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ONCOLOGY: RESEARCH ARTICLE

Medulloblastoma and familial adenomatous polyposis: Good prognosis and good quality of life in the long-term?

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Abstract

Introduction: Mutations of the APC (adenomatous polyposis coli) gene correlate mainly with familial adenomatous polyposis (FAP), but can occasionally be pathogenic for medulloblastoma (MBL) wingless-related integration site (WNT) subtype, the course of which has only recently been described.

Methods: We retrieved all patients with documented germline APC mutations and a diagnosis of MBL to examine their outcome, late effects of treatment, and further oncological events.

Results: Between 2007 and 2016, we treated six patients, all with a pathogenic APC variant mutation and all with MBL, classic histotype. None had metastatic disease. All patients were in complete remission a median 65 months after treatment with craniospinal irradiation at 23.4 Gy, plus a boost on the posterior fossa/tumor bed up to 54 Gy, followed by cisplatin/carboplatin, lomustine, and vincristine for a maximum of eight courses. Five of six diagnostic revised MRI were suggestive of the WNT molecular subgroup typical aspects. Methylation profile score (in two cases) and copy number variation analysis (chromosome 6 deletion in two cases) performed on four of six retrieved samples confirmed WNT molecular subgroup. Four out of six patients had a positive family history of FAP, while gastrointestinal symptoms prompted its identification in the other two cases. Four patients developed other tumors (desmoid, MELTUMP, melanoma, pancreatoblastoma, thyroid Tir3) from 5 to 7 years after MBL.

Discussion: Our data confirm a good prognosis for patients with MBL associated with FAP. Patients' secondary tumors may or may not be related to their syndrome or treatment, but warrant adequate attention when planning shared guidelines for these patients.

KEYWORDS
APC, FAP, good prognosis, secondary tumors, WNT medulloblastoma

Abbreviations: APC, adenomatous polyposis coli; CRC, colorectal carcinoma; FAP, familial adenomatous polyposis; FIQ, full intelligence quotient; MBL, medulloblastoma; Wg, wingless; WNT, wingless-related integration site

1 | INTRODUCTION

APC (adenomatous polyposis coli) is a tumor suppressor gene that has multiple important functions. It encodes a protein that is an essential component of the wingless (Wg)-related integration site (WNT) signaling pathway; together with axin and GSK-3beta, it regulates the intracellular localization and degradation of beta-catenin, influencing cell adhesion and migration capacity, and it controls cell replication.

Sporadic (nonhereditary) somatic mutations or loss of APC gene function are early events leading to colon cancer.[1] Germline mutations in the APC gene are responsible instead for a form of hereditary predisposition to the onset of colic adenomas known as familial adenomatous polyposis (FAP). Patients with FAP characteristically develop numerous intestinal polyps (adenomas). According to the guidelines,[2–5] they need intensive endoscopic surveillance from 10 to 14 years of age, and prophylactic total colectomy no later than the second decade of life to reduce the risk of colorectal carcinoma (CRC). The recommended options for prophylactic total colectomy in this setting are: total rectal preservation and ileorectal anastomosis (TC/IRA) or total proctocolectomy with ileoanal canal anastomosis (PC/IPAA). The choice is dictated mainly by the number and distribution of polyps in the rectum ($\geq$ or $<$30).

Patients with FAP can also develop lesions outside the colon, including gastric and duodenal polyps, desmoid tumors, thyroid tumors, hepatoblastomas, epidermoid cysts, osteomas, and congenital hypertrophy of the retinal pigment epithelium.[6]

The occurrence of brain tumors in FAP patients remains rare (in no more than 1% of cases), medulloblastoma (MBL) being the most likely central nervous system tumor to be described in carriers of APC germline pathogenic variants, typically in pediatric age.[7] The molecular changes underlying MBL are the same as those involved in the morphogenesis of the cerebellum, that is the Sonic Hedgehog pathway (involved in controlling the normal proliferation of cerebellar granules) and the WNT pathway (including APC and beta-catenin).[8] Some of the most significant insight on the biological pathways involved in the pathogenesis of MBL has come from investigating rare family syndromes that predispose to its onset. APC is an essential component of the physiological activation of the WNT/Wg pathway, necessary for the normal development of neural cells. Activation of this pathway identifies a unique molecular subgroup of MBL with distinct DNA methylation patterns, gene expression profiles, genomic anomalies, and clinical outcome.[9] In independent biological studies based on clinical trials,[10] this subgroup exhibits a particular behavior and has been found associated with a favorable clinical outcome (with an overall survival exceeding 90%). WNT-MBLs lack a blood-brain barrier and this feature may explain why these tumors are highly susceptible to chemotherapy and radiotherapy.[11] The overall good prognosis of WNT-MBL has solicited a hypothesis for treatment de-escalation ongoing in many trials and concerning both total dose of craniospinal irradiation (CSI) and total duration of treatment with reduced number of adjuvant chemotherapy courses.[12,13]

Although WNT/Wg-positive MBL tend to have classical histological features in the vast majority of cases (or may rarely resemble large cell/anaplastic lesions) and arise in older children, they are hard to distinguish from other tumors with similar clinical and histological characteristics, and have to be identified at the molecular level.

The aim of the present study was to describe the outcome of patients with MBL and FAP with APC germline pathogenic mutations treated for both conditions at our institute in the last 10 years.

2 | METHODS

From the years 2007 to 2016, we retrieved all records of patients with MBL and FAP, adopting the following main inclusion criteria:

1. Documented germline APC mutations;
2. Centrally reviewed histopathological diagnosis of MBL;
3. No age limit;
4. One or more conventional brain MRI studies, reviewed by the authors (Luisa Chiapparini; Alessandra Erbetta);
5. Genetic counseling for FAP, and documentation and assessment of family history.

For two patients who were probands, APC germline analysis was performed on genomic DNA extracted from blood samples by Sanger direct sequencing. Moreover, large deletions or duplications were investigated by multiplex ligation-dependent probe amplification (MLPA). Four patients who were not probands were submitted to predictive genetic test in order to find the mutation present in the family.

MRI studies were reviewed according to Patay criteria.[14] Briefly, on the basis of anatomic lesion patterns, Patay distinguished four location-based subtypes: (a) midline intraventricular as subtype A, (b) midline extraventricular as subtype B, (c) off-midline intraventricular as subtype C, and (d) off-midline extraventricular as subtype D, which represent a continuum. WNT-subgroup MBLs are in fact close to the midline, yet there are also lateralized tumors originating from structures around the foramen of Luschka.

To further confirm MBL WNT subtype, we retrieved all possible tumoral residual samples of the six patients. DNA methylation profiling and copy number variation were performed after selecting tumor areas with the highest tumor cell content ($\geq$70%) for DNA extraction, and samples were analyzed using Illumina Infinium Human Methylation EPIC Bead Chip (EPIC) (Illumina, San Diego, CA) arrays according to the manufacturer's instructions.

By examining these patients' diagnostic and treatment data, we aimed to: (a) describe their progression-free survival and overall survival; (b) confirm the favorable prognosis reported in the recent literature,[15] and describe the potential (clinical, therapeutic, pathological, and molecular) prognostic factors associated with

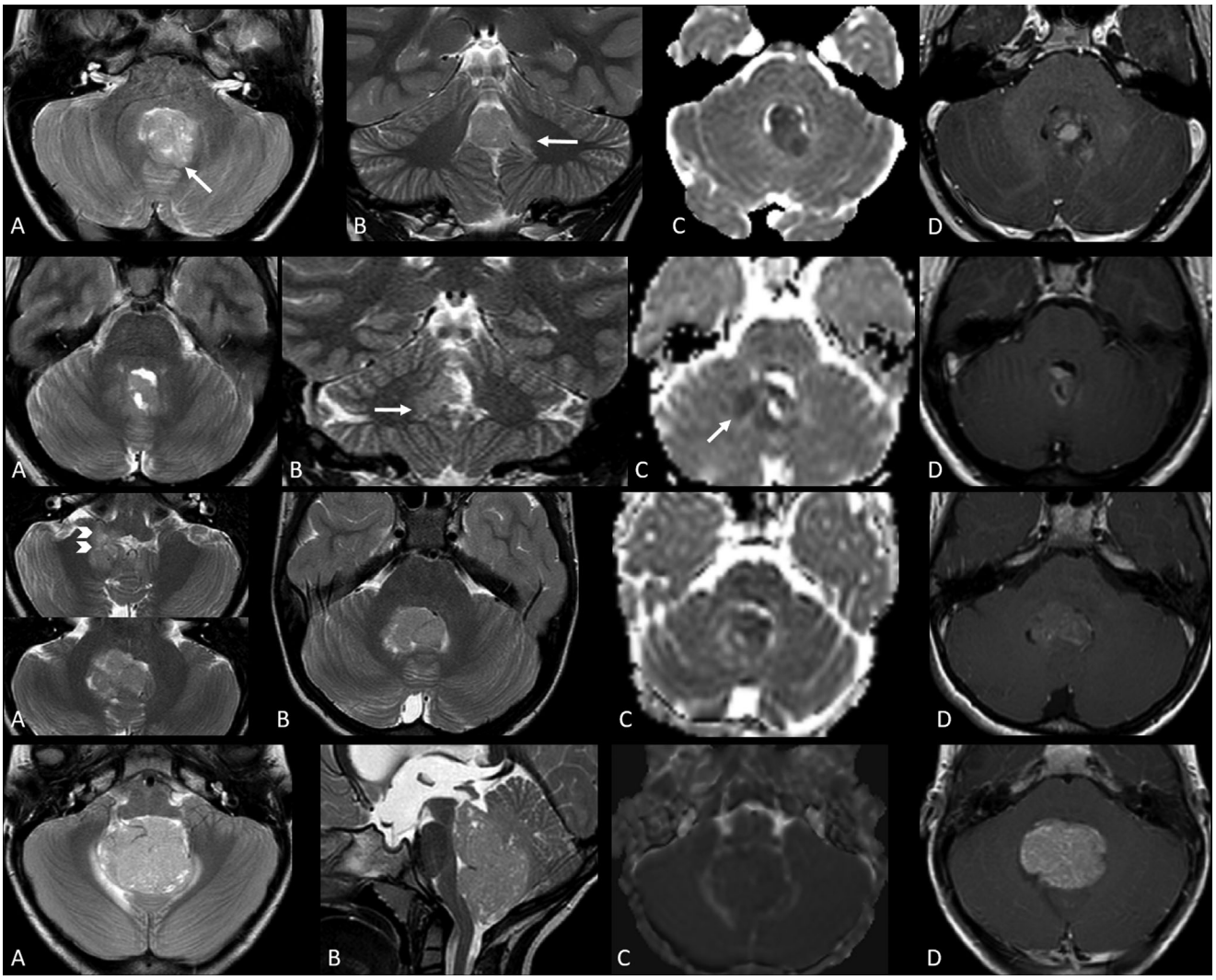

FIGURE 1 Brain MRI in cases 1-4. T2-wi (A,B), ADC (C), and T1-wi after contrast medium (D) showing tumors in the posterior fossa located in the fourth ventricle. In cases 1-3, the masses appear to be gross midline, with no definite laterality. Note involvement of the left (case 1) and right (case 2) postero-lateral recesses of the fourth ventricle in subtype B (arrows), and of the right antero-lateral recess of the fourth ventricle in subtype A (arrowheads in case 3). In case 4, the tumor is midline, with no obvious laterality. Subtype A is the most central of all WNT medulloblastomas.[14] All tumors show similar signal abnormalities and enhancement patterns

successful treatment; and (c) examine in-depth the complex hereditary genetic mechanism behind the onset and course of MBL in these patients.

We also considered acute, that is CSI duration, chemotherapy courses received, total drug doses administered, and long-term toxicities, that is endocrine and neurocognitive deficits, of the treatments administered. All survivors' current state of health and social status were reported with a view (if possible and judged necessary) to reducing the postsurgical treatment of this particular group of MBL in the light of patients' prognosis and the toxicity they experienced.

Oncological disease-free survival after the diagnosis of MBL was calculated with Kaplan-Meier methods.

The study was approved by our institution's independent ethical committee (prot. 166/20). Patients or parents gave their consent to this analysis.

3 | RESULTS

3.1 | Patients' MBL-related features

Six patients (five of them females) were diagnosed between 2007 and 2016 and met our inclusion criteria. They were a median of 10 years old (range 6-26 years) at MBL diagnosis. All patients presented at diagnosis with a clinical picture correlating with the tumor site (ie, cerebellar deficits, endocranial hypertension, strabismus). None of them had had MRI before the suspect of brain tumor diagnosis for surveillance purposes.

The original MRI findings could be retrieved for review in five of six cases. Tumors were classified on the basis of site, T2-weighted and DWI signal intensity, and contrast enhancement in accordance with the classification of WNT MBL proposed by Patay et al, and already

TABLE 1 Patients oncological histories, FIQ, and present status

Patients	Sex	Age at diagnosis (years)	CSI duration	Boost	OS months	Oncological event-free survival	Desmoid (age)	Other malignancies (age)	FIQ at time after diagnosis (months)	Present status
#1	F	26	46	PF	90	54, uncensored	Y (28 years)		76, after 2 years	University degree, married, fully independent
#2	F	12	44	PF	142	129, uncensored	N	N	73, after 2 years	Working after completing a professional course
#3	F	13	44	PF	90	71, uncensored	N	MELTUMP (23 years)	86, after 7 years	Attending university
#4	M	10	43	TB	42	42, censored	N	Melanoma (19 years)	89, after 3 years	Special education program and extra-help teacher
#5	F	6	39	TB	60	60, uncensored	N	Thyroid Tir3 and pancreatoblastoma (11 years)	98, after 5 years	Special education program
#6	F	6	42	TB	44	44, censored	N	N	n.a.	Standard education program

Abbreviations: CSI, craniospinal irradiation; FIQ, full intelligence quotient; OS, overall survival; PF, posterior fossa; TB, tumor bed.

summarized above.[12] All tumors were located in the IV ventricle and characterized by uneven T2 hyperintensity, patchy contrast enhancement, and low ADC levels on DWI. Two were subtype A, and three were subtype B. Hydrocephalus was absent in three and present in two cases (Figure 1, case 5 not shown).

All patients underwent complete surgical excision of their tumors, which were all attributed to classic histotype and WNT subtype, as WNT is deregulated where there is a germline APC pathogenetic mutation. For all patients, beta-catenin immunostaining was assessed in tumoral tissue. Nuclear positivity at immunohistochemistry was found in two of six patients' samples. For further confirmation of WNT subtype, four samples, having sufficient amount of tissue and adequate DNA, were analyzed by DNA methylation profiling and copy number variation.[16]

Two samples had a methylation subgroup classifier score of 0.99 for WNT and the other two had both chromosome 6 deletion, thus confirming molecular subgroup.

All patients were homogeneously treated irrespective of age under or over 18 years, as already reported.[17] Importantly, all patients received CSI up to a total dose of 23.4 Gy, and a boost to the posterior fossa (in three patients) or tumor bed (in the other three) up to a total dose of 54 Gy, delivered in fractions of 1.8 Gy, without any interruption due to acute side effects of hematological toxicity (Table 1).

In one patient (who was 26 years old at diagnosis), the postoperative schedule including cisplatin, vincristine, and lomustine was changed—replacing cisplatin with carboplatin and omitting vincristine—due to ototoxicity after the second course and severe peripheral neurotoxicity with gait impairment.

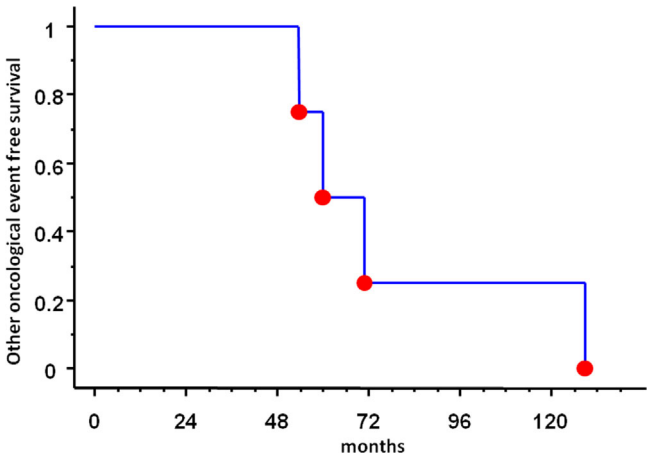

FIGURE 2 Survival free of other oncological events

All patients were in complete remission at 44-142 months after diagnosis (median 65 months) and were in active follow-up at the time of this report. To complete the epidemiological framework of our cases, we report two further patients under 16 years of age at diagnosis who were diagnosed and treated in the same period and without clinical high-risk features, on a total of 48, had MBL classified as WNT subgroup: both were alive in complete remission at the time of this report.

3.2 | Late effects

Three patients had hypoacusia for acute tones, three had hypothyroidism (accompanied by thyroid nodules in two cases), two had growth

TABLE 2 Patient FAP histories

Patients	Proband	Age at genetic test(years)	APC pathogenic variant - nucleotide HGVS	APC pathogenic variant - protein HGVS	No. of polyps at first endoscopic exam (age)	Total colectomy (age)
#1	Y	31	c.(?_-85)_(*1_?)del	p.(0)	Colonoscopy (symptoms): 30 (11 years)	IRA (24 years)
#2	Y	25	c.3329C>G	p.(Ser1110*)	Colonoscopy (symptoms): 50 (25 years)	N
#3	N	9	c.3768dupA	p.(Glu1257Argfs*19)	Colonoscopy: >100 (15 years)	IRA (16 years)
#4	N	8	c.3183_3187delACAAA	p.(Gln1062*)	NA	N
#5	N	8	c.3927_3931delAAAGA	p.(Glu1309Aspfs*4)	NA	N
#6	N	10	c.4145_4150delTCATGTinsA	p.(Leu1382Hisfs*2)	Colonoscopy: >100 (13 years)	N

hormone deficits, and five had vitamin D deficiency. One patient was married and having fertility treatment.

Three patients were still in mainstream school, with special education program and extra-help teacher in one case each (at MBL diagnosis 6 and 10 years old, respectively), while the third one did not need any education-tailored program or help (6 years old at diagnosis).

One patient, 13 years old at diagnosis, was attending university; one, 12 years old at diagnosis, was working after completing a professional course, and one, 26 years old at diagnosis, had a university degree, was married and stayed at home, fully independent. Full intelligence quotients (FIQ) were available for five patients after 2-7 years from diagnosis (Table 1).

Table 1 also shows each patient's oncological history after treatment for MBL. One patient developed a melanocytic tumor of uncertain malignant potential (MELTUMP), one a melanoma, another a thyroid nodule (classified as Tir3, ie, uncertain malignancy, after needle biopsy), and a pancreatoblastoma a mean 6 years after MBL.

Figure 2 shows patients' subsequent oncological disease-free survival, which was 50% at 5 years.

3.3 | Patients' FAP-related features

As shown in Table 2, all patients harbored a pathogenic germline variant of the APC gene that was responsible for a truncated protein in five cases and the complete loss of the protein in one. Two of the six patients were probands, and FAP was diagnosed after the onset of gastrointestinal symptoms (8 years after treatment for MBL in one case). The other four patients belonged to families with already genetically determined polyposis. Two patients underwent total colectomy with IRA, while four have yet to undergo surgery. One of the patients who had total colectomy developed an intra-abdominal desmoid tumor 4 years after this prophylactic surgery.

Patients' FAP-related family histories are shown in Table 3. Five of the six patients had a family history of polyposis, three had a family history of CRC, and none of the patients had a family history of CNS tumors. Other tumors were described in the families of three patients.

4 | DISCUSSION

APC somatic mutations are not generally found in sporadic MBL, but this tumor may be associated with patients harboring the APC germline pathogenic mutations that cause FAP syndrome.[18] APC gene mutations generally start from a KRAS proto-oncogene point mutation, with DNA hypomethylation activating the proto-oncogene. This is followed by a loss of the APC alleles that serve as a tumor suppressor gene. MBL associated with FAP syndrome comes from neural stem cells containing the homozygous APC mutation.[19]

MBL accounts for 80% of the brain tumors found in patients with FAP, a condition associated with a seven-fold relative lifetime risk of any brain tumor, and with a 90 times higher risk of MBL.[20]

The molecular subtype in the context of FAP is WNT/Wg. APC mutations are involved in around 7% of WNT/Wg molecular subtype MBL.[21–26] It is noticeable that in our series, some cases despite APC germline mutations do not show nuclear β-catenin accumulation, but it must be emphasized that there are some limits of immunohistochemistry that make the technique not always reliable.[27,28] These patients' radiological features were superimposable on those reported by Patay et al in the context of WNT molecular subgroup MBL[14] and later confirmed by other authors.[29] There are no guidelines for brain tumor surveillance in the context of FAP, probably because there are still no registries available to consult that reliably show how many people with inherited or sporadic colorectal cancer develop MBL, or vice versa.[30] In members of a family with FAP who do not yet have polyposis, neurological symptoms should prompt radiological examination of the CNS, because brain tumors manifest before the polyposis is diagnosed in more than one in two FAP patients.[31] This was also the case in two of our six patients. A major effort by the SIOP to move in this direction is in progress as part of the PNET5 trial,[12] with the creation of a registry

TABLE 3 Patient family histories

Patients	History of polyposis	History of CRC	History of CNS tumors	History of desmoid tumors	Other malignancies
#1	Y; mother, sister, brother, maternal uncle, maternal grandmother	N	N	Y; mother (37 years)	Y; sister - papillary thyroid cancer (15 years), maternal grandmother - gastric cancer (67 years)
#2	N	N	N	N	Y; paternal grandfather - prostate cancer (70 years)
#3	Y; mother, brother, maternal grandfather	N	N	Y; mother (30 years)	Y; maternal grandfather - testicular seminoma (40 years)
#4	Y, father, paternal grandmother, paternal great-aunt, paternal great-grandmother	Y; paternal grandmother (39 years), paternal great-grandmother (53 years)	N	N	N
#5	Y; mother	Y; mother (38 years)	N	N	N
#6	Y; father, sister, 2 paternal uncles, paternal grandfather	Y; father (33 years), paternal grandfather (46 years)	N	N	Y; paternal cousin - Ewing sarcoma (16 years), paternal grandmother - breast cancer (63 years)

Abbreviations: CNS, central nervous system; CRC, colorectal cancer; N, no; Y, yes.

for all patients with MBL harboring constitutional genetic mutations, including APC.

What we are still lacking, however, is therapeutic guidelines that take into account both the good outcomes reported in a handful of more recent papers[15] and the genetic fragility of these patients. They spontaneously develop many different types of tumors and are obviously more susceptible to secondary tumors after adjuvant treatment for MBL. It is sadly remarkable that the only death of a patient, in the series recently reported by a cooperative French group,[15] was due to a triton tumor 14 years after MBL had been diagnosed.

As already emphasized, patients with WNT-MBL are currently treated with de-escalating protocols aiming at maintaining good outcome with reduced late effects.[12,13] This FAP patient subgroup is even more fragile, deserving special attention in their disease story. Moreover, a very recent paper reported a meta-analysis on WNT-MBL relapses showing the usefulness of adjuvant cyclofosfamide in reducing relapses.[32]

In our smaller but single-institution series, apart from desmoid and thyroid tumors, three patients developed other three tumors possibly unrelated to FAP, despite having received lower doses of CSI than the French series, and standard chemotherapy.

Few data characterize the cognitive abilities of individuals with FAP, but the role of APC protein in the development of the central nervous system is well known,[33] and a very recent paper has underlined the significantly lower performance on IQ and in a variety of neurocognitive functions in a population of 24 patients compared to non-FAP pairs.[34] The results of our small series in terms of cognitive performances, FIQ, and social life are therefore not only to be attributed to MBL and its treatment but also to the pervasive activity of FAP.[34]

Collecting these now better-defined cases of MBL in patients with FAP will broaden our understanding of their MBL outcome and hopefully enable their better-tailored treatment and rehabilitation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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