Child's Nervous System (2019) 35:795–800
https://doi.org/10.1007/s00381-019-04075-6

ORIGINAL ARTICLE

Establishing reproducible predictors of cerebellar mutism syndrome based on pre-operative imaging

Heng Zhang[1,2] · Zhiyi Liao[1,2] · Xiaolei Hao[1,2] · Zhe Han[1,2] · Chunde Li[1,2] · Jian Gong[1,2] · Wei Liu[1,2] · Yongji Tian[1,2]

Received: 26 December 2018 / Accepted: 27 January 2019 / Published online: 6 February 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Purpose To establish some explicit, feasible, and reproducible predictors for CMS.

Materials and methods This study was a retrospective case study. Data were obtained from 82 patients with medulloblastoma at a single center, Beijing Tiantan Hospital. Based on medical records, we created two independent samples: the CMS group comprising 23 patients and the non-CMS group comprising 23 patients. Pre-operative imaging was studied by performing quantitative assessments of specific indicators.

Results The CMS group showed greater differences in pre-operative imaging data with the non-CMS group. The A_{axi}/d_{axi} ratio in pre-operative MR imaging captured in the axial plane was used to quantify the compression of the cerebellum and brainstem, and significant differences were observed between the CMS group and non-CMS group ($p = 0.0002$). In the sagittal plane, $D_{sag}{*}d_{sag}$ was used to quantify the area of the tumor that invaded the brainstem, and significant differences were observed between the two groups ($p = 0.0003$). In the coronal plane, A_{cor}/d_{cor} was used to quantify the compression of the upper functional brain region, and significant differences were noted between the two groups ($p = 0.0219$). Additionally, Evans' index was introduced to quantify the degree of hydrocephalus. The CMS group tended to show an increased Evans' index ($p = 0.0027$).

Conclusion Based on pre-operative imaging data, some reproducible predictors, such as A_{axi}/d_{axi}, $D_{sag}{*}d_{sag}$, A_{cor}/d_{cor}, and Evans' index, were established.

Keywords Cerebellar mutism syndrome · Medulloblastoma · Reproducible predictors · Brainstem compression · Surrounding edema · Efferent cerebellar pathway

Introduction

Cerebellar mutism syndrome (CMS) is also called posterior fossa syndrome, which is a severe complication of posterior fossa surgery. A study of a large population revealed that CMS occurs in approximately 25% of patients with medulloblastoma [1], whereas the incidence was as high as 40% in another study [2]. Patients will recover from the main symptom of CMS, cerebellar mutism, or muteness, in several months. In another long-term follow-up study, patients presenting mutism suffered from long-term cognitive and emotional disorders, subsequently decreasing their quality of life [3].

Because medulloblastoma is the most common tumor in the posterior fossa, studies of the current mechanism and risk factors for CMS have mainly focused on patients with medulloblastoma. The mechanism of CMS remains unclear. Nevertheless, some researchers postulated that CMS is caused by secondary surgical damage to the efferent cerebellar pathway (ECP) [4–8]. The ECP pathway consists of four parts: D (dentate nucleus), R (red nucleus), T (thalamus), and P (premotor cortex). The mutism of these patients may be caused by the interruption of some parts of the pathway.

Researchers have confirmed several risk factors for CMS, among which the most typical risk factors include brainstem invasion [1, 9] and brainstem compression [10]. However, the methods used to quantify the risk factors are either non-specific measurement standards or are too difficult to make ensure their routine use in the clinic. We established some intuitive predictors using pre-operative imaging data to describe the tumor characteristics. Significant differences in

✉ Yongji Tian
ttyysw1tyj@163.com

[1] Department of Pediatric Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

[2] China National Clinical Research Center for Neurological Diseases, Center of Brain Tumor, Beijing Institute for Brain Disorders, Beijing Key Laboratory of Brain Tumor, Beijing, China

these predictors were observed between patients with CMS and the non-CMS group.

Patients and methods

Patients

This study employed a retrospective case study design. Cases were derived from the patients who underwent surgery at the Beijing Tiantan Hospital from January 2016 to December 2017. Patients were required to meet the following inclusion criteria for participation in the present study: (1) children with a post-operative pathological diagnosis of medulloblastoma (2) aged from 2 to 18 years (3) for whom complete pre-operative imaging data were available (pre-operative MR imaging is essential). Patients were excluded if they were diagnosed with a severe, preexisting language or cognitive impairment, or if they were lacking pre-operative MRI data. A reliable language assessment is not available for children aged less than 2 years, and thus these patients were excluded. Before the investigation, we received the approval of the Ethics Review Committee of Beijing Tiantan Hospital.

Methods

Eighty-two patients were included. We collected text information from 82 patients with medulloblastoma, including admission records, course records, surgical records, and discharge records, which was established as the database of medical records. Then, we reviewed the database of medical records to determine which children were diagnosed with CMS. Due to the limitations of retrospective case studies, we defined the children who experienced muteness within a week after the operation as patients with CMS. We defined 23 patients with CMS as the CMS group. Because the distributions of molecular subtypes and age differed between children in the CMS group (23 patients) and non-CMS group (59 patients), we selected 23 non-CMS patients as the non-CMS group based on their molecular subtypes and age to minimize the possible effects of the two factors on the results of the study. Imaging data were collected later than the text information, which occurred after patients were stratified into a group, to minimize the selection bias and ensure the reliability of the results. Based on the imaging data, we analyzed data from the 46 patients in the two groups in the other database, called the database of pre-operative imaging, such as head CT and head MRI. In the search for measurable characteristics, we established some specific predictors to present the morphological features of the tumors by studying MR imaging captured in the axial, sagittal, and coronal planes. In addition, we introduced Evans' index (EI), which was measured using a pre-operative CT scan or T2-weighted imaging to quantify the degree of hydrocephalus. (We thought that the CT scan was better to measure Evans' index. Of course, if the CT scan was not available, T2-weighted imaging was the secondary choice for the measurement).

Measurement methods (Fig. 1)

1. A_{axi}, d_{axi}, A_{axi}/d_{axi}: captured from the axial plane of T1-weighted imaging, A_{axi} was defined as the angle between the tumor and the bottom of basilar artery. The bottom of basilar artery was used for the common end vertex. The d_{axi} was defined as the nearest distance from the bottom of basilar artery to the tumor. We could easily point out that if the A_{axi} and d_{axi} were fixed, the compression of the cerebellum and brainstem by the tumor was all placed. And the more increasing angle and more decreasing distance, it meant the tumor was more inclined to the pons of the cerebellum or the brainstem and more obvious brainstem compression. Thus, we defined the A_{axi}/d_{axi} as the indicator to quantify the compression of the cerebellum and brainstem by the tumor. If surrounding cystic change was existed, it was also included in the range of tumor.
2. D_{sag}, d_{sag}, $D_{sag}*d_{sag}$: captured from the sagittal plane of T1-weighted imaging, D_{sag} was described as the distance from the upper point to the lower point of the brainstem invaded by the tumor. The d_{sag} was defined as the depth of the invasion of the brainstem by the tumor. $D_{sag}*d_{sag}$ was used to approximately calculate the area of the brainstem invaded by the tumor in the sagittal plane. The range of tumor was including the solid component and the cystic component of the tumor.
3. A_{cor}, d_{cor}, A_{cor}/d_{cor}: captured from the coral plane of T1-weighted imaging, A_{cor} was defined as the angle between the tumor and the bottom of the third ventricle while the bottom of the third ventricle was set as the common end vertex. The d_{cor} was defined as the nearest distance from the bottom of the third ventricle to the tumor. In the similar way of A_{axi}/d_{axi}, we used the ratio of A_{cor}/d_{cor} to quantify the compression of the upper brain functional area by the tumor. The range of tumor was including the solid component and the cystic component of the tumor.
4. Evan's index: captured from the CT scan or T2-weighted imaging, Evan's index was defined as the ratio of the greatest distance between the frontal horns and the greatest distance between the brain parenchyma.

Statistical analysis

Statistical analyses were performed using statistics software (Statistical Package for the Social Sciences Statistics, Version

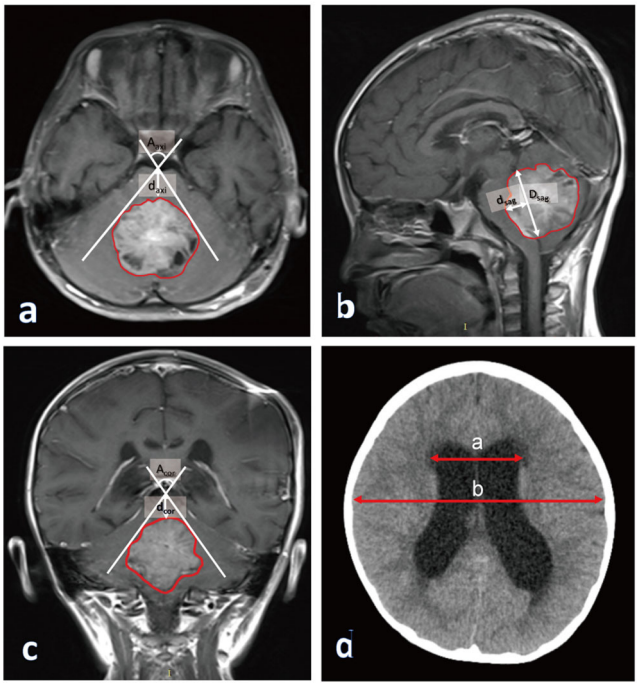

Fig. 1 **a** The fixed point O is the bottom of the basilar artery. A_{axi} represents the scope of tumor invasion in the cerebellar hemisphere, and d_{axi} represents the vertical distance from point O to the tumor. **b** D_{sag} represents the range of tumor invasion to the brainstem, and d_{sag} represents the extent of brainstem invasion. **c** The fixed point P is the bottom of the third ventricle, A_{cor} represents the scope of tumor invasion into the cerebellar hemisphere, and d_{cor} represents the distance from the tumor to point P. **d** Evans' index is defined as the ratio between the maximal diameter of the frontal horns and the inner diameter of the skull. Evans' index = a/b

20.0; IBM, Armonk, New York), and two-sample *t* tests were used to compare means from the CMS group with the non-CMS group. The level of statistical significance was < 0.05.

Results

Of the 82 children diagnosed with medulloblastoma, 23 (28%) children suffered from CMS, whose mean age was 6.17 ± 0.48 years. In the other group sorted by molecular subtype and age, 23 children were selected as the non-CM group, who have the same distribution of molecular subtype and similar ages (mean age of 5.79 ± 0.49 years) (Table 1).

Measurement results

By quantifying the tumor characteristics, we measured all the data two times and reported the means as the final results. Using two sample *t* tests, A_{axi} exhibited an extremely significant difference between the two groups ($p = 0.0001$), and d_{axi} was significantly different between the CMS group and non-CMS group ($p = 0.0014$). In the sagittal MR imaging, D_{sag} ($p = 0.0023$) and d_{sag} ($p = 0.0003$) were extremely significantly different. In the coronal MR imaging, A_{cor} ($p = 0.0009$) and d_{cor} ($p = 0.0026$) showed extremely significant differences. In addition, in pre-operative CT scans or T2-weighted MR imaging, we observed significant differences in Evans' index between the CMS and non-CMS groups ($p = 0.0027$).

We further analyzed quantified indicators of MRI multidimension by calculating A_{axi}/d_{axi}, $D_{sag}*d_{sag}$, and A_{cor}/d_{cor}. A_{axi}/d_{axi} (the compression of the cerebellum and brainstem by the tumor) significantly differed between the two groups ($p = 0.0002$). A_{cor}/d_{cor} (the compression of the upper functional brain region by the tumor) was significantly different ($p = 0.0219$). $D_{sag}*d_{sag}$ (the invasion area of brainstem) showed a significant difference at $p = 0.0003$. (Table 2).

Discussion

CMS is a complex syndrome that occurs after posterior fossa surgery and manifests as a combination of various clinical symptoms in addition to cerebellar mutism or muteness, including neurological dysfunction (such as ataxia, hypotonia, oropharynx, movement disorders, and pseudo-bulbar paralysis) and neurocognitive syndrome (cerebellum cognitive emotional syndrome or CCAS) [11]. At the same time, the occurrence of post-operative mutism poses a substantial challenge for post-operative nursing care and adjuvant radiotherapy or chemotherapy.

Currently, pre-operative MRI revealed a potential correlation between the pre-operative characteristics of the tumors in children and the occurrence of post-operative mutism [12, 13], and the risk factors for CMS have become an area of intense investigation. McMillan and colleagues postulated that brainstem compression is the independent risk factors for CMS. Inspired by their findings, we further studied the data of pre-operative imaging and established some reproducible predictors. We adopted more rigorous methods to control for the unbalanced distributions of some characteristics, such as the age at operation and histological types of neoplasms, between patients with CMS and non-CMS patients, such as grouping based on molecular subtypes and age and only selecting patients with medulloblastoma as the case group. In further studies, we explored images captured in multiplanes to establish some efficient predictors that would quantify tumor characteristics. The results for the cross-sectional characteristics of tumor were similar to the findings reported by McMillan et al., suggesting that the methods were reproducible. In the base of that, we found a significant difference between the CMS group and the non-CMS group by calculating the ratio of A_{axi}/d_{axi}. Comparing their means of two groups, we found that the CMS group seemed to be tender to have a more obvious compression of the brainstem and cerebellum. In the similar way, we got that the CMS group,

Table 1 Demographic characteristics of patients in the two independent samples

Patients ($N = 46$)	Non-CMS group ($N = 23$)		CMS group ($N = 23$)	
	Mean (SD)	Number	Mean (SD)	Number
Age	5.79 (0.48)		6.17 (0.49)	
Gender				
Male		17 (74%)		14 (61%)
Female		6 (26%)		9 (39%)
Chief complaint				
High cranial pressure		19 (83%)		21 (91%)
Cerebellar ataxia		7 (30%)		12 (52%)
Recurrence		1 (4%)		1 (4%)
Others		3 (13%)		3 (13%)
Shunt operation				
No		8 (35%)		5 (22%)
Yes		15 (65%)		18 (78%)
Extent of resection				
Gross total		15 (65%)		10 (43%)
Nearly total		8 (35%)		13 (57%)
Subtotal		0 (0)		0 (0)
Molecular subtypes				
SHH		9 (39%)		9 (39%)
WNT		1 (4%)		1 (4%)
G3		0 (0)		0 (0)
G4		13 (57%)		13 (57%)
Metastasis				
No		21 (91%)		20 (87%)
Yes		2 (9%)		3 (13%)
Location				
Fourth ventricle		19 (83%)		23 (100%)
Left cerebellar hemisphere		1 (4%)		0 (0)
Right cerebellar hemisphere		3 (13%)		0 (0)

in the coral plane, has an increasing compression into the upper functional brain region by calculating the ratio of A_{cor}/d_{cor}. This has not been found in other studies. The brainstem invasion or infiltrate has been noted in some study. But how to measure the degree of invasion did not well defined. We wanted to introduce the product of $D_{sag}*d_{sag}$ to quantify the extent of brainstem invasion. In addition, we introduced Evans' index to quantify the degree of pre-operative hydrocephalus and found that the CMS group exhibited an increased Evans' index, indicating that the degree of pre-operative hydrocephalus was linked to the occurrence of post-operative CMS. To our knowledge, pre-operative hydrocephalus causes restricted edema in the surrounding white matter and results in adjacent axonal injury [14], which is often self-healing [15]. This condition may be linked to transient aphasia symptoms. On the other hand, Evans' index also reflects the speed of disease progression. Generally, children with a rapid progression often exhibit a greater degree of hydrocephalus. After surgery, for the removal of obstructions in the four ventricles, the pressure is relieved and the lateral ventricle pressure is substantially decreased, which may lead to conduction beam damage of related pathways.

Summary above, we could draw the conclusion that the CMS group has some characteristics below: increasing compression into the cerebellum or brainstem, obvious invasion or infiltrate into the brainstem, greater compression into the upper functional brain region, and accompanying with more serious hydrocephalus. Combined with the understanding of the ECP pathway, we thought that the occurrence of post-operative CMS might be the outcome of the edema caused by the pre-operative compression or the secondary injury by the operation. The edema in surrounding cerebellar tissue might trigger off the temporary interruption of the ECP pathway. And when the edema got remission, the fiber bundle up and down still needed a long time to go back to normal. And in one interesting study hosted by Concezio Di Rocco et al., they

Table 2 *T* tests results

Patients ($N = 46$)	CMS group ($N = 23$)	Non-CMS group ($N = 23$)	p values
cEvans' index	0.37 ± 0.05	0.32 ± 0.06	0.0027**
Axi-plane			
d_{axi} (cm)	1.44 ± 0.16	1.69 ± 0.30	0.0014**
A_{axi} (°)	74.04 ± 6.01	63.4 ± 10.32	0.0001***
A_{axi}/d_{axi} (°/cm)	52.46 ± 8.78	39.62 ± 12.10	0.0002***
Sag-plane			
d_{sag} (cm)	0.81 ± 0.17	0.58 ± 0.22	0.0003***
D_{sag} (cm)	4.54 ± 0.60	3.72 ± 1.04	0.0023**
$D_{sag}*d_{sag}$ (cm^2)	3.65 ± 0.81	2.33 ± 1.35	0.0003***
Cor-plane			
d_{cor} (cm)	0.96 ± 0.29	1.31 ± 0.44	0.0026**
A_{cor} (°)	70.63 ± 6.20	61.03 ± 11.07	0.0009***
A_{cor}/d_{cor} (°/cm)	82.61 ± 27.55	58.67 ± 39.69	0.0219*

* $p<0.05$; ** $p<0.01$; *** $p<0.001$

found patients with pre-operative language impairment were more likely to develop post-operative CMS and PLI can be considered a subclinical state of CMS in some children with posterior fossa tumor [16]. This study enriched the mind of people to nicely understand the CMS.

Now, we lack the tool to classify the risk of post-operative occurrence of CMS, and captured in the pre-operative imaging, quantified predictors could help to mark which patient has an increasing tendency to develop post-operative CMS. Our study firstly introduced some intuitive measurement to quantify the characteristic of tumor and they could simply separate the high-risk patients from the pre-operative vague people. They could also give light to the development of risk assessment scale (score) of post-operative CMS.

Conclusion

Further clinical research of cerebellar mutism syndrome is needed. With regard to the increasing concerns about imaging studies of patients with CMS, which has the advantages of no extra costs and intuitive assessments of tumor characteristics, our study was initially based on the multi-direction evaluation of pre-operative imaging data. In our study, some quantitative and reproducible predictors, such as A_{axi}/d_{axi}, $D_{sag}*d_{sag}$, A_{cor}/d_{cor}, and Evans' index, were applied to predict the occurrence of pediatric CMS, which showed potential sensitivity and specificity. A prospective cohort study is needed for additional validation. The mechanism of CMS requires further research in the future, and the establishment of predictors based on pre-operative imaging data would help pediatric neurosurgeons to identify high-risk patients and develop specific precautions.

Funding This study was funded by the Beijing Natural Science Foundation (7172041).

Compliance with ethical standards

Before the investigation, we received the approval of the Ethics Review Committee of the Beijing Tiantan Hospital

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Robertson PL, Muraszko KM, Holmes EJ, Sposto R, Packer RJ, Gajjar A, Dias MS, Allen JC (2006) Incidence and severity of post-operative cerebellar mutism syndrome in children with medulloblastoma: a prospective study by the Children's Oncology Group. J Neurosurg 105:444–451. https://doi.org/10.3171/ped.2006.105.6.444
2. Beckwitt TS, Krieger MD, O'Neil S, Jubran R, Tavare CJ (2012) Symptoms before and after posterior fossa surgery in pediatric patients. Pediatr Neurosurg 48:21–25. https://doi.org/10.1159/000337730
3. Wells EM, Khademian ZP, Walsh KS, Vezina G, Sposto R, Keating RF, Packer RJ (2010) Post-operative cerebellar mutism syndrome following treatment of medulloblastoma: neuroratiographic features and origin. J Neurosurg Pediatr 5:329–334. https://doi.org/10.3171/2009.11.PEDS09131
4. Koh S, Turkel SB, Baram TZ (1997) Cerebellar mutism in children: report of six cases and potential mechanisms. Pediatr Neurol 16:218–219. https://doi.org/10.1016/S0887-8994(97)00018-0
5. Morris EB, Phillips NS, Laningham FH, Patay Z, Gajjar A, Wallace D, Boop F, Sanford R, Ness KK, Ogg RJ (2009) Proximal dentatothalamocortical tract involvement in posterior fossa syndrome. BRAIN 132:3087–3095. https://doi.org/10.1093/brain/awp241
6. Ellis DL, Kanter J, Walsh JW, Drury SS (2011) Posterior fossa syndrome after surgical removal of a pineal gland tumor. Pediatr Neurol 45:417–419. https://doi.org/10.1016/j.pediatrneurol.2011.09.011
7. Chua F, Thien A, Ng LP, Seow WT, Low D, Chang K, Lian D, Loh E, Low S (2017) Post-operative diffusion weighted imaging as a

predictor of posterior fossa syndrome permanence in paediatric medulloblastoma. Childs Nerv Syst 33:457–465. https://doi.org/10.1007/s00381-017-3356-7

8. Catsman-Berrevoets C, Patay Z (2018) Cerebellar mutism syndrome. Handb Clin Neurol 155:273–288. https://doi.org/10.1016/B978-0-444-64189-2.00018-4
9. Doxey D, Bruce D, Sklar F, Swift D, Shapiro K (1999) Posterior fossa syndrome: identifiable risk factors and irreversible complications. Pediatr Neurosurg 31:131–136. https://doi.org/10.1159/000028848
10. McMillan HJ, Keene DL, Matzinger MA, Vassilyadi M, Nzau M, Ventureyra EC (2009) Brainstem compression: a predictor of postoperative cerebellar mutism. Childs Nerv Syst 25:677–681. https://doi.org/10.1007/s00381-008-0777-3
11. Charalambides C, Dinopoulos A, Sgouros S (2009) Neuropsychological sequelae and quality of life following treatment of posterior fossa ependymomas in children. Childs Nerv Syst 25:1313–1320. https://doi.org/10.1007/s00381-009-0927-2
12. Law N, Greenberg M, Bouffet E, Taylor MD, Laughlin S, Strother D, Fryer C, McConnell D, Hukin J, Kaise C, Wang F, Mabbott DJ (2012) Clinical and neuroanatomical predictors of cerebellar mutism syndrome. Neuro-Oncology 14:1294–1303. https://doi.org/10.1093/neuonc/nos160
13. Sergeant A, Kameda-Smith MM, Manoranjan B, Karmur B, Duckworth J, Petrelli T, Savage K, Ajani O, Yarascavitch B, Samaan MC, Scheinemann K, Alyman C, Almenawer S, Farrokhyar F, Fleming AJ, Singh SK, Stein N (2017) Analysis of surgical and MRI factors associated with cerebellar mutism. J Neuro-Oncol 133:539–552. https://doi.org/10.1007/s11060-017-2462-4
14. Ding Y, McAllister JN, Yao B, Yan N, Canady AI (2001) Axonal damage associated with enlargement of ventricles during hydrocephalus: a silver impregnation study. Neurol Res 23:581–587. https://doi.org/10.1179/016164101101199045
15. Del BM, Zhang YW (1998) Cell death, axonal damage, and cell birth in the immature rat brain following induction of hydrocephalus. Exp Neurol 154:157–169. https://doi.org/10.1006/exnr.1998.6922
16. Di Rocco C et al (2011) Heralding cerebellar mutism: evidence for pre-surgical language impairment as primary risk factor in posterior fossa surgery. Cerebellum 10(3):551–562. https://doi.org/10.1007/s12311-011-0273-2