Medulloblastomas associated with an APC germline pathogenic variant share the good prognosis of CTNNB1-mutated medulloblastomas

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Abstract

Background. Medulloblastomas may occur in a predisposition context, including familial adenomatosis polyposis. Medulloblastomas related to a germline pathogenic variant of adenomatous polyposis coli (*APC*) remain rare and poorly described. Their similarities with sporadic WNT medulloblastomas still require description.

Methods. We performed a multicentric retrospective review of 12 patients treated between 1988 and 2018 for medulloblastoma with an identified or highly suspected (personal or familial history) *APC* germline pathogenic variant. We report personal and familial history *APC* gene pathogenic variants whenever available: clinical and histologic characteristics of the medulloblastoma, treatments, and long-term outcome, including second tumor and late sequelae.

Results. Medulloblastomas associated with *APC* pathogenic variants are mainly classic (11/11 patients, 1 not available), nonmetastatic (10/12 patients) medulloblastomas, with nuclear immunoreactivity for β -catenin (9/9 tested cases). Ten of 11 assessable patients are disease free with a median follow-up of 10.7 years (range, 1–28 y). Secondary tumors included desmoid tumors in 7 patients (9 tumors), 1 thyroid carcinoma, 2 pilomatricomas,

1 osteoma, 1 vertebral hemangioma, and 1 malignant triton in the radiation field, which caused the only cancer-related death in our series.

Conclusions. Medulloblastomas associated with an *APC* pathogenic variant have an overall favorable outcome, even for metastatic tumors. Yet, long-term survival is clouded by second tumor occurrence; treatment may play some role in some of these second malignancies. Our findings raise the question of applying a de-escalation therapeutic protocol to treat patients with *APC* germline pathogenic variants given the excellent outcome, and reduced intensity of craniospinal irradiation may be further evaluated.

Key Points

1. *APC*-mutated medulloblastomas and other WNT cases share similar features.
2. *APC*-mutated medulloblastomas have an overall favorable outcome.

Importance of the Study

Medulloblastomas related to an *APC* germline pathogenic variant remain rare, and their characteristics and prognosis poorly described. Based on a multicentric retrospective cohort of 12 patients with a median follow-up of 10.7 years, we have found that *APC*-mutated medulloblastomas are mainly nonmetastatic, classic medulloblastomas, with nuclear accumulation of β -catenin in all 9 tested cases, strongly supporting their belonging to the WNT subgroup. All the

more, our study highlighted the excellent outcome for medulloblastomas occurring in this genetic context. We also noticed a high incidence of secondary tumors, for which the combined role of multimodal treatments and genetic background can be discussed. Altogether, our study raises the question of applying lower craniospinal radiation dose for these patients, as currently proposed for WNT medulloblastomas with a catenin beta-1 pathogenic variant.

Medulloblastoma is the most common malignant brain tumor in children.¹ The most recent revision of the World Health Organization (WHO) in 2016² classifies this malignancy into 4 histologic subgroups—classic, desmoplastic, extensive nodularity, and large cell/anaplastic³—and 4 molecular subgroups: wingless (WNT)-activated, sonic hedgehog (SHH)-activated *TP53* mutant, SHH-activated *TP53* wildtype, and non-WNT/non-SHH (Group 3 and Group 4).⁴ Among these groups, WNT medulloblastoma has consistently been associated with a favorable outcome in children less than 16 years old⁵; they are therefore considered for treatment de-escalation within the International Society of Paediatric Oncology–Europe (SIOPe) PNET5 trial (NCT02066220). In the vast majority of cases, the WNT signature is a consequence of a somatically acquired hotspot pathogenic variant in the catenin beta-1 (*CTNNB1*) gene, inducing a constitutive activation of the WNT– β -catenin pathway.

Medulloblastomas occur mainly sporadically^{6,7}; however, germline pathogenic variants in cancer predisposing genes have been described in about 6% of all cases.⁷ While Groups 3 and 4 have not been clearly associated with any specific genetic syndromes apart from occasional reports,^{7–10} it is now well known that SHH and WNT subgroups may be associated with various familial cancer syndromes. SHH medulloblastomas show the highest prevalence for cancer predisposition syndromes, since up to 15–20% of patients in this subgroup may have a germline pathogenic variant in *SUFU*, *PTCH1*, *TP53*, *BRCA2*, or *PALB2*.^{7,11–13} WNT medulloblastomas are so far

exclusively associated with adenomatous polyposis coli (*APC*) germline pathogenic variants, in the setting of familial adenomatous polyposis (FAP).^{14–16} This observation is supported by the role of the APC protein, an essential component of the WNT signaling pathway that, together with axin and GSK-3 β , controls the intracellular localization and degradation of β -catenin.¹⁷ Apart from intestinal tumors, *APC* germline pathogenic variants predispose to a broad spectrum of lesions, including desmoid tumors, hepatoblastomas, pilomatricomas, epidermoid cysts, osteomas, and congenital hypertrophy of the retinal pigment epithelium.^{18–20} The occurrence of brain tumor in patients carrying *APC* germline pathogenic variants remains rare, not exceeding 1% on previous studies.¹⁶ Thus, although medulloblastomas represent the most classical brain tumor type described in *APC* germline pathogenic variants and/or FAP contexts, few reports have specifically described their precise characteristics in this condition so far. Our study aims to describe histologic and clinical characteristics of a series of medulloblastomas arising in a context of FAP or *APC* germline pathogenic variants.

Patients and Methods

This multicenter observational chart review was conducted retrospectively in pediatric oncology departments from the French Society against Cancers and Leukemias in Children and Adolescents (SFCE). Patients were identified from the

local SFCE physicians, the French National Registry of Childhood Solid Tumors, and the laboratory of genetic diagnosis of the Pitié-Salpêtrière hospital (a national reference laboratory for *APC* gene analysis). Inclusion criteria comprised (i) medulloblastoma, whatever the age at onset, AND (ii) proven *APC* germline abnormality, OR (iii) personal and/or familial histories fitting with FAP or Gardner syndrome. Patients with personal or familial histories of Lynch syndrome were not included in this study. In accordance with French legislation, data were processed anonymously. The local institutional review board at the Curie Institute approved the study.

Demographic and clinical characteristics and radiological data were collected. We reported patients' treatments and collected data on short- and long-term side effects and/or sequelae. We reported second malignant or benign tumor occurrence and determined overall survival (OS) and second tumor-free survival (STFS) based on the Kaplan–Meier method.

Genetic data were reported for patients and their relatives whenever appropriate. The identification of *APC* pathogenic variants was based on Sanger sequencing; *APC* pathogenic variants were reported either from the patient (pts 1 to 3, 7, 10, and 11) or from a related index case (pts 4, 5, 6, 9, and 12); additionally, familial segregation marker analysis was performed for patient 8.

Histologic and molecular information collected for medulloblastomas included morphological subtype (from the WHO 2016 classification) and immunostaining for β -catenin at diagnosis if available. A histologic review was requested from the referring pathologists of each care center; additionally, a central histopathologic review was performed for 11 cases (P.V.).

Results

Twelve patients, 7 males and 5 females, were treated at pediatric oncology departments for medulloblastoma in a context of known or highly suspected FAP between 1988 and 2018.

Familial Histories and Context at Diagnosis

Familial histories are presented in [Table 1](#) (pedigrees of 5 patients in [Supplementary Fig. 1a–e](#)). Familial digestive histories (polyposis and/or digestive cancer)—including first-degree family and distant relatives—were present for all patients. Polyposis was reported in all but one family. Colorectal cancer was reported in relatives of 8 patients, and unspecified digestive cancer in relatives of 2 patients. Extra-intestinal lesions fitting with Gardner syndrome were found for families of patients 7 and 8, including epidermal inclusion cysts, thyroid lesions, and thoracic parietal fibroma. Pedigree analysis also reported other malignant tumors for some patients' families, such as neuroblastoma for patient 1's first cousin, renal cancer for patient 8's grandfather, hepatic cancer for patient 10's mother, renal cancer for patient 11's father, hepatoblastoma for patient 12's half-brother, and pancreatic cancer for patient 12's

father and grandmother. At the time of medulloblastoma diagnosis, all patients had familial gastrointestinal histories suggestive of FAP (polyposis for 8 patients, digestive cancer without information about its association with a polyposis for 4 patients). *APC* pathogenic variants had been previously identified in 5 families. Three patients had personal polyposis histories before the diagnosis of medulloblastoma, including 1 patient with an identified *APC* pathogenic variant, and 1 patient was known to carry an *APC* pathogenic variant in a familial context without personal previous history.

Genetic Results

Exhaustive genetic data were available for 11/12 patients, and confirmed the *APC* germline pathogenic variant for all of them. Of note, *APC* pathogenic variants involved exon 15 in 8/11 patients ([Table 1](#)). For patient 8 with typical FAP presentation treated in 1989, familial marker segregation was the only available analysis in 1994 and confirmed the expected segregation with chromosome 5 markers.

The *APC* gene was analyzed in the tumor of only one patient (pt 7); it showed two deleterious *APC* pathogenic variants, one present at the constitutional level (c.3183_3187del (p.Gln1062*)), and a second somatic pathogenic variant leading to a frameshift (c.3758del (p.Ser1253Leufs*12)).

Clinical Features of Medulloblastoma

The clinical characteristics of medulloblastomas are described in [Table 2](#) and [Figure 1A–C](#). All but one patient were below 18 years old at diagnosis of medulloblastoma, with a median age of 11.5 years (range, 6–32 y). Median time between first symptoms and diagnosis was 2.4 months (range, 0–12 mo). Of note, patient 8 had suffered from tinnitus and sciatic pain for 7 months before the cerebellopontine angle tumor was discovered. Patient 12 had suffered from hearing loss for 1 year before diagnosis was made in a context of febrile headaches.

Anatomic and Histologic Characteristics of Medulloblastomas

Seven tumors arose from the cerebellar vermis, 3 in the cerebellum peduncle, 1 in the fourth ventricle, and 1 in the cerebellopontine angle ([Fig. 1D](#)). The tumor was localized in 10 patients and metastatic in 2 patients (M2 for pt 11, M3 for pt 3 according to Chang's classification²¹).

The histopathologic analysis revealed a classic type for all cases, which could be confirmed by a central review in 11 tumors ([Table 2](#)). Noteworthy, 5/11 cases contained numerous Homer Wright rosettes, a feature not usually seen in sporadic WNT-activated medulloblastoma. Immunostaining for β -catenin was available for 9 cases (at diagnosis or during central review), which, as expected, presented diffuse nuclear accumulation of the protein. Of note, staining for Yes-associated protein 1 was found positive in 7/8 cases tested.

Table 1 Medical history and genetic characteristics of patients

Patient #	Familial History (any event at any time)				Status at the Time of Medulloblastoma		Pathogenic Variant of APC		
	Polypsis (any degree relatives)	Colorectal Cancer (any degree relatives)	CNS Tumor (any degree relatives)	Other	Familial Context (first degree unless specified)	Personal Context	Exon	Pathogenic Variant (protein change if specified)	Predicted Consequence
1	Y	N	N	N	Y (^a father)	N	11	c.1477_1478insT (NA)	NA
2	Y	Y	N	N	Y	N	15	c.3180_3184del (p.Gln1062*)	Frameshift Stop at 1062
3	Y	Unspecified digestive cancer	Y mother, 2 y	N	Y	Y ^c	15	c.3183_3187del (p.Lys1061fs*1062)	Frameshift Stop at 1062
4	Y	N	N	Mother, gastric adenoma	Y (^a mother)	N	15	c.4118delC (p.Pro1373Leufs*42)	Frameshift
5	Y	Y	N	N	Y (^a mother/sister)	Y ^b	15	c.3147G > A (p.Trp1049*)	Nonsense Stop at 1049
6	Y	Y	N	N	Y	N	15	c.3184C > T (p.Gln1062*)	Nonsense Stop at 1062
7	Y	Y	N	Father, parietal fibroma	Y	N	15	c.3183_3187del (p.Gln1062*)	Frameshift Stop at 1062
8	Y	Y	N	Sister, thyroid cancer	Y <i>second degree</i>	N	NA	NA	NA
9	Y	Y	N	N	Y (^a father)	Y ^c	15	c.3189_3192del (p.Glu1064Lysfs*61)	Frameshift Stop at 1124
10	N	Y	N	Mother, hepatic cancer	Y	N	14	c.1917dupA (p.Arg640Thrfs*11)	Frameshift
11	Y	Unspecified digestive cancer	N	Father, renal cancer	Y <i>second degree</i>	N	10	c.1353T > A (p.Cys451*)	Nonsense Stop at 451
12	Y	Y	N	Pancreatic cancer, father/grandmother hepatoblastoma, half-brother	Y (^a father, relatives)	Y ^{b,c}	15	c.3184C > T (p.Gln1062*)	Nonsense Stop at 1062

Y = yes, N = no, NA = not available. Pathogenic variant of APC previously identified: ^afamily member affected, ^bin the patient, ^cpolyposis.

Table 2. Medulloblastoma characteristics and treatment

Patient #	Characteristics at diagnosis			Treatment		
	Age (year)	Year of Diagnosis	Primary Tumor Location	Presence of Metastasis	Histologic Subtype	Immunohistochemistry for β -catenin
1	8	2005	Cerebellar vermis	N	Classic ^{a,b}	+
2	6	2000	Cerebellar vermis	N	Classic ^b	+
3	32	2009	Cerebellopontine angle	Y S2 nerve root	Classic ^b	NA
4	18	2015	Fourth ventricle	N	Classic ^{a,b}	NA
5	12	2016	Cerebellar vermis	N	Classic ^{a,b}	+
6	11	1999	Cerebellar vermis	N	Classic ^b	+
7	7	2016	Cerebellar vermis	N	Classic ^{a,b}	+
8	10	1989	Cerebellar vermis	N	Classic ^{a,b}	+
9	14	2010	Middle cerebellar peduncle	N	Classic ^{a,b}	+
10	14	2006	Middle cerebellar peduncle	N	Classic ^b	+
11	7	1988	Cerebellar	Y 4 th ventricle floor	NA	NA
12	13	2018	Middle cerebellar peduncle and cerebellopontine angle	N	Classic ^b	+

Y = yes, N = no, C = cranial, S = spinal, HD = high dose, NA = not available. ^aHistologic review performed locally, ^bcentral review, ^chyperfractionated radiotherapy.

Y (36/60 - 3)

Y (36/68^c - 1)

Y (36/54 - 7)
Boost (54) on metastasis

Y (24/54 - 2)

Y (36/68^c - 3)

Y (25/55 - 3)

Y (23.4/54 - 1)

Y (30/52 - 3)

Y (30,6C-36S/54 - 6)

Y (24/54 - 2)

Y (35/55 - 2)

Y (23.4/54 - 6)
Boost (59) on residue

Table 3 Short- and long-term outcomes

Patient n°	Acute Side Effects (treatment relation)	Last Follow-up		Status	Long-Term Sequelae	Familial Adenomatosis Polyposis Spectrum Occurrence		Other Tumor Occurrence (age, year)
		Age (year)	Time Since Diagnosis (year)			Polyposis number (age, year)	Extra-Intestinal Type (age, year)	
1	N	19	11.4	CR	N	8 polyps (12)	Desmoid tumor (9)	N
2	Y (surgery)	19	14.0	Dead ^a	Neurocognitive and endocrine disorder, hearing loss	Few polyps (14)	N	Cavernoma (13), malignant triton tumor (19)
3	N	39	7.6	CR	Neurocognitive and endocrine disorder, hearing loss	850 polyps (18)	N	N
4	Y (chemotherapy)	20	2.6	CR	Neurocognitive and ophthalmologic disorder	50 polyps (20)	N	N
5	Y (surgery, chemotherapy)	14	2.6	CR	Neurocognitive disorder	Not examined	Epidermal inclusion cysts (NA), desmoid tumor (13)	N
6	Y (chemotherapy)	24	13.3	CR	Neurocognitive disorder, hepatic steatosis	>100 polyps (16)	Desmoid tumor (18)	N
7	Y (surgery, chemotherapy)	8	1.0	CR	Neurocognitive disorder	Not examined	Pilomatricoma (8)	N
8	N	34	25.1	CR	Neurocognitive and endocrine disorder	>100 polyps (16)	Pilomatricoma (11), desmoid tumor (21), fibroma (33), thyroid carcinoma (23)	Vertebral hemangioma (30)
9	N	21	7.1	CR	Endocrine disorder, hearing loss	>100 polyps (13)	Desmoid tumor (17)	N
10	Y (surgery, chemotherapy)	24	10.7	CR	Neurocognitive disorder, hearing loss	Polyps (number unspecified) (15)	Desmoid tumor (19), osteoma (19), epidermal inclusion cysts (22)	N
11	Y (surgery)	34	27.7	CR	Neurocognitive and endocrine disorder	Polyps (number unspecified) (19)	Desmoid tumor (25), CHRPE (19)	N
12	Y (chemotherapy)	14	0.7	CR	NC	>100 polyps (9.5)	N	N

Y = yes, N = no, CR = complete response, NA = not available, CHRPE = congenital hypertrophy of the retinal pigment epithelium. ^aDeath due to malignant triton tumor at 19 years old.

Fig. 1 Characteristics of patients and tumors. (A) Box-plot showing the age distribution at diagnosis, in years; line at median with interquartile range. (B) Distribution of presence (green) or absence (red) of personal (left) or familial (right) history of tumor at time of medulloblastoma diagnosis. (C) Absolute number of metastatic status (upper bar), classic histology (middle bar), and molecular subgroup (lower bar) of cases. NA = not available. (D) Axial (left panels) and coronal (right panel) MRI sections of 2 medulloblastomas from the cerebellopontine angle and the cerebellar peduncle.

Treatment Regimen of Medulloblastomas

Treatments are summarized in [Table 2](#). Initial surgery resulted in total ($N = 7$) or subtotal (residue $<1.5 \text{ cm}^2$, $N = 3$) resection for all but 2 patients (pts 9 and 12) who underwent only biopsies at diagnosis. Then, 8 patients received standard-risk adapted treatments. Among them, 6 patients received an association of chemotherapy and conventional fractionated radiotherapy (CFRT) in accordance with the ongoing protocols or recommendations at this time, including an 8-drugs-in-1-day regimen, MSFOP-93, PNET 4 and PNET 5 (NCT02066220).^{22–24} Two patients received hyperfractionated radiotherapy (HFRT) according to the protocol of the Medulloblastoma–French Society of Pediatric Oncology (MSFOP)²⁵ either as the sole treatment or after one course of chemotherapy. Four patients received high-risk treatments: patient 3 was treated according to adult metastatic medulloblastoma guidelines consisting of craniospinal irradiation with pre and post chemotherapy with VP16-carboplatin; patient 9, for whom no tumor resection was performed, was treated according to the French PNET HR+5 protocol (2 cycles of VP16-carboplatin, then 2 cycles of thiotepa, with stem cell support, followed by CFRT and temozolomide maintenance chemotherapy [NCT00936156]); patient 11 was treated according to the SIOP II protocol²⁶ with pre and post irradiation chemotherapy. Patient 12 is still receiving treatment according to the French PNET HR+5 protocol, applied to this patient because of an unresectable tumor.

Craniospinal irradiation modalities are detailed in [Table 2](#). The median dose was 32.5 Gy for CFRT (range, 23.4–36) and 36 Gy for HFRT; tumor bed median dose was 54 Gy in CFRT (range, 52–60) and 68 Gy in HFRT. Of note, patient 3 received a boost on a metastatic sacrum site (total dose, 54 Gy), and patient 12 received a boost on a residual tumor (total dose, 59 Gy).

Acute Toxicity and Long-Term Sequelae

Acute and long-term side effects are reported in [Table 3](#). Altogether, no specific unexpected acute severe adverse event or specific severe long-term sequel was noticed.

Postsurgical side effects, related to the position of the tumor, included 4 cerebellar syndromes, 2 posterior fossa syndromes, 2 facial palsy, 2 oculomotoric disorders, and 1 incomplete transient hemiplegia. Transient Common Terminology Criteria for Adverse Events (CTCAE, v4.03) grades 3 and 4 hematological toxicity were noticed for 4 patients, leading to dose modifications or early stop of chemotherapy; transient neuropathic pain defined as CTCAE grade 2 was observed in patients 7 and 10.

Long-term sequelae were within expected range by local physicians. They mainly consisted of neurocognitive disorders (8/11 evaluable patients), including cognitive impairment (pts 2, 5, 6, 8, 11) and neurologic sequelae such as cerebellar syndrome (pts 4–8, 10, and 11), or facial palsy (pts 5, 7). Endocrine sequelae included growth hormone deficiency (pts 2, 8, 9, 11), hypogonadism (pts 3, 9, 11), and

thyroid deficiency (pts 9, 11). Hearing loss (CTCAE grade 2) was reported for 4 patients, within the expected severity in all cases.

Secondary Tumors

All patients presented other lesion(s) within the spectrum of FAP (Table 3, Fig. 2A). Adenomatous polyposis and intestinal lesions were the most prominent (10/10 patients over the age of 12 years). Systematic colonoscopy after medulloblastoma diagnosis allowed diagnosing polyposis in 7 patients at a median age of 15.9 years, whereas the other 3 patients (pts 3, 9, and 12) were diagnosed for polyposis prior to medulloblastoma at 18, 13, and 9.5 years old, respectively. The median age at detection was 15.3 years (range, 9.5–20 y). Prophylactic colectomy was performed for 7 patients at a median age of 16.7 years, including 2 patients with high-grade dysplasia, but no colorectal carcinoma.

Desmoid tumors occurred in 7 patients (with multiple desmoid tumors in one of them) at a median age of 17.6 years (range, 9.6–32.3 y). The median time between the diagnosis of desmoid tumors and completion of therapy was 3.3 years (range, 1.3–10.4 y). An abdominal location (mesentery or abdominal wall) was noticed in all but 2

cases. All 5 patients with abdominal desmoid tumors had previously undergone prophylactic colectomy, with a median time between surgery and onset of desmoid tumor of 3.6 years (range, 1–12.7 y). All tumors were theoretically in the field of spinal irradiation but the exact dosimetry at the tumor site was not available, except for patient 9 (9–15 Gy).

The 2 non-abdominal tumors were an occipital meningeal desmoid tumor 16 months after completion of therapy (pt 1) and an intracranial tumor arising in the posterior fossa soft tissues 19 months after completion of therapy (pt 5); hence, both occurred in a surgically operated and irradiated anatomic site (36–47 Gy for pt 5, not specified for pt 1).

Two patients presented pilomatricomas. Patient 8 presented multiple pilomatricomas from the age of 11 years, 2 of them occurring in the irradiation field, 1 and 4 years after radiotherapy. Patient 7 developed multiple pilomatricomas in the irradiation field (scalp) at 8 years of age (ie, 16 mo after radiotherapy).

One patient developed a thyroid carcinoma within the irradiation field at 23 years of age (pt 8) and one patient developed a triton tumor in the irradiation field (see below).

Other benign second lesions were noticed for 2 patients: cavernoma for patient 2 and vertebral hemangioma for patient 8, both in the irradiation field, 7 and 20 years, respectively, after completion of therapy.

Fig. 2 Outcome: survival and second tumors. (A) Relative distribution of second tumors according to histologic subtype (number of patients). (B) Overall survival (OS) and (C) secondary tumor-free survival (STFS) (including desmoid tumor, malignant triton tumor, and thyroid carcinoma) according to the Kaplan–Meier method; time in years.

Outcome

At last follow-up, 10/11 patients were alive, with persistent complete response (pt 12 is still under treatment). A malignant triton tumor, localized in the cauda equine (which was included in the irradiation field), led to the death of patient 2 at 19 years of age. Overall and second tumor-free survivals (including desmoid tumor, malignant triton tumor, and thyroid carcinoma) are described in [Figure 2B, C](#).

Discussion

In a large retrospective and prospective study, Waszak et al found *APC* germline pathogenic variants in up to 7% of all WNT medulloblastomas,⁷ which, knowing the frequency of this molecular subtype among all medulloblastomas would result in an approximate frequency of 1%. Our series consist of 12 patients in 30 years, which emphasizes the rarity of this presentation; however, such a retrospective study most probably underestimates the true frequency of the condition. In our cohort, medulloblastomas were found to be the first personal clinical feature of *APC* germline pathogenic variants for all but 3 patients, prior to polyposis or colorectal cancer discovery, in accordance with published data.²⁷ For all patients, however, polyposis or other digestive history suggestive of an *APC* pathogenic variant in first-degree or distant relatives was already known at the time of medulloblastoma diagnosis. Familial history should thus be carefully looked for in order not to miss this predisposition syndrome, even though absence of any familial history doesn't rule out the diagnosis given the high de novo mutation rate (approaching 30% according to previous literature).²⁸ In addition, a systematic screening of *APC* in WNT medulloblastomas without a *CTNNB1* pathogenic variant may, as proposed by Waszak et al,⁷ allow a more efficient discovery of *APC* germline pathogenic variants in these patients. Such a systematic approach may lead to a more accurate estimation of the actual frequency of this association among patients with medulloblastomas.

Given the rarity of the syndrome, little is known about the clinical characteristics of medulloblastomas occurring in an *APC* pathogenic variant context. Our series emphasizes some recurrent features such as (i) a constant classic histopathology, (ii) a frequent lateral location (ie, in the pontocerebellar angle or in the peduncles, a feature also reported in sporadic WNT medulloblastomas²⁹), and (iii) a predominant nonmetastatic status. Given the scarcity of tumor material for many patients in our retrospective series, we were not able to subgroup our cases by molecular methods. Yet, immunostaining for β -catenin, available for 9/12 cases, confirmed that these *APC* medulloblastomas belong to the WNT subgroup. Similarly, the lack of tumor material did not allow us to compare the genomic features, such as monosomy 6, of *APC* medulloblastomas and sporadic *CTNNB1*-mutated WNT medulloblastomas. Nevertheless, Waszak et al already reported that 3 out of 5 *APC*-mutated WNT medulloblastomas also showed monosomy 6, which finally suggests that this genetic feature is not restricted to sporadic WNT medulloblastomas.⁷

Despite different modalities in treatment strategies, the excellent outcome associated with *APC*-mutated medulloblastomas is another striking finding. Overall and relapse-free survival were excellent, up to 100% at 5 years, approaching data published for sporadic WNT medulloblastomas,^{30–32} even if the study included patients with high-risk features (ie, metastatic or unresected tumor) treated according to high-risk medulloblastoma protocols. This overall excellent outcome is very consistent with the Waszak et al series,⁷ which included 9 patients, and strongly suggests that *APC*-mutated WNT medulloblastomas share the same excellent prognosis as their *CTNNB1*-mutated counterparts.

However, one should keep in mind that, in patients with cancer predisposition syndromes, OS might also be determined by the occurrence of secondary malignancies. Our series illustrates the very high risk for second tumors to occur in this population, in particular intestinal polyposis and carcinomas. The diagnosis of FAP led to systematic screening colonoscopy, and pre-symptomatic polyposis was detected for all of those who reached the exposed age. Current recommendations suggest programming the first colonoscopy in patients with FAP at the age of 10 years, with referral of prophylactic colectomy depending on the endoscopic phenotype.^{27,33} The critical survival benefit provided by an appropriate surveillance emphasizes the necessity to diagnose the predisposition context early enough (ie, as soon as WNT medulloblastoma is discovered).

Of note, our series also points out some extra-digestive secondary tumors, mainly desmoid tumors. The rate of desmoid tumors in our cohort was higher than in the general population of patients with FAP (7/12 patients, or 58% vs 10–15% expected)^{34–36}; additionally we observed an earlier onset (ie, 17.6 y vs >30 y).^{36,37} Three factors could be involved in this higher risk. Firstly, the genetic background that increases the risk of medulloblastoma may also impact the risk of desmoid tumors. Secondly, all patients developed desmoid tumors in surgically operated regions, in line with the well-known risk conferred by surgery in all FAP patients.³⁶ Finally, the role of irradiation can also be questioned; however, the overlap between both surgically operated and irradiated sites precludes any conclusion about the independent role of irradiation. While the responsibility of irradiation remains questionable for desmoid tumors in the irradiation field, it is quite more plausible for thyroid carcinoma, which is known to be both associated with FAP and related to irradiation; the causality of irradiation is even more likely for malignant triton tumor, which caused the only cancer-related death in our series. Combined with the excellent relapse-free survival of our cohort, this increased risk of radiation-induced second tumor raises the question of applying lower craniospinal radiation dose for these patients, and could thus justify their access to de-escalation therapeutic protocol as currently proposed for WNT medulloblastomas with a *CTNNB1* pathogenic variant in the PNET5 study.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

APC | familial adenomatosis polyposis | Gardner syndrome | medulloblastoma | WNT

Funding

None.

Acknowledgments

We are grateful to the neuropathologists and to the logistic organization (Karen Silva) from the French rare tumor network (RENOCLIP). We are grateful to the clinical research associates (Catherine Soler, Nathalie Couteau) for their help in data collection.

Conflict of interest statement. None.

Authorship statement. Aurore Surun, Laurence Brugières, Cécile Faure-Contier, Pierre Leblond, Anne-Isabelle Bertozzi, Claire Berger, Nicolas André, Eric Sariban, Sandra Raimbault, Léa Guerrini-Rousseau, Claire Alapetite, Christelle Dufour, François Doz, and Franck Bourdeaut provided clinical data. Pascale Varlet, Marc Polivka, Marie-Bernadette Delisle, Alexandre Vasiljevic, Claude-Alain Maurage, and Dominique Figarella-Branger provided histologic review.

Fabienne Prieur, Françoise Desseigne, Hélène Zattara, Rosine Guimbaud, Florence Coulet, and Chrystelle Colas contributed to genetic data and counseling to families.

Brigitte Lacour contributed to identify cases through the registry. François Doz, Chrystelle Colas, and Laurence Brugières contributed to the study design.

All authors contributed to writing, reviewing, and editing.

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