Review

The Entity of Cerebellar Mutism Syndrome: A Narrative Review Centered on the Etiology, Diagnostics, Prevention, and Therapeutic Options.

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Abstract: Cerebellar mutism syndrome (CMS), also known as posterior fossa syndrome, is encountered in a subset of children who have undergone an operative procedure of the posterior cranial fossa, mainly involving the vermis, and the most frequent underlying pathology is proved to be medulloblastoma. The most common characteristics of this syndrome include an often transient, although protracted, language impairment, emotional lability, along with cerebellar, and brainstem dysfunction. Nevertheless, a significant number of patients experience persistent neurological deficits and lasting neurocognitive impairment. A lot of research and clinical studies have been performed in order to better delineate this syndrome. The main obstacles in our way to highlight all aspects of this syndrome were related with an inconsistent nomenclature, poorly defined diagnostic criteria, and uncertainty surrounding risk factors and etiology. Currently, there is a combination of diagnostic criteria that are regarded as prerequisites in order to establish the diagnosis of CMS. These include language impairment and emotional lability, as proposed by the international Board of the Posterior Fossa Society in their consensus statement. Several risk factors are recognized as implicated in the pathogenesis of this syndrome, including midline tumor location, diagnosis of medulloblastoma, younger age at diagnosis, and preoperatively established language impairment. A proposed etiology of CMS includes disruption of the cerebellar outflow tracts, the cerebellar nuclei, and their efferent projections through the superior cerebellar peduncle. Specific treatment for CMS is lacking, and it continues to be directed at symptom management. Our aim is to present a comprehensive narrative review of CMS etiology, diagnosis, risk factors, clinical presentation, and clinical management. Moreover, we attempt to recognize the most widely recognized priorities of the research community in order to expand our knowledge in the era of diagnostics, prevention, and therapeutic options for patients suffering from CM, or who are at risk for development of this syndrome.

Keywords: cerebellal mutism syndrome; cerebello-cerebral diaschisis; posterior fossa tumor; vermis language impairment

Introduction

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The term cerebellar mutism syndrome is universally used in order to describe the loss, transient or permanent, of speech that is intimately related to any kind of cerebellar insult. Initially, CMS was reported in 1958, referring to a child who was mute after resection of a tumor involving the posterior fossa posterior fossa· this entity was termed akinetic mutism [1,2]. The first relevant cases of postoperative mutism affecting pediatric population, which was a subsequent of surgery involving the structures of the posterior fossa, were recorded in the 1970s [3,4]. Subsequently, in 1984, Wisoff and Epstein reported their experience, centered on children who developed delayed onset cranial nerve palsies, emotional lability, and speech impairment. They collectively named this constellation of findings as pseudobulbar palsy [5]. After that, in 1985 Rekate et al. presented the first small case series that was attempting to describe this entity. A manuscript was published that focused on six cases of cerebellar mutism that occurred after an operation involving the posterior cranial fossa [6]. Kirk et al. used the term posterior fossa syndrome in order to describe the same combination of clinical and neurological findings that was attributed to the term cerebellar mutism syndrome [7]. After this initial demarcation of this pathological entity, over 400 cases have been reported in the literature [8]. Cerebellar mutism most often is not observed as an isolated neurological finding, but, instead, it is a component of a more complex constellation of neurological deficits. More precisely, it accompanies a widespread cluster of neurological, emotional and behavioral disturbances. Based on the complexity of this entity, as well as on the fact that it incorporates multiple individual signs and symptoms, the term cerebellar mutism is frequently encountered in the current literature cerebellar mutism syndrome or posterior fossa syndrome. According to a recently published paper [1], this syndrome is characterized by a constellation of symptoms including mutism/reduced speech, emotional lability, cerebellar syndrome, brainstem dysfunction, hypotonia, and oropharyngeal dysfunction/dysphagia [9-13].

Regarding the most common conditions that underly this syndrome, it is widely accepted that the most common scenario refers to children that have undergone operation for a pathologic condition that affects the posterior cranial fossa. Nevertheless, it is not restricted in this patient population and it may accompany other pathologic conditions that are affecting the cerebellum, either in adults, or in children [14,15]. In childhood, the majority of solid tumors involve the central nervous system and, more specifically, the cerebellum (approximately 80% of them) [16]. Mutism is considered as a severe and devastating adverse neurological sequalae of neurosurgical approaches centered on resection of tumors of the posterior fossa, and its relative prevalence could not be underestimated. Its clinical course is largely unpredictable, with spontaneous resolution being the most frequent outcome, this not true for the other deficits that constitutes this entity. Namely, dysarthria, cognitive and behavioral disturbances as well as language disorders that are evident during the mute phase, are not always adequately resolved, and thus constitute a disabling condition for the patient.

The exact incidence of cerebellar mutism syndrome after posterior fossa surgery in children remains to be specified, probably because the recognition of relevant cases underestimates their true prevalence as the diagnostic criteria are not strict and universally adopted. Nevertheless, it ranges between 11% and 29% [8], even though more recent prospective studies that incorporated larger groups of pediatric patients reported an incidence of 27.7% [17] and 24% [11] respectively. The patients' mean age at presentation were 6–7 years, based on those reports. Nevertheless, whenever sex and patient age were investigated as possible independent risk factors for the development of the syndrome, no statistically significant correlation or differentiation could be established. On the contrary, the histopathology of the offending lesion was recognized as a potential contributor of the risk for the establishment of the syndrome. Namely, medulloblastoma resection indicated a higher correlation rate (40%), in comparison with pilocytic astrocytoma (16%) or ependymoma (4%) [12,17,18,19,20,21]. There is significant variability regarding the estimated rate of occurrence of this syndrome after posterior fossa tumor surgery, mainly due to the absence of strict definition criteria of the syndrome

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[9,22,23]. Another important parameter of this syndrome is related to the determination of the most important risk factors that have an impact on the possibility for the establishment of the relevant neurological deficits. Namely, midline tumor location and medulloblastoma histologic variant [24-28], younger patient age [9], left handedness, aggressive resection, infiltration of the brainstem, tumor diameter >5 cm has been implicated accordingly.

Another implicating factor was considered to be the existence of pre-surgical language deficiencies, although this association was based on a smaller patient population [29]. Although the entity of cerebellar mutism syndrome is inherently related to tumor lesions of the cerebellum, sporadical cases have been reported that implicated other pathologic conditions as precipitating factors. These included trauma [30], stroke [31] and inflammation [32].

Clinical presentation and time course

The time course of cerebellar mutism syndrome has three distinct phases. More precisely, cerebellar mutism is not evident after the initial recovery of the patient from the operation. Instead of that, there is a time interval between the operation and the establishment of the syndrome, which varies from few hours up to several days after the surgical procedure [11,33]. Moreover, mutism is always a transient disability with unpredictable duration, with reports depicting a time range between a few days to several months [14]. The resolution of mutism is not spontaneous and follows a gradual process. As is already mentioned, after the mute phase, several parameters of the syndrome continue to be evident, to various extent and in different combinations (motor speech and language deficits, cognitive, emotional and behavioral disorders).

During the mutistic phase high-pitched crying is the only form of vocalization [11]. During this phase, a constellation of neurological signs may be evident, indicating the existence of cerebellar and/or brainstem injury. These may include ataxia, involuntary eyelid closure, pyramidal tract signs, horizontal gaze paralysis, cranial nerve palsies and oropharyngeal dyspraxia [7]. The spectrum of this syndrome incorporates behavioral and emotional disturbances, which may manifest with emotional lability, apathy and autistic like behavior [34,35]. Bizarre personality changes may be evident as forced laughing or crying.

The dissolution of the components of mutism does not follow a universal pattern but, instead, can follow one of several different pathways [36,37]. It may be followed by dysarthria without any signs of higher language dysfunction [38], or a language disorder without dysarthria may be recorded. Another clinical scenario is that behavioral disturbances constitute the next manifestation of this syndrome. However, this concept is not universally accepted, as some researchers consider that dysarthria is a common characteristic that is evident in virtually every patient who is recovering from the acute phase of the syndrome [39]. The existence of long-term neurological deficits, as well as persistent neurocognitive impairment has been widely accepted as characteristics of that entity [18,40,41]. Differences in evaluation criteria and subgroups of selected patients could be the incriminating factor, capable to interpret the divergent inconsistent findings of reported studies. It would be beneficial to define universally accepted criteria on how to evaluate speech and language outcome for future studies. Because of that, the Posterior Fossa Society made an attempt to define this syndrome as a 'postoperative pediatric cerebellar mutism syndrome, characterized by delayed onset mutism/reduced speech and emotional lability, commonly accompanied by hypotonia, oropharyngeal dysfunction, cerebellar motor deficits, cerebellar cognitive affective syndrome, and brain stem dysfunction [12]

Attempting to define the specific components of dysarthria attributed to cerebellar mutism syndrome, the most commonly reported features include the existence of slow speech rate and the use of short but grammatically correct speech. Also, there is a report [37], which was centered on two children that had a telegraphic language in the post mutistic phase.

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Regarding the behavioral changes that characterize the post-mutistic phase, these share a lot in common with autism. It is common concept that the affected children had a decreased ability to be part of a team with their colleagues and avoided physical and eye contact. Another important remark is that speech is devoid of emotional inflections and was seldom utilized as a mean of communication [37]. Emotional disturbances are frequently present and consist of lability and irritability [36,37]. Regarding the long-term constituents of cerebellar mutism syndrome, they consist of ataxia, speech or language dysfunction, including dysarthria and dysfluent/slower speech, and intellectual impairment [11].

DISCUSSION

Possible causes of cerebellar mutism

The fact that this syndrome is accompanied with a wide, and divergent, spectrum of clinical manifestations, which come to clinical attention at different time periods, is an obstacle to the establishment of a universal anatomic-pathophysiological circuit, capable to interpret this entity. Several proposals have been adopted, hypothesizing that local tissue damage of the cerebellum and brainstem should be implicated in the development of the syndrome. Apart from that, dysfunction of regions of cerebral cortex, because of damage to cerebello-cortical pathways, should be taken into consideration. Another important factor that may play a role is the discrimination of the offending lesions under the terms permanent and transient (e.g., edema). The proposed offending mechanisms should not be considered as contradictory· on the contrary, they may share different and distinct roles to the pathophysiology of cerebellar mutism syndrome, acting at individual time points.

The current concept regarding the pathophysiologic explanation of the clinical features of the syndrome that occur during its distinct phases could be summarized under the following statements:

Mutism itself is inherently related to supratentorial dysfunction, mediated by crossed cerebello-cerebral diaschisis. This refers to a condition which is characterized by to an asymmetry of blood flow or metabolism in supratentorial structures contralateral to a remote cerebellar lesion [48,49]. Injury of the dentato-thalamocortical pathway is suggested to be the offending pathology of the crossed cerebello-cerebral diaschisis [49,50]. There are reports that support the existence of an association between damage of the frontal cortex and mutism [45,46,47,48]. Another fact that supports that concept is the existence of reports which correlate behavioral disturbances in children with cerebellar mutism with frontal cortex dysfunction [34,49-51]. Based on that evidence, we could state that the initial phase of symptoms relevant with cerebellar mutism are primarily attributed to cerebral cortical dysfunction, caused by crossed cerebello-cerebral diaschisis.

Regarding dysarthria, its anatomic substrate has been proposed to be damage of the dentate and interposed nuclei and in the cerebellar cortex with lesions of the paravermal lobule VI [52-54]. This is supported by the intimate anatomical relationship of cerebellar nuclei to the cerebellar midline, rendering them vulnerable to (permanent or transient) lesioning during tumor resection.

A distinct role of the cerebellum to language function, which is not limited to motor speech articulation, has been extensively investigated [55]. Agrammatic speech was the most frequently encountered component of aphasia of cerebellar origin· the posterolateral hemispheric region, along with the adjacent compartments of the dentate nuclei are considered to contribute to language.

Finally, intra-operative tissue damage to the region of the vermis is reported to share an intimate relationship with persisting affective disturbances as part of the ‘‘cerebellar cognitive affective syndrome’’ [56]. Apart from that, a lot of researchers have developed imaging-based predictive models in order to elucidate the underlying pathophysiology of CMS [26,57].

Neuroimaging and CMS

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The DTC pathway represents an important outflow tract from the cerebellar nuclei towards the cerebral cortex, as it connects the dentate nucleus, via the contralateral red nucleus and thalamus, to the contralateral cerebral cortex There is consensus that interruption of this pathway constitutes the main pathological substrate for CMS [8,58]. Abnormal signal intensities in regions that involve the proximal efferent cerebellar pathway, the middle cerebellar peduncle and the vermis have repeatedly been reported [35,38,42,59,60,61] [21,29,30,35,36,49]. A recent survey identified that lesions that are located along with the cerebellar outflow could be considered as predictors for the development of CMS [62].

The existence of postoperative vermian lesions should not be considered as equivalent to the development of CMS. Several experts state that the recognition of diffusion abnormality in the region of the vermis is not conclusive of the appearance of CMS [42,63]. Another useful sequence that is capable of assessing the integrity of white matter tracts is the diffusion tensor imaging, and this has been utilized in order to assess the integrity of the DTC pathway in cases of established CMS.

Intraoperative MRI could be considered as a sufficient adjunct in order to verify the existence of MRI abnormalities that take place during or immediately after the operation. More precisely, diffusion-weighted imaging [64] can verify the existence of vasogenic or cytotoxic oedema, intimately related with the surgical approach.

Pathophysiology and anatomy

Albeit numerous hypotheses have been proposed, centered on the pathogenesis of POPCMS, a comprehensive delineation of the underlying pathologic substrate needs to be performed. The development of this syndrome is intimately related with several anatomical structures that are located within the infratentorial and supratentorial compartments. This fact has led to the acceptance that a variety of mechanisms are implicated, as well as domes that are located both in the vicinity of the surgical field and at a distance from that, are responsible for its appearance [65,66].

An intraoperative surgical lesion located to the relevant anatomical substrates, more precisely the pECP, has been widely accepted as a precipitating factor for the establishment of POPCMS. A common immediate post-operative imaging finding is the establishment of cerebral edema in the vicinity of the resection cavity, which could be vasogenic or cytotoxic in origin. Post-operative edema reaches its maximum density at about 24 hours after the operation, remains relatively consistent for the next 3 days and is gradually disappeared at post-operative day 7 [67]. The importance of that remark is enhanced by several radiological studies, which have established the existence of a definitive correlation between oedema in the pECP domes and the establishment of POPCMS [35,38,68]. The availability of intra-operative MRI has led to the conclusion that the edema should be intimately correlated with surgical interventions and not with other pathophysiological interactions [69]. All these references suggest the implication of direct surgical maneuvers in the region of the pECP as an offending mechanism for POPCMS, along with the provoked, during the surgical approach, direct axonal injury [70,71].

Another implicated mechanism includes the tissue damage that is provoked by the thermal injury that is related with the operative procedure [58]. Researchers mention that the increased heat which is associated with the tumor aspiration via the CUSA could potentially be involved with the tissue damage to the brain parenchyma which surrounds the lesion, more precisely the pECP structures [72,73,74,75]. The anatomical distribution of this insult shares a lot in common with the distribution of the abnormal signal patterns that are delineated on the DWI sequence in individuals suffering from POPCMS. In accordance with that hypothesis, it has been mentioned that the restricted use of CUSA, in combination with avoidance of excessive retraction, as well as the judicious utilization of electrophysiological monitoring, is an effective, aiming toward the reduction of the incidence of POPCMS [68].

Anatomical substrate of CMS

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It is almost universally accepted that damage that involves the DTC pathway constitutes the main anatomical substrate of CMS [76,77]. Several different pathophysiologic mechanisms have been implicated in the context of DTC disruption, namely cerebral cerebellar diaschisis, edema, perfusion deficit and cerebellar vermis injury. A brief description of the aforementioned mechanisms follows.

Cerebral Cerebellar Diaschisis

This phenomenon is described as the functional deficit that refers to a definitive region of the brain and is causally related with a damage that has occurred to another, remote, brain region. The net effect of such an insult is the generation of an excitatory input to the inhibited area [42]. The disruption of these pathways leads to the loss of excitatory input from the cerebellum to the relevant recipient cerebral cortical areas. These include the motor, premotor, and prefrontal regions, which are known to interfere with the functions that are affected by cerebellar mutism and result in their loss of function [8,42,78]. Although diaschisis was initially encountered as a transient phenomenon, recent evidence has shown that it could be related to long-term damage, which was affecting the associated remote parenchymal brain areas [79]. This remark offers the substrate in order to explain the language and cognitive deficits that were registered in a significant percentage of patients suffering from CMS, even after 1 year after the establishment of its diagnosis [11,38]. There seems to be a time interval between the establishment of remote hypoperfusion from the onset of symptoms that displays a significant variation among different studies [80,81]. Nevertheless, this observation may serve as an explanation for the delayed onset of CMS symptoms.

Edema

The development of postoperative edema is another suggested mechanism, mainly because its appearance and evolution follow a parallel time course with the relatively delayed onset of CMS [60]. Supportive evidence on that is derived from diffusion tensor imaging studies, which have definitively shown the relation between edema and the development of post-operative mutism, located in the superior cerebellar peduncles, the pons and mesencephalon [35,60]. Nevertheless, a drawback of this proposed mechanism is related with its inability to provide an explanation about the fact that mutism does not subside after the resolution of the postoperative edema, whereas a group of symptoms may persist lifelong [35].

Perfusion Deficit

This theory provides an explanation regarding the delayed onset of CMS, according to which it may be causally related to the development of perfusion deficit. The establishment of postoperative vasospasm could provide a feasible explanation for the delay in the onset of CMS· apart from that, the transient ischemia that eventually follows vasospasm is in accordance with the clinical manifestation and eventual remission of CMS that occurs with the re-establishment of blood flow [71,82].

Cerebellar Vermis Injury

Tissue damage that refers to the cerebellar vermis and is related with the surgical approach to the offending lesion has been recognized to be of critical importance in the development of CMS [77]. We have identified connections of the vermis with the cerebellar nuclei that are believed to play a critical role to the development of fluent speech [77,83]. The trans-vermian approach, which involves splitting of the vermis in order to access tumors in the midline of the posterior fossa, has been proposed as a potential risk factor, albeit its contribution is not completely elucidated [77,84,85].

Prevention and Treatment

Although initially most experts considered that dysarthria that was attributed to post-operative CMS could recover in a short-term fashion without any residual deficits

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[38,86], this concept was not verified by subsequent studies. More precisely, it was realized that a wide spectrum of permanent defects was observed, the most evident of which was persistent dysarthria, language impairment, and dysphagia [11,88]. De Smet et al [89] and Huber et al [90] conducted studies centered on the long-term course of dysarthia encountered under the term of CMS. More precisely, Smet stated that all children suffering from pCMS exhibited dysarthria in the early phase of CMS, whereas in 91.7% of them, persistent motor speech deficits were recorded up to 12 years after surgery. Their recorded data were in accordance with other findings, which reported persistent motor speech defects in the long-term, and approved the standpoint that CMS should be considered as a prognostic factor for long-term dysarthria in children operated for cerebellar tumors [29,87].

Another important aspect of this issue is the identification of the most important risk factors that are crucial for the development of CMS. More precisely, according to Di Rocco et al [29], the existence of pre-operative language impairment was considered as an important risk factor for development of CMS. They demonstrated that, even preoperatively, impairment of selective speech and language functions can be present, when they examined patients with posterior fossa tumors. More precisely, there are only limited data published in the literature focused on this issue [91]. Apart from the results published from Di Rocco et al, several other articles simply mentioned the existence of preoperative language impairment as a potential risk factor for the establishment of CMS postoperatively [10,11,15,37,48,65,76,78]**.** On the contrary, only Beckwitt-Turkel evaluated extensively the significance of preoperative language impairment, and conducted similar conclusions [94]. According to a recent report [42], 28.5% of children presented preoperative language impairment and developed cerebellar mutism postoperatively. Moreover, when these patients were followed up for a long period of time, it appeared that the complete resolution of CMS occurred after a protracted time period.

Another issue that is of great clinical significance relates with the rehabilitation of speech and language problems established during and after the mute phase. Currently, no treatment modality centered on the speech and language disorder of CMS is available. Nevertheless, several efforts have been performed in order to ameliorate the neurological deficits that are associated with mutism in its acute stage, based on pharmaceutical intervention. Namely, corticosteroids, fluoxetine, thyrotropin-releasing hormone, bromocriptine, midazolam, and zolpidem have been utilized, albeit their efficacy is not verified at all [95].

Despite an effective and widely accepted therapeutic protocol for these children is lacking, timely intervention for children harboring tumors of the posterior fossa has been considered as an effective means to minimize speech and language deficits [96]. Based on current data, it seems that rehabilitation of speech and language in pediatric patients suffering from CMS necessitates a multi-phase implementation of evidence-based guidelines and recommendations that specify and underline the most significant risk factors, the registered specific deficits, and clinical data that are centered on the evolution of the syndrome over time [97,98,99]. Another issue that has extensively been studied in the literature is centered on the long-term neurocognitive outcomes of children suffering from CMS. According to most studies, it seems that these children demonstrate a wide spectrum of neurocognitive and neuroemotional deficits during their follow-up after their operative treatment [11,68].

Minimizing the risk of CMS

A systematic effort directed toward the elimination of the possibility for development of CMS should be oriented on the comprehensive determination of the implicated predisposing factors, either preoperative or intraoperative [84]. Attempting to develop a preoperative evaluation scale to stratify the potential risk, Walker et al [26] introduced a model which included six relevant factors. These included primary tumor location, as it was specified by MRI, bilateral middle cerebellar peduncle involvement (invasion and/or compression), dentate nucleus invasion, and age at surgery > 12.4 years.

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The ability to accurately predict that risk based on data that could be collected on preoperatively has a great impact on the determination of our surgical plan, namely the selection of the safest approach and the extent of anticipated resection.

Another important issue that continues to constitute a matter of considerable debate relates to the selection of the safest surgical approach, that is a comparison between a telovelar versus a trans-vermian approach. A lot of studies exist that have proposed that a split-vermis approach may be associated with an increased risk of CMS [100-103]. On the contrary, other authors have noted that the avoidance of splitting of the vermis did not have any significant impact on the development of CMS [104]. Although the telovelar approach has been considered as an alternative surgical option which is beneficial in terms of avoiding CMS, its actual advantage remains questionable. According to a recent review (minimize risk), the combined selection of a telovelar approach, the restricted use of CUSA, and the avoidance of intraoperative retraction constitutes the most effective method for the prevention of the development of CMS. Our tenet should be to refine our surgical strategy and investigate the majority of available measures in order to implement a therapeutic protocol capable of essentially minimizing the overall prevalence of CMS.

Conclusion

Cerebellar mutism constitutes a considerable and possibly underestimated complication in a significant proportion of pediatric patients that have undergone a posterior fossa surgery for tumor resection, especially when it is located in the midline. It self-subsides by its own but is frequently associated with long-term speech deficits and other neurocognitive dysfunction. Preoperative tumor infiltration into the brainstem, as well as evidence of post-operative insult of the bilateral dentato-thalamocortical tract are currently considered as the major risk factors for the development of this syndrome. When the implicated pathophysiological substrate for this syndrome is considered, dysfunction of the frontal cortex, mediated by crossed cerebello-cerebral diaschisis, is the presumed primary factor. There is lack of definitive evidence centered on the treatment of this syndrome, and this, at least, may be attributed to the fact that there have not been any controlled studies for the treatment or prevention of cerebellar mutism.

Another important issue of this entity is that it is often accompanied with long-term neurological symptoms, as well as neurocognitive deficits that persist throughout life. These defects have a negative impact on the overall quality of life and pose significant restrictions to the patients' ability to carry out activities of daily living, imposing significant obstacles to patients and their families. It is of utmost importance to obtain a deeper knowledge of all aspects of this syndrome and the most effective way to achieve this goal is through a concentrated effort to formalize the diagnostic criteria, specify significant clinical predictors and outcomes, and recognize the etiology and treatment of CMS.

Abbreviations

CMS: cerebellar mutism syndrome
DTC: dentatothalamo-cortical (pathway)
MRI: magnetic resonance imaging
POPCMS: post-operative cerebellar mutism syndrome
pECP: proximal efferent cerebellar pathway
CUSA: Cavitron ultrasonic aspirator

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