0.01$; **Table 2**). Meningiomas were mainly associated with adrenal NET: 8/12 patients with MEN1 with meningiomas harbored an adrenal NET ($P = 0.001$ vs. the whole series), whereas 3/8 patients with MEN1 with ependymomas, 3/5 patients with MEN1 with astrocytomas, 2/4 patients with MEN1 with schwannomas, and 363/1408 patients with MEN1 from the AFCE-GTE MEN1 cohort harbored an adrenal NET.

In the present series, meningiomas were also associated with pituitary adenomas: 75% (9/12) of patients with MEN1 with meningiomas harbored pituitary adenomas versus 36.7% of patients with MEN1 from the AFCE-GTE MEN1 cohort (202/551; $P = 0.008$; ref. 7). In contrast, ependymomas tend to be less frequent in patients with MEN1 with pituitary adenomas: 25% (2/8) of patients with MEN1 with ependymomas harbored pituitary adenomas ($P = 0.06$ vs. patients from the AFCE-GTE MEN1 cohort; ref. 7).

The subtypes of associated pituitary adenomas were various, including prolactinomas, growth hormone–secreting adenomas, ACTHomas, and nonfunctioning pituitary adenomas. No other significant association was observed between the different tumors

Table 1. Crude and European SIRs for CNS tumors (except pituitary tumors) from the present MEN1 cohort and from the French Gironde CNS Tumor Registry (extracted data from 2015 to 2019) used for the calculation of the standardized incidence ratio for CNS tumors (except pituitary tumors) in the present MEN1 cohort. Incidence rates are expressed per 100,000 person-years.

		MEN1 Cohort: incidence rates		French Gironde CNS Tumor Registry: incidence rates (2015–2019)				
Tumors	Gender	Crude (95%CI)	European standardization (95% CI)	Crude	European standardization	Observed patient number	Expected patient number	SIR (95% CI)
CNS tumors	All patients	39.1 (27.2–56.3)	47.4 (28.9–65.8)	16.3	11.7	29	6.4	4.5 (3.2–6.5)
	Male	40.7 (23.6–70.1)	56.0 (22.1–89.9)	8.5	6.4	13	1.4	9.5 (5.5–16.4)
	Female	37.9 (23.2–61.9)	42.8 (20.8–64.7)	23.8	13.8	16	5.0	3.2 (2.0–5.2)
Meningiomas	All patients	16.2 (9.2–28.5)	18.9 (7.7–30.1)	13.3	9.1	12	4.8	2.5 (1.4–4.5)
	Male	18.8 (8.4–41.8)	23.1 (3.2–43.1)	5.6	3.4	6	0.5	11.8 (5.3–26.4)
	Female	14.2 (6.4–31.7)	16.2 (2.9–29.5)	20.8	14.4	6	4.2	1.4 (0.6–3.1)
Ependymomas	All patients	10.8 (5.4–21.6)	13.6 (3.2–23.9)	0.6	0.6	8	0.5	17.6 (8.8–35.1)
	Male	12.5 (4.7–33.4)	20.9 (0–44.2)	0.5	0.7	4	0.2	19.1 (7.2–51)
	Female	9.5 (3.6–26.3)	9.7 (0–19.6)	0.7	0.5	4	0.3	16.2 (6.1–43.3)
Astrocytomas and oligodendrocytic tumors	All patients	6.8 (2.8–16.2)	8.0 (0.4–15.5)	1.1	1.2	5	0.9	5.8 (2.4–13.9)
	Male	3.1 (0.4–22.2)	3.3 (0–9.8)	1.5	1.8	1	0.6	1.7 (0.2–12)
	Female	9.5 (3.6–25.2)	11.1 (0–22.8)	0.7	0.7	4	0.3	14.8 (5.6–39.5)
Schwannomas	All patients	5.4 (2.0–14.4)	6.9 (0–14.1)	1.3	0.8	4	0.3	12.7 (4.8–33.9)
	Male	6.3 (1.6–25)	8.6 (0–21.5)	0.8	0.4	2	0.1	35.3 (8.8–141)
	Female	4.7 (1.2–19)	5.7 (0–14.1)	1.8	1.1	2	0.3	7.7 (1.9–31)

observed in patients with MEN1 and CNS tumors or MESA tumors individually (**Tables 2** and **3**). No association was observed between the type of mutation and MESA tumors, and there was no intra-familial association.

Tumor features

Tumor features are summarized in **Table 3**. Half of the patients with meningioma (6/12) were operated on. Neuropathology conclusions were not available for one old case. Non-operated cases were asymptomatic, stable, and/or with limited size. Meningiomas were exclusively intracranial but with various locations. The female/male ratio was 1/1. The standardized incidence rate for meningioma was 23.1 per 100,000 person-years for males and 16.2 per 100,000 person-years for females (**Table 1**). The age-adjusted SIR was 11.8 for males and 1.4 for females and was particularly high for young population of ages 15 to 24 years (**Table 1**). The mean time between MEN1 and meningioma diagnosis was 7.4 years (3 years

before to 22 years after MEN1 diagnosis). Neuropathological results confirmed a meningothelial subtype in 4/5 operated cases, including one case with a World Health Organization (WHO) grade 2 meningothelial atypical meningioma (Ki 5%–6%). In the remaining non-meningothelial case, the meningioma was transitional atypical WHO grade 2 with a low mitotic index. Meningioma was never a cause of death in the cohort. The mean follow-up time from meningioma diagnosis was 10.8 years.

All ependymomas ($n = 8$) but one were operated on. Two were intracranial: one in the pineal location (21) and the other frontal intraventricular anaplastic (**Table 3**). Six of the seven operated ependymomas were classified as WHO grade 2 with two papillary subtypes. The remaining non-operated ependymoma presented typical features on MRI and was non-symptomatic and nongrowing. The female/male ratio was 1/1. The age-adjusted SIR for ependymomas was 17.6 (**Table 1**). One patient was operated for a frontal intraventricular anaplastic ependymoma and then treated by

Table 2. MESA patient characteristics and comparison with non-MESA patients from the MEN1 cohort.

$N = 1,498$	Available for computation	With CNS tumor ($N = 29$)	Without CNS tumor ($N = 1,469$)	P-value
Age at MEN1 diagnosis	1,361	40.4 years (35.2–45.7)	38.1 years (38.2–40.0)	0.3
Hyperparathyroidism	1,403	27/29 (93.1%)	1,252/1,374 (91.1%)	0.7
Sex, male/female	1,437	13/29 (44.8%)	612/1,408 (43.5%)	1
Bronchial NET	1,361	2/29 (6.9%)	83/1,332 (6.2%)	0.9
Thymic NET	1,360	1/29 (3.4%)	55/1,331 (4.1%)	0.8
Duodeno-pancreatic NET	1,373	24/29 (86.2%)	972/1,344 (72.3%)	0.1
Zollinger–Ellison	1,397	9/29 (31.0%)	328/1,368 (23.9%)	0.4
Pituitary NET	1,369	17/29 (58.6%)	585/1,340 (43.7%)	0.1
Adrenal NET	1,362	15/29 (51.7%)	363/1,333 (27.2%)	<0.01
Deaths	1,437	11/29 (37.9%)	293/1,408 (20.8%)	0.04
Probability of life at 70 years	1,374	15.4% (95% CI, 1.0–47.0)	42.5% (95% CI, 36.7–48.2)	0.04

Table 3. Clinical and histological features of patients with MEN1 with CNS tumors.

MEN1 patient	Gender	Age at MESA diagnosis (years)	Age at MEN1 diagnosis (years)	Location	Surgery	WHO grade	Subtype	Ki 67	Pituitary adenoma	Adrenal NET
Meningiomas										
1	F	32	28	Suprasellar	Yes	1	Meningothelial	NA	No	Yes
2	F	50	38	Frontal	No				Yes	No
3	M	45	39	Parasagittal	No				Yes	No
4	M	34	34	Parasagittal	Yes	2	Atypical transitional	NA	Yes	Yes
5	F	40	34	Parasagittal	No				No	Yes
6	M	48	34	Temporo-occipital	Yes	1	Meningothelial	NA	Yes	Yes
7	F	27	29	Cerebellopontine angle	Yes		NA		Yes	Yes
8	M	60	40	Parasagittal	Yes	2	Atypical meningothelial	5%	No	Yes
9	M	62	59	Frontal	Yes	1	Meningothelial	NA	Yes	No
10	M	42	20	Frontal	No				Yes	No
11	F	49	49	Occipital	No				Yes	Yes
12	F	51	33	Occipital	No				Yes	Yes
Median		46	35							
Mean		45	37							
Ependymomas										
13	M	61	68	C6-C7	Yes	2		7%	No	No
14	M	71	35	T5	No				Yes	No
15	M	38	37	T5-T6	Yes	2		1%	No	Yes
16	F	52	56	C1-T1	Yes	2	Papillary	NA	No	Yes
17	F	44	38	Pineal	Yes	2		NA	No	Yes
18	F	29	21	T7-T10	Yes	2	Papillary	NA	Yes	No
19	M	37	16	T6-T9	Yes	2		2%	No	No
		29		Frontal intraventricular	Yes	3		30%	No	No
20	F	29	20	C7-T1	Yes	2		2%	No	No
Median		38	36							
Mean		43	48							
Astrocytic and oligodendroglial tumors										
21	F	9	18	T8-T9	Yes	NA			Yes	No
22	F	30	33	Intraventricular	Yes	1	Astrocytoma		Yes	No
23	M	44	40	Supratentorial	Yes	2 then 4	Astrocytoma then Glioblastoma at 7 years		No	Yes
24	F	47	36	Supratentorial	Yes	3	Oligoastrocytoma deletion 1p19q		Yes	Yes
25	F	66	50	Supratentorial	No				No	Yes
Median		44	50							
Mean		39	36							
Schwannomas										
26	M	64	62	Vestibular	Yes				No	Yes
27	M	33	32	Vestibular	No				Yes	No
28	F	20	56	Lumbar	Yes				Yes	No
29	F	60	37	Lumbar	No				Yes	Yes
Median		47	47							
Mean		47	47							

complementary radiation therapy and for a spinal ependymoma 8 years later. The mean time between MEN1 and ependymoma diagnosis was 8 years (from 8 years before to 35 years after MEN1 diagnosis). The mean follow-up time from ependymoma diagnosis was 8 years (1–24 years). One patient died from the tumor (21).

All but one of the five cases of low-grade gliomas were operated on. One was dorsal intramedullary, and histological conclusions were non-contributive for this case. One was a WHO grade 1 astrocytoma with an intraventricular location. The patient died 1 month after surgery because of brain hematoma. One was a WHO grade 2 astrocytoma with WHO grade 4 transformation 7 years later. One was a WHO grade 2 oligoastrocytoma with WHO grade 3 transformation 20 years later with 1p-19q codeletion. These two cases were classified following the 2007 WHO classification, and no tumor material was available for review or genomic analysis. Three of five patients died because of the tumor malignancy or in the postoperative period. The non-operated patient presented typical MRI features with temporal T2-weighted hypersignal without radiological progression during the first 3 years of follow-up. The mean time between MEN1 and astrocytoma diagnoses was 13 years (−9 to 16 years). The mean follow-up time from astrocytoma diagnosis was 13 years (3–25 years). The age-adjusted SIR of astrocytomas and oligodendrocytic tumors was 5.8 (**Table 1**).

Schwannomas were operated on in 2/4 cases. On imaging, two were vestibular and two were spinal. No specific features were noted. The female/male ratio was 1/1. The mean time between MEN1 and schwannoma diagnosis was −3 years (from −36 years before to 22 years after MEN1 diagnosis). The mean follow-up time from schwannoma diagnosis was 14 years (0–46 years). None of the patients died because of a schwannoma. The age-adjusted SIR of Schwannoma was 12.7 (**Table 1**).

Survival analysis

Of the 29 patients with MEN1 harboring CNS tumors, 11 died (37.9%). Four deaths were related to CNS tumors: two patients died because of malignant transformation of an astrocytoma, one patient because of an aggressive ependymoma, and one patient following surgery for an astrocytoma (**Table 2**).

Somatic molecular analysis

Among the 29 patients with MEN1 harboring CNS tumors, FFPE tissue was available for DNA analysis in seven cases: two meningiomas and five ependymomas (**Table 4**). A MEN1 loss of heterozygosity was observed in the DNA from 1/2 meningiomas and 3/5 ependymomas, reflecting the loss of the wild-type allele, as a second somatic MEN1 mutation was found in another ependymoma (**Table 4**; Supplementary Fig. S1). Overall a MEN1 biallelic inactivation was not found in only two tumors: one meningioma for which the loss of the MEN1 wild-type allele was not observed and one ependymoma for which a loss of the MEN1-mutated allele was observed. The quantity of somatic DNA from four tumors (#4, #8, #15, and #16) was sufficient to search for somatic mutations in the 13 genes that are considered drivers in meningioma, including the NF2 gene. For patient #4, bearing an atypical transitional meningioma without MEN1 biallelic inactivation, we observed a somatic NF2 pathogenic variant c.905_916delinsA, p.(Gly302AspfsTer26) associated with a loss of the NF2 wild-type allele. For patient #8, bearing an atypical meningothelial meningioma with a biallelic MEN1 inactivation, we found a PIK3CA pathogenic variant c.1090 G>A, p.(Gly364Arg) at 25% allelic frequency (**Table 4**). This variant has already been described (22). Finally, for patient #15, bearing an ependymoma with a biallelic MEN1 inactivation, we identified a loss of the NF2 wild-type allele.

Because the majority of meningiomas in patients with MEN1 were meningothelial, genomic MEN1 status was analyzed in a series of 21 randomly selected sporadic meningothelial meningiomas (Supplementary Table S1). No MEN1 mutation was detected by Sanger sequencing, but a heterozygous loss of 11q13.1-11q13.2 was seen by MLPA in 2 of the 21 (9.5%) tumors (patients #SM16 and #SM21). Of the 21 tumors, 71% (15/21) harbored a somatic driver mutation in one of the 13 genes (Supplementary Table S1). The chr11q13 deletion observed in the two tumors was associated with a NF2 biallelic inactivation in one tumor (#SM21), but no somatic driver mutation was identified in the other (#SM16; **Table 5**). Then, the frequency of ch11q13 deletion in this series of 21 meningothelial tumors was compared with that in a series of 20 non-meningothelial tumors (Supplementary Table S2). The chr11q13 deletion was observed in only 1/20 (5%) non-meningothelial meningiomas (#SM30; **Table 5**; Supplementary Table S2).

Finally, considering the high proportion of ependymomas in patients with MEN1, the genomic profile, specifically MEN1, was also analyzed in a series of nine sporadic ependymomas. These tumors were randomly selected according to their clinical and histological characteristics, which were similar to those of ependymomas from patients with MEN1 (WHO grade 2, located in the spine or posterior fossa). No MEN1 mutation or deletion was found in these sporadic tumors (Supplementary Table S3).

Discussion

First large study on this topic

The MEN1 ACFE/GTE cohort is one of the largest cohorts of patients with MEN1, which makes obtaining strong epidemiological data possible. Many studies were already performed based on this cohort by analyzing pituitary adenomas, breast cancer, or DP-NETs (12, 23, 24). We therefore attempted to compare the frequency and incidence of CNS tumors in the MEN1 population versus the general population.

CNS Tumors

The standardized incidence rate of CNS tumors was more than 2-fold higher in the MEN1 population than in the French and US populations without including pituitary tumors (**Table 1**; refs. 25, 26). This is confirmed by a SIR also highly elevated at 4.5 (3.2–6.5) for the MEN1 population versus the French general population (**Table 1**).

Meningiomas

Large CNS tumor registries are rare and few of them have been collecting data relative to benign tumors for a long period of time (27, 28). Moreover, meningiomas may be asymptomatic for extended periods, or may never be diagnosed, and it is important to note that the incidence rate for meningiomas increases with age (29).

In the present study, meningioma incidence in the MEN1 population was at 16.2 per 100,000 person-years (8.2–28.5). In the general population of Gironde (a French department), meningioma incidence was measured at 6.8, and in the Central Brain Tumor Registry of the United States (CBTRUS) it was measured at 9.5 per 100,000 person-years (**Table 1**; refs. 26, 28). The SIR was calculated at 2.5 (1.4–4.4) and was particularly high for men [11.8 (5.3–26.4)] and for young patients (15–24 and 25–64 years; **Table 1**). Meningioma frequency in the present study was at 0.85%. Previous population-based studies indicated that the estimated general population prevalence of meningioma was around 50 to 55 per 100,000 person-years (30, 31). In 2010, based on the CBTRUS, Porter and colleagues published an estimated prevalence rate of 70.7 per 100,000 person-years (0.07%), with an incidence rate for meningioma at 6.0 (95% CI, 5.8–6.1) per 100,000 person-years, and a 10-year survival rate at 0.64 (95% CI, 0.6–0.7) for nonmalignant meningiomas (nonmalignant meningiomas represent around 97% of all meningiomas; ref. 32).

In addition to registries, population-based neuroimaging studies have been performed (33–36). The meta-analysis performed by Morris and colleagues (37) concluded that the prevalence of meningioma was 0.29% (95% CI, 0.13–0.51). Vernooij and colleagues (35) performed brain MRI in 2,000 asymptomatic people from the general population. The percentage of meningioma was 0.9%. However, the mean age of the population was 63.3 years (range, 45–97 years), and for people aged 45 to 59 years, the prevalence rate was only 0.5%.

In the prospective study conducted by Asgharian and colleagues (38), meningioma prevalence in 74 patients with MEN1 (with suspected or proven pancreatic NET) reached 8%, which is considerably higher than that in our series. The control population included

Table 4. Neuropathological and molecular features of the two meningiomas and five ependymomas from patients with MEN1 for which somatic DNA was available.

Patient number	Gender	Age at diagnosis (years)	Tumor	WHO grade	Location	Germline MEN1 mutation	Percentage of tumoral cells	MEN1 LOH	NF2 alteration
4	M	34	Atypical transitional meningioma	2	Parasagittal	c.252_253delTAinsG, p.(Ile85SerfsTer3)	80%	No	c.905_916delinsA p. (Gly302AspfsTer26), gene deletion
8	M	60	Atypical meningothelial meningioma	2	Parasagittal	c.1037_1038delCT, p.(Thr346SerfsTer20)	100%	Yes, loss of the wild-type allele	No[b]
13	M	61	Ependymoma	2	Spine	c.1628C>G, p.(Ser543Ter)	NA	Yes, loss of the wild-type allele	NA
15	M	38	Ependymoma	2	Spine	c.249_252delGTCT, p.(Ile85SerfsTer33)	100%	Yes, loss of the wild-type allele	NA
16	F	52	Papillary ependymoma	2	Spine	c.515A>T, p.(Asp172Val)	100%	Yes, loss of the wild-type allele	NO
17	F	44	Ependymoma	2	Pineal	c.1259T>A, p.(Ile420Asn)	NA	Yes, loss of the mutated allele	No
19	H	37	Ependymoma	2	Spine	c.1330del, p.(Leu444)[a]	NA	No,[a] second hit c.784-9G>A	NA

Abbreviation: LOH, loss of heterozygosity.
[a]Loss of the mutated allele and somatic MEN1 mutation.
[b]PIK3CA pathogenic variant c.1090 G>A, p.(Gly364Arg).

185 patients with sporadic Zollinger–Ellison syndrome. All patients had received serial brain imaging studies during follow-up. Only one patient developed a meningioma in the control population versus six among patients with MEN1. The six meningiomas were asymptomatic; one was operated on. Therefore, the rate of meningiomas operated on was 16.6% (1/6) in Asgharian and colleagues (38) versus 50% (6/12) in the present study. The difference in the prevalence of meningiomas could potentially be explained by the lack of serial brain imaging studies and central MRI review in the 1,498 patients from the present study because of the low CT-scan and brain MRI quality for the first patients included in the 1990s in the French cohort database. In conclusion, the difference in meningioma prevalence and incidence between the MEN1 population and the general population remains difficult to accurately assess, but all relevant studies on the subject strongly suggest a higher rate of meningiomas in symptomatic patients with MEN1.

In our cohort, 6/12 patients were young (ages ≤45 years), and the median age at diagnosis was 46 years versus 57 years, 56, and 66 years, respectively, in the French Gironde, the French operated on, and the US meningioma populations (27, 29, 39, 40). The meningioma male to female ratio was at 1/1 with similar incidence rates between males and females, which is different from the sporadic meningioma population (M/F ratio at 1/2 or 1/3; refs. 26, 28). We also found that most MEN1 meningiomas were meningothelial subtypes with benign features (mostly non-symptomatic and non-operated, with a low Ki67 proliferation index). In accordance with the results of Asgharian and colleagues, the locations were varied, including the skull base, convexity, and posterior fossa, suggesting the lack of a specific mutational pattern (38). In the present series, meningiomas were significantly and positively associated with pituitary adenomas and adrenal NETs, in contrast to ependymomas. We do not have obvious explanation. More frequent pituitary imaging in patients with pituitary tumor could be suggested, but all patients with MEN1 should have pituitary imaging every three years as meningiomas are slow-growing tumors. Moreover, this

association was not observed with ependymomas. Interestingly, the association of sporadic meningiomas and sporadic pituitary adenomas remains largely suggested and debated, and the relationship is unclear (41–47). For adrenal tumors, patients with MEN1 with CNS tumors do not have obvious reasons to undergo more abdominal imaging than patients with MEN1 without CNS tumors.

MEN1 is a tumor suppressor gene that requires a second hit at the somatic level to induce tumor. The most frequent somatic event is the loss of the remaining wild-type allele due to chromosome 11q13 deletion. To distinguish whether these MESA tumors were sporadic tumors or arising as a part of the MEN1 syndrome, MEN1 deletion was analyzed in tumor DNA. Unfortunately, somatic DNA was available for only the two WHO grade 2 meningiomas, which were not so representative of the series. Nevertheless, MEN1 biallelic inactivation without NF2 alteration was observed in the meningothelial meningioma (#8). The allelic frequency of the PIK3C1 mutation, also present in this tumor, was only at 25%, suggesting a second event in tumorigenesis. In contrast, the transitional meningioma (#4) did not present MEN1 deletion but harbored a NF2 biallelic inactivation. These data are in agreement with the literature, showing that NF2 is frequently mutated in transitional meningiomas and rarely in meningothelial meningiomas (18, 48). Overall, tumorigenesis seems to be related to NF2 alterations in the transitional meningioma (#4) and to MEN1 in the meningothelial meningioma, which should be considered a MEN1 lesion (#8).

To better understand the relationship between the MEN1 gene and meningiomas, and considering that the majority of meningiomas from patients with MEN1 are meningothelial, we assessed the MEN1 alterations in sporadic meningothelial meningiomas in comparison with that in sporadic non-meningothelial meningiomas. Whereas no somatic MEN1 mutation was identified, a chr11q13 deletion was observed in 9.5% (2/21, #SM16 and #SM21) of meningothelial tumors. In non-meningothelial tumors, this percentage reached 5% (1/20, #SM30). Bi and colleagues identified chr11 deletion in approximately 10% of meningiomas and more

Table 5. Neuropathological and molecular features of sporadic meningiomas harboring *MEN1* LOH.

Patient	Gender	Age (years)	WHO grade	Subtype	Location	Necrosis	Ki 67	Mitosis	Somatic mutation	Mutated gene	Mutation	Mutated allele frequency	MEN1 sequencing	MEN1 LOH
SM 16	M	43	1	Meningothelial	Posterior fossa	No	7%	1 per 10	No	No	—		Wild type	Yes
SM 21	F	77	2	Meningothelial	Frontal (multiple meningiomas)	Yes	12%	2 per 10	yes	NF2	c.1021C>T, p.(Arg341Ter) + del NF2	44%	Wild type	Yes
SM 30	F	74	1	Fibroblastic	Temporal fossa	No	3%	No	Yes	NF2	c.666delT, p.(Phe222LeufsTer29) and mosaic NF2 deletion	42%	NA	Yes

frequently in high-grade meningiomas (18, 48). The involvement of chr11q13 deletion was unlikely in the sporadic meningothelial and non-meningothelial tumors (#SM21 and #SM30) because they harbored a *NF2* biallelic inactivation. However, chr11q13 involvement could be suspected in the meningothelial tumor (#SM16) without other genomic alterations as observed in approximately 25% of meningiomas (49). Therefore, the involvement of MEN1 mutation in sporadic meningiomas remains particularly uncertain.

Ependymomas

Ependymomas are a relatively rare type of glial tumor that constitutes approximately 2% of all primary CNS tumors with an incidence rate of 0.4/100,000 person-years in the United States and in France (25, 26). In the present study, ependymoma incidence in the MEN1 population reached 10.8 (95% CI, 5.4–21.6)/100,000 person-years with a frequency of 0.5% (8/1,498) with spinal or cranial locations (**Table 1**). These tumors, which include different subtypes, affect all age groups, and approximately half are located in the spinal cord. In the United States, the 10-year relative survival rate and the prevalence rate for all subtypes and all locations are 78.6% (95% CI, 76.3–80.6) and 4.1 (95% CI, 4.0–4.2)/100,000 person-years (≈0.004%), respectively (50). In the population-based neuro-imaging study by Vernooij and colleagues (35), only one case of ependymoma was observed among the 2,000 recruited patients with brain but not spine MRI (0.05%). In patients with MEN1, only a few isolated cases of ependymomas have been reported in the literature (21, 51–54). The median age at diagnosis was 38 years in the present cohort versus 45 years in the US general population and 42 years in the French operated-on population (25, 27). In conclusion, we show, for the first time, that the prevalence and incidence of ependymomas are increased in patients with MEN1.

In the five tested ependymomas from patients with MEN1, a somatic biallelic gene inactivation was observed in four tumors, three through a *MEN1* deletion and one through a second somatic *MEN1* mutation. Cuevas-Ocampo and colleagues also observed a somatic *MEN1* deletion in an ependymoma from a patient with MEN1 (51). Moreover, ependymoma prevalence in our MEN1 population is considerably higher than that in the general population. Overall, all these elements suggest that ependymomas should be considered part of the MEN1 syndrome.

The ependymomas in our cohort, which were mostly WHO grade 2, were from different subtypes and locations. Only the two intracranial tumors, one pineal case (#17; ref. 21) with a benign neuropathological pattern and one intraventricular case (#19), presented an aggressive course.

To better understand the relationship between the *MEN1* gene and ependymomas, regardless of the MEN1 syndrome, we assessed *MEN1* deletion and mutation in a series of nine sporadic WHO grade 2 ependymomas. No somatic *MEN1* alteration was observed. This lack of *MEN1* deletion was in agreement with the literature showing that the 11q deletion is exceptional in ependymomas (55).

Astrocytic and/or oligodendrocytic tumors

Among the 1,498 patients with MEN1, our study included one WHO grade 1 astrocytoma and four diffuse low-grade gliomas (0.3%) at the time of diagnosis. Recently, a xanthoastrocytoma was reported in a patient with MEN1 (56).

The incidence and prevalence of diffuse low-grade gliomas are estimated at 1/100,000 person-years and 10/100,000 persons (0.01%), respectively (26, 39, 57, 58). On the other hand, a meta-analysis of brain MRI studies in the healthy population showed a

prevalence of 0.05% (37). The incidence rate of low-grade glioma was at 6.8/100,000 person-years (95% CI, 2.8–16.2) in the present series (**Table 1**). At diagnosis, no malignant glioma was reported in the present series, but two low-grade gliomas presented a malignant transformation. In the French Gironde CNS Tumor Registry and in the CBTRUS, the incidence of low-grade astrocytic and oligodendrocytic tumors was, respectively, at 0.8 and 1.13/100,000 person-years, and the incidence of all astrocytic and oligodendrocytic tumors (including low- and high-grade tumors) was, respectively, at 6.78 and 4.94/100,000 person-years (26). The median age at tumor diagnosis was 44 years in the present cohort versus 62 years in the US general population and 58 years in the French operated-on population (25, 27). Therefore, the incidence for low-grade astrocytic and oligodendrocytic tumors was higher in the MEN1 population than in the general population.

Schwannomas

In the present study, schwannoma incidence was at 5.4 (95% CI, 2.0–14.4)/100,000 person-years versus 2.33 in the French Gironde CNS Tumor Registry (**Table 1**; ref. 28) In the United States, the incidence of nerve sheath tumors is 2.0 (95% CI, 1.99–2.03)/100,000 person-years (26). The prevalence of incidental vestibular schwannoma in studies of temporal bones at autopsy varied from 0% to 2.4% (59). Similarly, the prevalence of incidental vestibular schwannomas in population-based neuroimaging studies varied from 0.02% to 0.2% (35, 36, 60, 61). In the present study, we identified 4/1,498 cases (0.3%) of schwannoma, including two vestibular schwannomas (0.15%). Therefore, the incidence and frequency of nerve sheath tumors seem to be higher in patients with MEN1 than in the general population, although the number of reported cases remains low (62, 63). The age-adjusted SIR was at 12.7 (4.8–33.9; **Table 1**). The median age at tumor diagnosis was 46 years in the present cohort versus 55 years in the US general population and 52 years in the French operated-on population (25, 27).

The role of MEN1 in CNS tumor tumorigenesis

The molecular relationship between CNS tumors and *MEN1* alterations remains unclear. A cell autonomous effect induced by *MEN1* double hits is present in a minority of CNS tumors of patients with MEN1. Based on the accurate epidemiological data presented here, we cannot argue a simple co-occurrence of tumors. Moreover, the sexual dimorphism, obvious in sporadic meningiomas with a predominance of females (2:1), disappears for meningiomas in patients with MEN1, suggesting other tumorigenesis pathways. Moreover, the lack of *MEN1* mutation at the somatic level in sporadic tumors, not only in CNS as meningiomas or ependymomas but also in pituitary adenomas, raises questions about the oncogenic mechanisms of *MEN1*.

The hypothesis could be the existence of non-cell autonomous effects that promote CNS tumor tumorigenesis. In other words, the deregulation of CNS tumor proliferation may depend on the paracrine activity of surrounding cells induced by *MEN1* alterations. Numerous data clearly demonstrated the role of the microenvironment in tumorigenesis as meningeal immunity cells (64); however, experimental works are required to support this hypothesis.

CNS tumors and survival

Whether CNS tumors impact the survival of patients with MEN1 is also an important issue. The mortality rate was significantly higher in patients with MEN1 harboring CNS tumors than in patients with MEN1 without CNS tumors, mainly because of poor

outcomes related to malignant gliomas. All of the meningiomas from our series were benign and did not impact survival.

Study limitations

Systematic pituitary MRI is required for the follow-up of patients with MEN1 to assess the occurrence of pituitary adenomas. Nevertheless, we did not perform a MRI central review, which could lead to underestimation of asymptomatic non-operated CNS tumors. Moreover, the first patients included in the data collection in the 1990s were followed up with old-generation CT-scan and MRI, which could also lead to underestimation of asymptomatic non-operated CNS tumors. Systematical spine MRIs were not performed, which could lead to underestimation of non-symptomatic intra- or extradural spinal tumors.

In contrast, intensive imaging surveillance of patients with MEN1 could lead to a surveillance bias and then to overestimation of tumor frequency, particularly for non-symptomatic tumors. The present cohort was compared with non-screened registries: the CBTRUS, the Gironde CNS Tumor Registry, and the Darlix and colleagues study which includes French operated-on CNS tumors (25, 27, 28). In the present study, nevertheless, all patients were not systematically screened: brain or spine MRIs were not systematically performed to search for CNS tumors. Pituitary MRI was performed every three years as recommended, and 68-Gallium DOTATOC PET was mostly performed to stage an already known duodeno-pancreatic tumor. For instance, operated-on meningiomas represent 63% of meningiomas in the Gironde CNS Tumor Registry versus 50% from the present cohort versus 15% from the Asgharian and colleagues study with central review (29, 38). Therefore, we cannot exclude an overdiagnosis bias because of the cumulative aspect of repeated imaging during the follow-up. However, it is probable that this bias would mainly concern non-symptomatic lesions and, in contrast, would be very limited for symptomatic and most operated lesions.

Moreover, we selected 2015–2019 data from the Gironde CNS Tumor Registry given that an increase in CNS tumor incidence was observed between 2000 and 2012 in Gironde (French department) and no major changes were observed for the incidence of malignant and nonmalignant CNS tumors in the US population during the last two decades (27, 28). This point could lead to underestimation of the difference between the CNS tumor incidence rates from the present MEN1 cohort and the other compared general population registries. Nevertheless, the CNS tumor incidence rates remain higher in the present MEN1 cohort.

A central neuropathological review was performed for cases of meningiomas and ependymomas with molecular analysis, but not in other cases of MESA, related to a lack of available tumor material. Nevertheless, WHO classification changes in the last decades were not major for MESA and, therefore, should not impact the study results. Genomic analyses were not possible for astrocytomas and oligodendrocytic tumors related to the lack of available tumor materials, leading to incomplete conclusions about the involvement of the MEN1 syndrome in the occurrence of these gliomas.

Impact of the present study on the follow-up of patients with MEN1

Pituitary MRI follow-up is already required for pituitary adenoma observation. ^{68}Ga-DOTATOC PET could also be performed in the case of DP-NET exploration. The results of the present study led to recommend watchful radiological analysis for meningioma detection.

Despite a higher rate of ependymomas in patients with MEN1 compared with the general population, ependymomas and other

CNS tumors with spinal location are present in less than 1% of the MEN1 population. The present data suggest concluding that systematical spinal MRI is not required for intra- or extra-axial spinal tumor detection. In contrast, careful neurological examination is recommended, and spinal MRI should be prescribed in the case of neurological examination alteration.

Conclusion

The frequency and the incidence of meningiomas (respectively, 0.8% and 16.2/100,000 person-years), ependymomas (0.5% and 10.8/100,000), astrocytic and oligodendrocytic tumors (0.3% and 6.7/100,000), and schwannomas (0.3% and 5.4/100,000) are higher in patients with MEN1 than in the general population. The association with the biallelic inactivation of MEN1 within these tumors supports the fact that meningiomas and ependymomas should be considered part of the MEN1 syndrome in the majority of cases. There is a lack of molecular data for low-grade gliomas and schwannomas even if the incidence is increased in the MEN1 population.

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Authors' Contributions

T. Graillon: Conceptualization, resources, data curation, formal analysis, funding acquisition, validation, investigation, methodology, writing–original draft, writing–review and editing. **P. Romanet:** Conceptualization, resources, formal analysis, methodology, writing–review and editing. **C. Camilla:** Resources, software, formal analysis, investigation, methodology. **C. Gelin:** Resources, formal analysis, investigation, methodology. **R. Appay:** Resources, formal analysis, investigation. **C. Roche:** Resources, formal analysis, methodology. **A. Lagarde:** Resources, formal analysis, investigation. **G. Mougel:** Resources, formal analysis, investigation, methodology. **K. Farah:** Resources, investigation. **M. Le Bras:** Resources. **J. Engelhardt:** Resources, methodology. **M. Kalamarides:** Resources. **M. Peyre:** Resources. **A. Amelot:** Resources. **E. Emery:** Resources. **E. Magro:** Resources. **H. Cebula:** Resources. **R. Aboukais:** Resources. **C. Bauters:** Resources. **E. Jouanneau:** Resources. **M. Berhouma:** Resources. **T. Cuny:** Resources. **H. Dufour:** Resources. **H. Loiseau:** Resources, methodology. **D. Figarella-Branger:** Resources, formal analysis, investigation. **L. Bauchet:** Supervision, methodology, writing–review and editing. **C. Binquet:** Resources, formal analysis, supervision, investigation, methodology, writing–review and editing. **A. Barlier:** Conceptualization, resources, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing–review and editing. **P. Goudet:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing–review and editing.

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Note

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