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Posterior fossa syndrome—time to unmute the silence on cerebellar mutism

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See the article by Khan et al, pp. 1586–1596.

The history of posterior fossa mutism remains an enigma. While Harvey Cushing's contribution to the surgery of posterior fossa tumors dates back to almost a century, it is only in 1948 that Cairns and then in 1958 that Daly and Love described cases of patients with symptoms of akinetic mutism following posterior fossa surgery.[1] However, these early reports were ahead of their time and did not receive much attention. It is only in 1985 that Rekate first used the term cerebellar mutism and that physicians involved in the care of these patients became increasingly aware of this entity.[2] Increasingly, posterior fossa syndrome (PFS) is being identified as one of the most challenging postoperative complications of posterior fossa surgery, affecting between 10% and 40% of children, especially medulloblastoma patients.[3] PFS associates a constellation symptoms including mutism, ataxia and dysmetria, emotional lability, swallowing disorders, and other neurological deficits, but there is also mounting evidence that PFS is also associated with increased long-term neurocognitive impairment.[4]

Injury to deep cerebellar nuclei and outflow tracts has been the most widely accepted hypothesis with regards to the etiology of PFS, although the exact mechanisms involved remain elusive. The pathophysiology of this syndrome has been extensively studied and it appears to be related to a bilateral injury of the dentato-thalamo-cortical pathways.[5] A prospective study from the Children's Oncology Group (COG) based on questionnaires collected data on 450 patients enrolled in 2 different medulloblastoma protocols. The incidence of mutism was 24%, with 92% affected patients exhibiting moderate or severe symptoms.[3] This study identified brainstem invasion as the only risk factor for cerebellar mutism, while cerebellar hemisphere location was associated with a decreased risk. Several retrospective studies have since identified various risk factors including tumor size, pathology, tumor location and invasiveness, age, subgrouping, and dominant hand laterality as predictive factors for PFS. Although the role of the surgical technique has often been mentioned and suggested a high rate of PFS with the transvermian approach, large series comparing telovelar and the transvermian approaches have failed to demonstrate an advantage for either technique and the increasing use of the former technique during the recent years has not been associated with a significant decrease in the rate of PFS.[6]

In the current issue of *Neuro-Oncology*, the study by Khan et al attempted at answering key questions regarding the spectrum of PFS and its natural history.[7] The authors provide a much-needed clinical categorization of PFS based on the severity of the mutism, keeping it simple and pragmatic. The main strength of this study is the inclusion of serial prospective and thorough neurological examinations. As a result, the authors were able to describe a spectrum of associated neurological symptoms—ranging from isolated ataxia to a combination of ataxia, apraxia, involuntary movements, behavioral issues, and ocular abnormalities. Based on these observations, Khan et al identified prognostic factors associated with poor/delayed speech (ie, high ataxia score and movement disorders) and poor/delayed gait recovery (ie, high ataxia score and older age).

One of the most emphasized conclusions of the study concerns the prognostic effect of high-volume vs low-volume centers regarding the risk of PFS. This issue remains a matter of ongoing debate. The prospective COG study mentioned earlier with 107 cases of PFS did not find any correlation between the size of neurosurgical centers and the rate of PFS.[3] In the current study, with St Jude Children's Hospital accounting for nearly 40% of patients of high-volume centers and 28 centers accounting for the remaining 60%, interpretation of these data is challenging, as the proportion of St Jude patients may account for a statistical bias. More studies are needed to confirm these findings, although the positive impact of larger centers has already been emphasized in the management of medulloblastoma patients.[8] Regardless, the strength of this work is the opportunity to give a new tool to pediatric neuro-oncologists and neurologists that can guide them in the management of this complex and challenging syndrome. Importantly, it emphasizes the need to thoroughly assess PFS patients early on to accurately evaluate their severity.

Over the last decades, efforts have been made by various cooperative groups and institutions to identify factors predicting

the risk of PFS, with none having been able to have a robust validation. The results from a prospective Nordic study attempting to focus on prognostic variables and to study the role of preoperative steroids are awaited.[9] Having now identified PFS as a major issue in the management of medulloblastoma patients, there is a need to develop clinical trials that can address all unanswered PFS-related questions and integrate the neurosurgical management into cooperative medulloblastoma protocols. This requires a close cooperation between oncologists and neurosurgeons with the aim to ultimately decrease the incidence of this complication. This includes an insight into surgical techniques including surgical routes (telovelar vs transvermian), the use of ultrasonic aspirator and fixed retractor systems, the use of intraoperative ultrasonography, and/or the administration of preoperative corticosteroids. In this context, it may also be important to discuss alternative strategies for high-risk patients, including the use of neoadjuvant therapy. There is also a need to develop specific interventions for patients with PFS. So far, only anecdotal case reports have suggested the potential benefit of agents such as bromocriptine or zolpidem.[10] However, with a rate of 25% or more in this population, there is clearly an opportunity to develop specific interventions aiming at improving both the short-term recovery and the long-term outcome of PFS. Ignoring PFS would be a mistake, as this complication accounts for much of the long-term neurological and neurocognitive morbidity seen in medulloblastoma survivors and there is an urgent need to focus on interventions that can mitigate the incidence and the impact of this complication.

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