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REVIEW PAPER

Consensus paper on post-operative pediatric cerebellar mutism syndrome: the Iceland Delphi results

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Abstract
Introduction Confusion has surrounded the description of post-operative mutism and associated morbidity in pediatric patients with cerebellar tumors for years. The heterogeneity of definitions and diagnostic features has hampered research progress within the field, and to date, no international guidelines exist on diagnosis, prevention, treatment, or follow-up of this debilitating condition. An international group of clinicians and researchers from multiple relevant disciplines recently formed a cohesive panel to formulate a new working definition and agree upon standardized methods for diagnosis and follow-up.
Methods Consensus was obtained using the modified nominal group technique, involving four rounds of online Delphi questionnaires interspersed with a structured consensus conference with lectures, group work, and open discussion sessions.
Results A new, proposed definition of "post-operative pediatric CMS" was formed, preliminary recommendations for diagnostic and follow-up procedures were created, two working groups on a new scoring scale and risk prediction and prevention were established, and areas were identified where further information is needed.
Discussion The consensus process was motivated by desire to further research and improve quality of life for pediatric brain tumor patients. The Delphi rounds identified relevant topics and established basic agreement, while face-to-face engagement helped resolve matters of conflict and refine terminolo-

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gy. The new definition is intended to provide a more solid foundation for future clinical and research work. It is thought as a consensus for moving forward and hopefully paves the way to developing a standard approach to this challenging problem with the advent of better scoring methods and ultimate goal of reducing the risk of CMS.

Keywords Cerebellar mutism · Posterior fossa syndrome · Cerebellar cognitive affective syndrome · Children · Cerebellar tumor surgery · Consensus

Abbreviations

AM	Akinetic mutism
CM	Cerebellar mutism
CCAS	Cerebellar cognitive affective syndrome
CMS	Cerebellar mutism syndrome
ISPNO	International Symposium on Pediatric Neuro-Oncology
MSD	Cerebellar mutism and subsequent dysarthria
PFS	Posterior fossa syndrome
R1	Round one (of the Delphi procedure)
R2	Round two
R3	Round three
R4	Round four
TCM	Transient cerebellar mutism

Introduction

Central nervous system tumors account for around 25 % of all cancers in children [1], of which more than 60 % arise in the posterior fossa [2]. Advances in imaging and treatment (particularly surgery and radiotherapy) have brought about a vast improvement in survival in this patient population over the past few decades [3–7]. One of the most troublesome post-operative complications of cerebellar and fourth ventricular tumor surgery is cerebellar mutism (CM) and its associated features. The condition has also been described in adult and pediatric patients who suffer from transient mutism after vascular incidents, infections, trauma, or metabolic disease [8–14], but children with cerebellar and fourth ventricular tumors represent by far the largest group.

There is a long history of the origin of the term CM and related definitions, which abound in the literature. The purpose of this paper is to present the results of an international consensus process specifically aimed at refining the terminology in the context of pediatric posterior fossa tumor patients. It features a new, proposed working definition of "post-operative pediatric CMS" and includes preliminary suggestions for diagnosis and follow-up of the patients. In order to present the new definition in a clear perspective, a selective review of older publications that added novel terms and definitions to the discussion is provided. For a comprehensive analysis of other aspects of the syndrome in this patient group (incidence, anatomy, pathophysiology, imaging findings, surgical methods, risk factors, etc.), see the systematic reviews that formed the basis for this work (the "Methods" section) and those subsequently published [15–17].

Terms and definitions: a historical overview

Absence of speech after posterior fossa tumor surgery was initially described as "akinetic mutism" (AM) by Daly and Love in 1958 after the removal of a cerebellar tumor in a child. Their patient also showed a range of cognitive, affective, and neurologic symptoms [18]. Anecdotal reports of mutism after posterior fossa surgery in children emerged again in the seventies [19, 20], and in 1984 Wisoff and Epstein reported on "pseudobulbar palsy after posterior fossa operations in children." They described this as delayed onset of supranuclear cranial nerve palsies associated with emotional incontinence and lability that resolved over weeks to months. Many of their patients suffered from mutism or speech problems as well [21]. The following year, Rekate et al. published an article on "muteness of cerebellar origin" which they defined as temporary loss of speech that is delayed in onset but is unassociated with cranial nerve dysfunction, motor paralysis, or loss of higher cognitive function—since known as CM [22].

In 1993, the neurology committee of the Children's Cancer Group in the USA designed a protocol to prospectively assess the incidence, severity, and causes of what they referred to as "cerebellar mutism syndrome" (CMS) in children after resection of a medulloblastoma. They created a brief "CMS survey" to assess post-operative onset and duration of mutism, ataxia, hypotonia, and irritability in the patients—the first and only scoring scale to date designed for this purpose. The results were published in 2006 [23], and the CMS survey has subsequently been used in other research projects (Gudrunardottir T. Nordic study of the cerebellar mutism syndrome in children with brain tumors of the posterior fossa. Posterior Fossa Society, June 2015, Reykjavik, Iceland, personal communication. Keating R.F. Multivariate analysis of risk factors involved with significant reduction in cerebellar mutism after resection of posterior fossa medulloblastoma. International Society for Pediatric Neurosurgery, September 2013, Mainz, Germany, personal communication) [24].

In 1994, Van Dongen et al. introduced the term "syndrome of cerebellar mutism and subsequent dysarthria" (MSD) in a detailed article on the causes and features of the mutism itself, speech-related sequelae, and associated neurological symptoms [25]. In October 1995, Kirk et al. published a "description of posterior fossa syndrome in children after posterior fossa brain tumor surgery" (PFS), which included a

variety of signs and symptoms including mutism or speech disturbances, dysphagia, decreased motor movement, cranial nerve palsies, and emotional lability [26]. In November 1995, Van Calenberg et al. followed with a publication on "transient cerebellar mutism" (TCM), which is a common synonym for CM [27]. During that same month, Pollack et al. published the results of a large study on incidence and pathophysiology of "mutism and pseudobulbar symptoms" after resection of posterior fossa tumors in children, noting that CM could indeed be associated with motor paralysis, cranial nerve palsies, and cognitive dysfunction and that the complex of symptoms belongs to a much broader syndrome ranging from isolated impairment of speech to global impairment of volitional activities [28].

Commencing in 1987, Schmahmann and Pandya published a range of pioneering articles on fiber pathways between the cerebrum and cerebellum. These studies introduced the notion of cerebellar contribution to higher function and the concept of dysmetria of thought, and in 1996, Schmahmann described a detailed topographic organization of behavioral and cognitive functions within the cerebellum [29–33]. In 1997, Schmahmann and Sherman then published the preliminary results of a study describing a persistent pattern of executive, visual-spatial, affective, and linguistic impairment termed the "cerebellar cognitive affective syndrome" (CCAS) in 20 adults with various lesions of the cerebellum (none of whom became mute) [34, 35]. That same year, as editor of the 1997 Cerebellum and Cognition monograph, Schmahmann invited Pollack to write a chapter on his observations of similar symptoms in the pediatric population, with the suggested title "posterior fossa syndrome" [36]. Pollack accepted the invitation, extensively quoting Schmahmann's work in an in-depth analysis of general features, anatomic substrate, pathophysiology, and [91]. In 2000, Levisohn et al. extended the description of the CCAS to the post-operative pediatric population, where 5 of 19 children with the CCAS also had transient post-operative CM (termed PFS in that publication) [37].

The need for a consensus

The spectrum of signs and symptoms included under all these descriptive terms varies from isolated mutism to a wide range of affective, behavioral, cognitive, neurological, and language- and speech-related symptoms. Their use is inconsistent, the only common denominator being CM in children who become mute after cerebellar or fourth ventricle tumor surgery, while the CCAS is most often used to describe adult and pediatric patients with various lesions of the cerebellum (including tumors) who do not necessarily become mute. A recent review found that the most common terms for mutism caused by cerebellar pathology were CM followed by PFS, CMS, CCAS, TCM, MSD, and AM (in that order) [38]. The heterogeneity of terms and diagnostic features in this field has made it challenging to interpret data and conduct meaningful comparisons across studies. Incidence figures are unreliable [39], and the three risk factors that have repeatedly been identified in children who become mute after cerebellar or fourth ventricle tumor surgery (tumor type, midline location, and brainstem involvement) are based on separate definitions; CMS, MSD, and PFS [23, 40, 41]. Studies on possible predictors of the condition in pediatric tumor patients have similarly made use of different terms; CM, CMS, and PFS [42–45]. Many patients have long-term sequelae [23, 46–62], surgical strategies are a matter of debate [17, 24, 56, 63–74], and yet no international guidelines exist on diagnosis, prevention, treatment, or follow-up of this debilitating condition. For these reasons, the board of the Posterior Fossa Society[1] initiated an international consensus process including a conference to review experience, clinical practice, and ongoing research at various centers around the world. The aims were to (a) create formal definitions of the clinical entities commonly known as CM and the PFS as seen in pediatric brain tumor patients; (b) agree upon standardized methods of diagnosing these conditions; and (c) agree upon standardized follow-up methods of monitoring acute and late sequelae. A second gathering with emphasis on prevention and treatment is scheduled for 2016 at the ISPNO meeting in Liverpool, England.

Method

The "modified Delphi," also known as the "modified nominal group technique," was selected as a mechanism for achieving agreement between an internationally dispersed, multiprofessional group of experts. Participants initially expressed their opinions privately via online questionnaires, the collated results of which were anonymously fed back to each member of the group. They were then brought together to discuss their views at a face-to-face consensus development conference, after which they again privately recorded their opinions through online questionnaires [75].

Initial drafts of proposed consensus statements were created using evidence from reviews (in English) that were published during the 21st century/in press when the consensus process began [8, 38, 39, 61, 76–89]. A consensus committee (A.T.M., E.M.W., K.S.W., R.F.K., C.C.) selected and modified the actual statements presented in all voting rounds. T.G. collected responses and acted as facilitator of the process, anonymizing responses for consideration of the committee. A.L.L. and D.A.W., who were unaware of the identity of

[1] International multi-disciplinary group of researchers and health care professionals including adult and pediatric neurosurgeons, adult and pediatric neurologists, (neuro)radiologists, (neuro)psychologists, speech pathologists, linguists and neuroscientists who are active within the field of posterior fossa research.

individual respondents, acted as opinion givers and guarantors of the process. Email invitations were sent to members of the Posterior Fossa Society (n = 42–46; four new members joined the Posterior Fossa Society during the Delphi rounds), who are all primary authors of previous articles on CM/PFS and/or experts in research and treatment of children with posterior fossa tumors. A web-based survey tool was used during each round, with multiple-choice format responses and commentary fields for amendments or suggestions. Response options consisted of (a) strongly agree, (b) agree, (c) not sure if I agree or disagree, (d) disagree, and (e) agree with amendment. A statement was accepted if >80 % of votes were in support from >60 % of respondents, where "in support" was defined as the combined votes of strongly agree, agree, or agree with amendment. Statements with <80 % support and inconsistent suggestions for amendments were discarded, while statements with either high (>80 %) support or low (<80 %) support, but suggestions for similar amendments from two or more respondents, were revised and resubmitted. This process, including round 1 (R1) and round 2 (R2), took place between November 2014 and April 2015. The consensus conference was then held in June 2015 attended by 25 participants, followed by round 3 (R3) and round 4 (R4) in August 2015. Twenty members of the Posterior Fossa Society completed all rounds of the Delphi questionnaires; 17 of those also attended the conference. To be considered valid members of the Iceland Delphi Group, invitees had to participate in the Delphi rounds and/or attend the conference in Reykjavik, Iceland. Each step of the consensus process is further described below and in Fig. 1.

Before the conference: R1 consisted of ten statements regarding definition and diagnosis, while R2 included eight statements with a focus on follow-up alongside various other topics raised in R1. On the 8th of June 2015, the anonymized results of both rounds including all comments were sent to all respondents in preparation for the consensus conference on June 20–21, 2015.

Consensus conference: The results of R1 and R2 were reviewed together with historical background, ongoing research, clinical experience, and practice. Three working groups discussed and presented issues related to the three main goals of the meeting (definition, diagnosis, and follow-up). All of this was then debated in plenum, driving negotiation and agreement. It was suggested that the PFS definition may gradually have become too broad and non-specific. It also became clear that it was necessary to prioritize among the three main goals in order to secure concrete results of the conference. An anonymous vote among participants concluded that securing a new definition was most important to start with. The working group on definition had already provided a draft, identifying CM and emotional lability as core features of the syndrome and other neuropsychological, neuropsychiatric, and neurological symptoms as additional clinical features. This concept was further developed during joint discussion sessions into four proposed consensus statements on post-operative pediatric CMS.

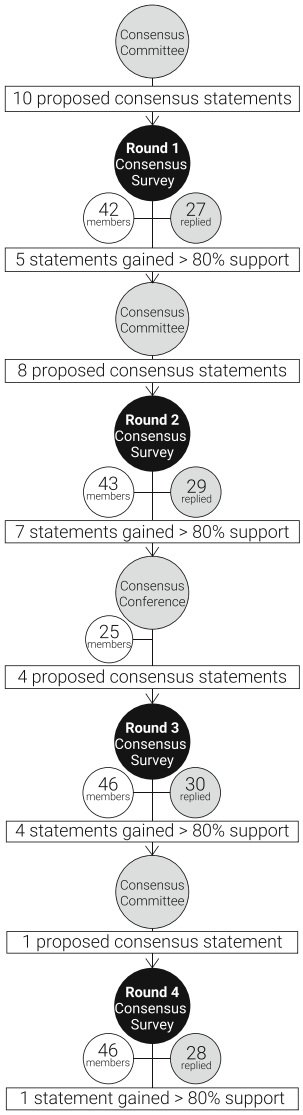

Fig. 1 The Iceland Delphi consensus process

After the conference: R3 consisted of the four proposed consensus statements on post-operative pediatric CMS from the conference, while R4 consisted of a single, modified statement on prognosis. This resulted in a new definition described under the "Results" section. For a detailed account of how statements were selected and presented in each of the rounds, see Appendix I.

Results

The main results of the Delphi rounds and the conference are the working definition below, which represents the current consensus on cerebellar mutism and associated symptoms in children after cerebellar or fourth ventricle tumor surgery:

Post-operative pediatric cerebellar mutism syndrome

> "Post-operative pediatric CMS is characterized by delayed onset mutism/reduced speech[2] and emotional lability after cerebellar or 4th ventricle tumor surgery in children. Additional common features include hypotonia and oropharyngeal dysfunction/dysphagia. It may frequently be accompanied by the cerebellar motor syndrome,[3] cerebellar cognitive affective syndrome[4] and brain stem dysfunction including long tract signs[5] and cranial neuropathies. The mutism is always transient, but recovery from CMS may be prolonged. Speech and language may not return to normal, and other deficits of cognitive, affective and motor function often persist."

Other results of the consensus process

Delphi Rounds: For a complete list of statements and voting results from all rounds, see Appendix II. Consensus Conference: The working group on definitions suggested a sharpening of the definition of CM itself, specifying it as absence of speech (verbal mutism) and not absence of non-verbal sounds (i.e. whining, crying, laughter).

The working group on diagnosis suggested the following procedures for all patients: Pre-operative neurological examination and assessment of speech and language, post-operative imaging within 48 h, and post-operative assessment score based on a new CMS scoring scale (for which they provided a draft). CMS-positive patients should then get a full multiprofessional assessment for the purposes of rehabilitation.

The working group on follow-up suggested that all patients be subject (if possible) to pre-operative and immediate post-operative CMS scoring, assessment of speech/language, and standardized parent-rated questionnaires on cognitive function mood/behavior, and adaptive skills. Post-operatively, but prior to radiotherapy, CMS-positive patients should then undergo brief neuropsychological assessment focused on processing speed, attention, executive function and memory, and a full neuropsychological assessment at 12 months posttreatment and then annually for the next 5 years. The group emphasized the need to establish a core battery of tests in this context and recommended that oncologists, neurologists, neuropsychologists, speech pathologists, linguists, physiotherapists, and occupational therapists all be involved in long-term follow-up of the patients.

Discussion

Now that children are surviving longer with the advent of new technologies and [4] the neurobehavioral manifestations of the disease and its treatment are more evident and pressing in the minds of patients, families, and care providers than ever before. The relatively recent recognition of the life-long consequences of cerebellar surgical injury has led to a revised balance of judgment that prioritizes both quality of survival and survival itself, which underscores the importance of a clear frame of reference when describing both serious sequelae and long-term prognosis of the survivors. The formation of a Posterior Fossa Society, the adoption of the nominal group technique incorporating a Delphi process, and the convening of an international consensus conference were motivated by the need to create a clear and widely agreed definition of the constellation of symptoms and signs that follow cerebellar tumor surgery in children to allow for more meaningful comparison of study results than has hitherto been possible. The process was also driven by a common desire to share research data and develop a better understanding of risk factors, possible preventive measures, and effective treatment interventions to reduce the syndrome's incidence and sequelae, with the overall aim of improving quality of life for this patient group. Therefore, the need for a consensus also extended to pragmatic recommendations for diagnosing the condition and assessing treatment outcomes. Two new working groups on (1) risk prediction and prevention of CMS and (2) a new CMS scoring scale have subsequently been formed.

The Delphi process was useful as a means to focus the questions and issues to be addressed, while face-to-face engagement at the consensus conference was instrumental in substantially revising and redefining some of the terminology, despite prior agreement at >80 % level in R1 and R2. The conference served the purpose of a mutually beneficial educational process, where interdisciplinary understanding was enhanced through sharing of previous experience, consideration of contemporary studies, and participation in structured workshops and discussion sessions. There was ample opportunity to view challenges from different perspectives and formulate novel views of problems and potential solutions. The

[2] Speech production that is severely reduced and limited to single words or short sentences that can only be elicited after vigorous stimulation [49].
[3] Impairment of gait (ataxia), extremity coordination (dysmetria), disordered eye movements, poor articulation (dysarthria), impaired swallowing (dysphagia) and tremor [90].
[4] A pattern of behavioral abnormalities that includes impairments of executive function (planning, set-shifting, abstract reasoning, verbal fluency, working memory), often with perseveration, distractibility or inattention; visual-spatial disorganization and impaired visual-spatial memory; personality change with blunting of affect or disinhibited and inappropriate behavior; and difficulties with language production including dysprosodia, agrammatism and mild anomia [35].
[5] Symptoms such as urinary retention/incontinence and hemiparesis, which are frequently observed in this patient population [40, 91].

conference was also a decision-making entity, in that disagreements regarding R1 and R1 voting results were largely resolved by the successful in-person engagement of all participants in Reykjavik.

This combined consensus approach resulted in a new proposed working definition of post-operative pediatric CMS. In order to develop an effective definition and a balanced set of outcome measures, it was necessary to identify core, common, and frequently associated features of the syndrome that would enable researchers to capture reliable and reasonably complete data. While our results did not consolidate all previous terms, we believe that we succeeded in establishing broad agreement around an operational definition together with a set of appropriate diagnostic and outcome measures. The new definition is not carved in stone, however. It represents a working approach to addressing the problem of post-operative pediatric cerebellar mutism in clinical practice in a more uniform manner than before, and is certainly open to modification at a later stage based on future studies and feedback from the larger scientific community.

These positive experiences and subsequent high levels of agreement achieved in voting in R3 and R4 emphasizes the value of in-person contact at this first structured scientific discussion of these topics worldwide. It also supports the selection of a combined consensus approach where the Delphi method is mixed with a face-to-face gathering. In our view, it was superior to an isolated Delphi method, as the final result would otherwise have been arrived at without debate and evidence sharing, producing a less robust conclusion more vulnerable to criticism at an early stage after publication.

Conclusion

The confusion that has surrounded the topic of CM and PFS in pediatric brain tumor patients, the relationship of these disorders to the CCAS in adults and children, as well as their anatomical and etiological interrelationship has hampered research progress for years. Members of the Iceland Delphi Group used a combined consensus approach to refine their thinking from different professional perspectives. It is hoped that the new definition will help resolve confusion and provide a more solid foundation for future clinical and research work. Ultimately, the goal must be to identify ways of preventing this complication from occurring; this should be greatly aided by agreeing on what is and what is not post-operative pediatric CMS. The prospect of an enhanced scoring scale (if adopted) will make diagnosis of the syndrome and the comparing of study results easier and more reliable. The validity of the definition and the scoring scale will need testing in future studies, and both may require revisions later on. Strategies for diagnostic and follow-up approaches have been proposed, and areas where further information is needed have been identified. The groundwork for international guidelines on diagnosis and follow-up has now been laid, and similar guidelines for treatment can be generated once standardized study results become available.

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Authors' contributions *Thora Gudrunardottir* initiated the consensus process, acted as facilitator of the Delphi Rounds, and organized the consensus conference. She drafted the initial manuscript, contributed substantially to and revised all versions, and approved it as submitted. *Angela T. Morgan* served on the consensus committee and applied for funding for the consensus conference. She contributed substantially to and revised all versions of the manuscript. She was responsible for graphics, critically reviewed the final manuscript, and approved it as submitted. *Andrew L. Lux* served as guarantor of the Delphi Process. He was also group discussion facilitator at the consensus conference and chaired the working group on follow-up. He contributed substantially to and revised all versions of the manuscript and approved it as submitted. *David A. Walker* served as guarantor of the Delphi Process. He was also group discussion facilitator at the consensus conference and chaired the working group on diagnosis. He contributed substantially to the manuscript, revised and approved it as submitted. *Karin S. Walsh* served on the consensus committee, contributed to and revised all versions of the manuscript, and approved it as submitted. *Elizabeth M. Wells* served on the consensus committee, contributed to, revised and approved the manuscript as submitted. *Jeffrey H. Wisoff* documented the consensus conference and revised and approved the manuscript as submitted. *Marianne Juhler* served as group discussion facilitator at the consensus conference and chaired the working group on definitions. She contributed to and approved the manuscript as submitted. *Jeremy D. Schmahmann* contributed substantially to the manuscript, revised and accepted it as submitted. *Robert F. Keating* served on the consensus committee, contributed substantially to and revised all versions of the manuscript, and accepted it as submitted. *Coriene Catsman-Berrevoets* served on the consensus committee, contributed substantially to and revised all versions of the manuscript, critically reviewed and accepted it as submitted. All authors participated in the consensus conference. For a list of all participants in the conference by specialty and country, see Appendix III.

Compliance with ethical standards

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