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Title: CEREBELLAR MUTISM SYNDROME IN CHILDREN AND ADULTS

Authors: Peter Mariën[1,2,†], Stefanie Keulen[1,3,4], Kim van Dun[5], Hyo Jung De Smet[1], Peter P De Deyn[6], Jo Verhoeven[7,8], Philippe Paquier[1,4,9,10]

Affiliations:
1.Research Group on Clinical and Experimental Neurolinguistics, Vrije Universiteit Brussel, Brussels, Belgium
2. Department of Neurology and Memory Clinic, ZNA Middelheim General Hospital, Antwerp, Belgium
3. Center for Language and Cognition, Universiteit Groningen, Groningen, The Netherlands
4. Research Center in Linguistics (LaDisco), Université Libre de Bruxelles, Brussels, Belgium
5. Research Group on Experimental and Applied Psychology, Vrije Universiteit Brussel, Brussels, Belgium
6. Department of Neurology, University Medical Center Groningen, Universiteit Groningen, The Netherlands
7. Department of Language and Communication Science, City University London, London, United Kingdom
8. Computational Linguistics and Psycholinguistics Research Center, Universiteit Antwerpen, Antwerp, Belgium
9. Departments of Neurology and Neuropsychology, Erasmus University Hospital, Université Libre de Bruxelles, Brussels, Belgium
10. Unit of Translational Neurosciences, School of Medicine and Health Sciences, Universiteit Antwerpen, Antwerp, Belgium

† Deceased

Correspondence to: Philippe Paquier
Services de Neurologie et de Neuropsychologie
ULB-Hôpital Erasme
808 route de Lennik
B-1070 Bruxelles
Belgique
E-mail: philippe.paquier@ulb.ac.be

Abbreviated Title: Cerebellar Mutism Syndrome

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0. Abstract

Cerebellar mutism can be considered the hallmark feature of the Cerebellar Mutism Syndrome (CMS), previously also frequently termed the Posterior Fossa Syndrome (PFS). The syndrome consists of specific linguistic, cognitive, behavioral, and affective symptoms following acute posterior fossa damage in children and adults. Although the symptoms have been exceptionally associated with non-tumoral etiologies, CMS usually develops after a brief period of relatively normal functioning in the immediate postoperative phase following posterior fossa tumor surgery. The incidence of CMS in the pediatric population is estimated to range between 7% and 50%. Although similar symptoms have been occasionally reported in adults, CMS is typically viewed as a clinical condition affecting children.

An international consensus as to the definition of CMS was recently reached. However, this accepted definition specifically addresses the pediatric variant of the syndrome associated with posterior fossa surgery (Post-Operative Pediatric CMS, POPCMS). In this chapter, the more general term CMS (instead of POPCMS) will be used to denote similar symptoms also occurring in adults, and with non-tumoral etiologies.

Although the semiology of CMS has extensively been described, the underlying pathophysiological mechanisms still remain largely unclear. This chapter presents a brief overview of the intriguing semiological combination of transient cerebellar mutism and cognitive, behavioral, and affective alterations following acute posterior fossa lesions. Furthermore, the most important pathophysiological hypotheses and the proposed therapeutic interventions will be briefly discussed.

1. Introduction

During the last three decades, insights into the non-motor role of the cerebellum in behavioral, cognitive, and affective processes have evolved from a mere afterthought to an exciting area of innovative research across disciplines. Recent advances in the understanding of the neuroanatomy of the cerebellum and its reciprocal connections with the supratentorial brain regions processing cognition, behavior, and affect, combined with evidence from functional neuroimaging studies, neurophysiological research data, and clinical neuropsychological findings have substantially adjusted the traditional view on the cerebellum as a sole coordinator of autonomic and somatic motor function (Beaton and Mariën 2010). A syndrome that includes the role of the cerebellum as an essential modulator within these different domains is the Cerebellar Mutism Syndrome (CMS).

CMS, previously termed the Posterior Fossa Syndrome (PFS) (Pollack 1997)[1], is now the official term to denote a syndrome following acute damage to the cerebellum that is characterized by a transient mutism combined with neurocognitive, behavioral, and affective disturbances (Gudrunardottir et al. 2016a). In 2015, the Posterior Fossa Society (http://www.posteriorfossa.org/) initiated an international Delphi consensus process in order to formulate a working definition of cerebellar mutism and PFS, and to agree upon standardized methods for diagnosis and follow-up. The international consensus meeting (Reykjavik, June 2015) organized to discuss and optimize the Delphi rounds proposals, resulted in the following, unanimously accepted working definition (Gudrunardottir et al. 2016b):

> "Post-operative pediatric CMS is characterized by delayed onset mutism/reduced speech 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, cerebellar cognitive affective syndrome and brain stem dysfunction including long tract signs and cranial neuropathies. The mutism is always

[1] Also referred to as "akinetic mutism" (Daly and Love 1958), "transient cerebellar mutism" (D'Avanzo et al. 1993), or "mutism and subsequent dysarthria" (MSD) (Van Dongen et al. 1994).

> 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." (p. 1199).

Whereas the definition of Post-Operative Pediatric CMS (POPCMS) specifically pertains to a pediatric condition associated with posterior fossa surgery, the more general term CMS also applies to an adult population (Mariën et al. 2013a) and to non-tumoral etiologies, such as traumatic brain injury (Ersahin et al. 1997; Koh et al. 1997; Fujisawa et al. 2005), vascular disorders (Dietze and Mickle 1990-91; Sinha et al. 1998; Nishikawa et al. 1998; Al-Anazi et al. 2001; Baillieux et al. 2007; Frassanito et al. 2009), and infectious pathologies (Riva 1998; Drost et al. 2000;, Mewasingh et al. 2003; Papavasiliou et al. 2004; Dimova et al. 2009; Parrish et al. 2010; Thabet et al. 2013).

While a recent, systematic review of the literature reported the incidence rate of POPCMS to range from 7 to 50 % of the studied population (Reed-Berendt et al. 2014)[2], the condition has only very occasionally been documented in adults following etiologically different posterior fossa lesions (e.g., Salvati et al. 1991; Kai et al. 1997; Ildan et al. 2002; Akil et al. 2006; Muthappan et al. 2012; Mariën et al. 2013a,b) or after focal damage of the brainstem (Messert et al. 1966; Frim and Ogilvy 1995; D'Avanzo et al. 1993). The age-related discrepancy in frequency of occurrence of CMS in children and adults is most often explained by (1) the higher incidence rate of posterior fossa tumors in children (Dolecek et al. 2012; Massimino et al. 2016), and (2) anatomical and functional, post-natal maturational factors, the incomplete myelination of the cortico-ponto-cerebello-thalamo-cortical loop rendering children more vulnerable to the impact of a cerebellar lesion (Ildan et al. 2002). In addition, Pols et al. (2017) recently suggested that the reason for this age-related difference might also be that in comparison with

[2] Reed-Berendt et al. (2014) explained the broad range by the variability of the diagnostic criteria and the lack of large population-based data.

adults, children have a smaller intravascular volume, thus being more vulnerable to hypovolemia. This means that even a relatively small quantity of intra-operative blood loss can result in a deficit in oxygen delivery susceptible to induce local ischemia in the surgical area and its immediate vicinity, including the deep cerebellar nuclei bilaterally.

CMS bears a close resemblance to another, cerebellar-induced syndrome which also comprises non-motor cognitive, behavioral, and affective symptoms. The latter combination of executive, visuospatial, affective, and linguistic symptoms was labeled the Cerebellar Cognitive-Affective Syndrome (CCAS) (Schmahmann and Sherman 1998) (see also Chapter 77, this volume). Whereas CCAS has not infrequently been described in children and adults with a broad range of etiologically heterogeneous acquired as well as developmental neurological disorders that primarily affect the cerebellar structures (e.g., Levisohn et al. 2000; Paulus et al. 2002; Mariën et al. 2008, 2010); Baillieux et al. 2010), CMS is most commonly found in children who underwent posterior fossa tumor surgery (Rekate et al. 1985; Pollack et al. 1995; Robertson et al. 2006; Wells et al. 2008). CMS and CCAS have often been regarded as related to one another, the difference between both being that CMS mostly follows acute damage to the cerebellum, and includes mutism and motor speech difficulties per definition –thus resulting in a severely invalidating condition– whereas CCAS does not necessarily incorporate mutism and motor speech difficulties, and can rather be viewed as a chronic condition (Gudrunardottir et al. 2016a).

This chapter briefly reviews the semiological characteristics of CMS in adults and children, looks at the attempts to treat the syndrome, and discusses the main pathophysiological explanations that have been proposed.

2. Semiological Characteristics of Cerebellar Mutism Syndrome

2.1. Cerebellar Mutism Syndrome in Children

In 1958, Daly and Love published what is assumed to be the first detailed report of the semiological characteristics of POPCMS. In this report the authors described the postoperative onset and evolution of the various cognitive, behavioral, and affective symptoms in a 14-year-old boy with a posterior fossa grade I astrocytoma. In addition to akinetic mutism, a range of postoperative behavioral and affective abnormalities were recorded as well:

> In the early evening following operation the patient was in a deep coma (…). Later that evening there was some lightening of the coma, and the patient began to move his extremities. The next day, the patient slept almost continuously but could be aroused by being spoken to. On command, he would grasp his father's hand. Although he lay inert, infrequent movements of all extremities suggested that no paralysis existed. He responded to aspiration by coughing and gagging, but he did not speak or utter any sounds. He did not move his eyes (…). By the third postoperative day the patient moved all extremities without signs of weakness. He would grasp objects firmly with both hands and protrude his tongue on request, but he remained mute. When food was placed in his mouth, he would not chew it; nevertheless he readily swallowed liquids put into his mouth. He was incontinent of feces. When undisturbed he was somnolent and inactive. When stimulated he seemingly was aware of, but indifferent to, his environment. (…) Noxious stimuli, such as venipuncture, were disregarded.
>
> In the succeeding days a slow but constant improvement occurred. One week after operation the patient appeared aware of his environment and cooperated slowly with the requests of his Spanish-speaking nurse. Yet he continued mute. (…) Although he seemingly recognized his parents, he showed no emotional response to them. His features were expressionless, and he had no interests in the activities about him. (…)
>
> At the end of two weeks he had yet to utter a sound. Dysphagia, which had been present initially, had virtually disappeared and he could chew and easily swallow food placed in his mouth. He obeyed simple commands and communicated with his parents by sign language. (…) He still slept excessively, although he could be roused readily. He moved more frequently than before and would move his limbs to avoid an awkward position. Because of his slow progress (…) he was given 40 mg. of methylphenidate hydrochloride intravenously; this produced marked increase in alertness and responsiveness. (…) He thenceforth received the drug by mouth in a total daily dose of 100 mg. in divided doses of 20 mg. each. This sharply accelerated the rate of improvement; he slept less, showed more spontaneous movements, and attempted to walk with help. However, he remained mute.

> One month after operation the patient was able to follow moderately complicated commands such as, "touch your right index finger to your left ear". When given several different commands successively, he had increasing difficulty and began to perseverate. Attempts at more accurate testing were difficult to evaluate, since it was not clear whether his failures resulted from lack of comprehension or apathy and indifference. In any event, on doing portions of the Stanford-Binet, Wechsler-Bellevue, and progressive matrices tests, the patient was unable to perform beyond the six-year level. He was able to read a simple written command and execute it properly. He could purse his lips, but could not whistle. He coughed vigorously and swallowed without trouble; yet he had still made no effort to speak. He usually lay quietly in bed, watching the activities around him. He showed no emotion, even with his parents. At his mother's request he would place his arms about her and kiss her; however, the action was a stiff mechanical gesture which suggested the behavior of a puppet. (…)
>
> On September 5 the patient spoke for the first time when he called his parents by name. Later that day he mentioned his sister's name, and when his father told him he was to be taken to a neurological conference, he asked: Why? (…) The complexity of his speech rapidly increased the next few days. Within one week he spoke lucidly, but with a scanning measured speech of cerebellar type. He became more interested in his environment and wanted to read magazines. He expressed interest in going home and told his parents that he wished to visit Chicago on the way.
>
> In the following two weeks the content of his speech and his affective behavior returned to normal. Although he was still troubled by his ocular palsies and ataxia, he worked vigorously at rehabilitation in the department of physical medicine. His normal affective response returned, and he would laugh appropriately at jokes and would in turn make jokes. He exhibited considerable interest in learning English and made rapid progress so that it was soon possible to speak to him in simple sentences. His parents felt that his vocabulary and syntax in Spanish had returned to the preoperative level. At the time of dismissal on September 27 he had mild cerebellar speech and moderate ataxia. The ocular palsies persisted but were improved.
>
> (…) On several occasions attempts were made to discontinue its [methylphenidate hydrochloride, 60 mg.] use. Whenever it was stopped for a period of a day, the patient became apathetic and somewhat somnolent. On resuming its use, he would return to a normal state of alertness. [p. 238-40]

Although Daly and Love (1958) did not explicitly mention a "symptom free postoperative interval", POPCMS in patients with tumoral pathologies typically develops in the immediate postoperative phase after a short period of relatively normal functioning[3]. De Smet et al.'s (2007a) critical review of the literature disclosed that in

[3] Postoperative spasm of the vessels supplying the cerebellum and the brainstem may cause ischemia and subsequent edema (Ferrante et al. 1990; Maffei et al. 2005), which may account for the delayed appearance of mutism after a period of (near) normal speech in the immediate postoperative phase (Ildan et al. 2002).

150 children, mutism developed between 0 and 11 days (mean 1.5 days, SD 1.7) after tumor surgery. In a more recent, systematic review of the literature (Reed-Berendt et al. 2014) it was found that in 216 pediatric patients, mutism onset occurred between 0 and 15 days post-surgery (mean 2.0 days, SD 2.2). Hence, the latter results are in line with previous findings, even though Reed-Berendt et al. (2014) only included POPCMS patients who underwent tumor surgery, whereas De Smet et al. (2007a) also included three pediatric patients with vascular etiology.[4]

The core symptom of POPCMS is total speechlessness or verbal mutism, but it is generally accompanied by (frontal-like) neurobehavioral abnormalities such as apathy, loss of drive or reduced initiative, unconcern, inconsolable crying, and whining. Other symptoms that have been observed are: the inability to initiate voluntary eye opening (eye-lid apraxia), urinary retention or incontinence without any apparent urological or pharmacological reason, autistic behavior, pathological laughing and crying, transient cortical blindness, compulsive pre-sleep behavior, and eating impairments due to the disruption of initiating the mastication and swallowing process in the absence of neurogenic dysphagia (e.g., Humphreys 1989; Pollack et al. 1995; Catsman-Berevoets et al. 2003; Dimova et al. 2004; Daniels et al. 2005; Baillieux et al. 2007; Catsman-Berrevoets and Aarsen 2010; Lanier and Abrams 2017).

Although a transient period of speechlessness is generally considered to be the prototypical feature of POPCMS, mutism occasionally does not materialize at all and a wide range of postoperative neurobehavioral deficits have been found instead. Symptoms such as a decreased initiation of voluntary movements (e.g., Kingma et al. 1994; Siffert et al. 2000), eye-lid apraxia (e.g., Sinha et al. 1998; Pollack 2001), executive dysfunction

[4] Of note: 82% of the tumor patients included by De Smet et al. (2007a) were included in the review by Reed-Berendt et al. (2014) (n= 161/196).

(e.g., Levisohn et al. 2000; De Smet et al. 2009), poor problem-solving (e.g., Pollack et al. 1995; Clerico et al. 2002), mnestic disorders (e.g., Humphreys 1989; Kingma et al. 1994), reduced attention-span (e.g., Kingma et al. 1994; Aarsen et al. 2004), visual-constructive deficits (e.g., Riva 1998; De Smet et al. 2009), and symptoms consistent with CCAS (e.g., Catsman-Berrevoets and Aarsen 2010), may occur in the absence of mutism as the neurobehavioral consequence of acute surgical damage to the cerebellum.

The majority of patients operated on for a posterior fossa tumor do not develop cerebellar mutism after surgery. However, since formal cognitive assessments are not a standard procedure in the postoperative follow-up, it seems likely that possibly relevant cognitive, behavioral, and affective symptoms remain largely unnoticed. As timely recognition and intervention of neurobehavioral symptoms are of crucial importance, formal pre- and post-operative investigations are strongly recommended in all patients, both children and adults, who undergo posterior fossa tumor resection.

The duration of the postoperative mutism may vary significantly among individuals. According to Reed-Berendt et al. (2014), it ranges from 1 day to 2.5 years (mean 42.59 days, SD 76.28). These authors, consequently, confirmed De Smet et al.'s (2007a) findings revealing a duration ranging from 0.5 day to 2.5 years (mean: 49.7 days, SD 85.5). When excluding the two cases presenting with an extremely long period of mutism (Doxey et al. 1999; Steinbok et al. 2003), the duration ranged from 0.5 day to 7 months (mean 41.5 days, SD 37.5) (De Smet et al. 2007a). Both studies were not able to confirm a relationship between the symptom free postoperative interval and the duration of the mutism.

De Smet et al. (2007a) found that in 165/167 (98.8%) reliable cases, dysarthria was unquestionably present after remission of cerebellar mutism. In the two remaining children, these authors assumed that dysarthric symptoms were masked by a combination

of overwhelming behavioral disturbances and lack of spontaneous verbal production. In 64 children for whom sufficient information on the post-mutism speech characteristics was available, De Smet et al. (2007a) recorded slow speech rate in 23/64 (35.9%), monotonous verbal output in 22/64 (34.4%), and ataxic speech in only 11/64 (17.2%) cases. Catsman-Berrevoets and Aarsen (2010) analyzed the speech characteristics of 40 children after remission of mutism. Five patients did not suffer mutism, but a reduced speech production. Slow speech rate affected 33/40 (82.5%) children and was the most frequently occurring deviant speech symptom. In addition, 13 of these children presented with a severely reduced verbal output, characterized by short but grammatically correct phrases. Surprisingly, excess and equal stress and irregular articulatory breakdown, which represent the two most specific cardinal features of ataxic dysarthria, were only found in 1/40 (2.5%) patient. Four other patients (10%) presented with only one of these features typical of ataxic dysarthria. A prominent voice tremor additionally occurred in two (5%) of these patients. Speech production of one patient (2.5%) was characterized by alternating loudness, which, according to Kluin et al. (1988) represents a specific feature of cerebellar speech pathology. In their literature review, Reed-Berendt et al. (2014) equally found that in the long-term follow-up, speech is often perceived as slow, slurred, dysfluent, dysprosodic and monotone, with decreased volume and increased pitch.

With regard to recovery of motor speech symptoms, the optimistic view that mutism is always transient (Van Dongen et al. 1994; Ersahin et al. 1996), and that dysarthria usually resolves within 1 to 3 months after the alleviation of mutism (Catsman-Berrevoets et al. 1999; Afshar-Oromieh et al. 2010), has now been tempered by several studies on the long-term sequelae of POPCMS which identified incomplete recovery of motor speech production (e.g., Cornwell et al. 2003; Steinbok et al. 2003; Aarsen et al.

2004; Huber et al. 2006, 2007; De Smet et al. 2012), thus confirming the less favorable outcome of dysarthric speech symptoms subsequent to mutism witnessed in earlier reports (e.g., Hudson et al. 1989; Daily et al. 1995; Jones et al. 1996; Doxey et al. 1999;). Steinbok et al. (2003), for instance, described seven patients with postoperative cerebellar mutism of whom one patient remained mute for 2,5 years post-surgery, two patients suffered from residual dysarthria, and three patients had a slow speech rate. These authors were the first to state that POPCMS is not a transient and benign syndrome but a condition that may be associated with disabling residual deficits. As to the long-term prognosis, Tamburrini et al. (2015) confirmed the presence of a persistent dysarthria in a third of the children who presented with POPCMC.

Apart from motor speech symptoms (dysarthria) –which as a rule occur after remission of mutism– a variety of concomitant non-motor language disturbances have been identified as well (De Smet et al. 2007b, 2013). These include word-finding difficulties (Levisohn et al. 2000; Aarsen et al. 2004; De Smet et al. 2009), impaired verbal fluency (De Smet et al. 2009), agrammatism (Riva and Giorgi 2000; Siffert et al. 2000), disrupted language dynamics (Siffert et al. 2000; Ozimek et al. 2004; De Smet et al. 2009; Di Rocco et al. 2011), comprehension deficits (Levisohn et al. 2000; Cornwell et al. 2003; De Smet et al. 2009), and reading (Scott et al. 2001) and writing problems (Aarsen et al. 2004).

At the emotional and affective level, adynamia and symptoms indicating inhibition of frontal lobe functions are often recorded. Many patients present with a lack of initiative, aspontaneity, apathy (Pollack 1997), mood lability or “pseudobulbar affect” (Gadgil et al. 2016), disinterest (Steinlin et al. 2003), emotional unsteadiness (Catsman-Berrevoets et al. 2003), flattened affect, inadequate emotional coping (Ozimek et al. 2004), diminished eye contact (Liu et al. 1998), and withdrawal (Daniels et al. 2005).

Again, in sharp contrast to the view that POPCMS is a transient phenomenon (Van Dongen et al. 1994), several long-term cognitive consequences of POPCMS have been identified, such as scholarly underachievement and major cognitive sequelae, among which a significant decline of general intelligence, executive dysfunction, disrupted memory, attentional deficits, and distorted spatial cognition (Vandeinse and Hornyak 1997; Levisohn et al. 2000; Steinlin et al. 2003; De Smet et al. 2009; Palmer et al. 2010). According to Reed-Berendt et al. (2014), the five most frequent neurocognitive impairments reported in 104 POPCMS patients during long-term follow-up were: attention deficits (37/104, 36%), impaired processing speed (33/104, 32%), reduced executive functioning (28/104, 27%), visual/perception difficulties (27/104, 26%), and impaired intelligence (25/104, 24%). Importantly, these impaired neurocognitive functions in some cases also correlated with long-term psychosocial issues (Hocking et al. 2011).

2.2. Cerebellar Mutism Syndrome in Adults

A comprehensive survey of the literature on CMS following posterior fossa surgery in adults yielded reports on 21 patients published between 1969 and January 2011, of whom 18 underwent a tumor resection (Mariën et al. 2013a). The remaining three patients were operated upon for an arteriovenous malformation (Dunwoody et al. 1997; Idiaquez et al. 2011), and a hematoma (Coplin et al. 1997). Between January 2011 and January 2018, six new instances of adult post-operative CMS (two vascular and five tumoral etiologies) were reported (De Smet and Mariën 2012; Damodaran et al. 2013; Gündüz et al. 2013; van Baarsen et al. 2013; Mariën al. 2013a; Manzano-Lopez Gonzalez et al. 2015), whereas two additional cases presented with CMS not induced by posterior fossa surgery (Mariën et al. 2013b; Sen et al. 2017).

In these 27 adult cases who had undergone surgery to the cerebellum for a tumor or vascular pathology, the onset of postoperative mutism ranged between 0 and 31 days (mean 3.83 days, SD 6.49). The duration of mutism ranged from 1 to 120 days (mean 38.59 days, SD 34.42). By comparison, the mean duration of mutism in children appears to last longer.

With respect to motor speech characteristics following the period of mutism, it appears that speech deficits were found to be dysarthric in 20/27 cases (74.1%). Speech was described as 'thick', cerebellar or ataxic, scanned or staccato, near normal or reduced in voice volume in nine patients (33.3%) (Moore 1969; D'Avanzo et al. 1993; Bhatoe 1997; Coplin et al. 1997; Dunwoody et al. 1997; Sherman et al. 2005; De Smet and Mariën 2012; Mariën et al. 2013a). Follow-up information varying between 2 months (Kai et al. 1997) and 4 years post-surgery (Adachi et al. 2005; Akhaddar et al. 2008) was provided for 21 of the 27 patients (77.8%) (Moore, 1969; Salvati et al. 1991; D'Avanzo et al. 1993; Coplin et al. 1997; Dunwoody et al. 1997; Kai et al. 1997; Caner et al. 1999; Ildan et al. 2002; Sajko et al. 2004; Adachi et al. 2005; Sherman et al. 2005; Akhaddar et al. 2008; De Smet and Mariën 2012; Damodaran et al. 2013; Gündüz et al. 2013; Mariën et al. 2013a; van Baarsen et al. 2013; Manzano-Lopez Gonzalez et al. 2015). Nine of the 27 patients (42.9%) (Moore, 1969; Dunwoody et al. 1997; Kai et al. 1997; Caner et al. 1999; Ildan et al. 2002; van Baarsen et al. 2013; Adachi et al. 2005; Sherman et al. 2005; Akhaddar et al. 2008) had normal speech at final follow-up. Of the remaining patients, eight had dysarthric symptoms (Salvati et al. 1991; Coplin et al. 1997; Kai et al. 1997; Ildan et al. 2002; De Smet and Mariën 2012; Damodaran et al. 2013; Gündüz et al. 2013; Manzano-Lopez Gonzalez et al. 2015), and one had scanning speech (D'Avanzo et al. 1997) persisting during follow-up.

Cognitive, behavioral, and emotional symptoms have only occasionally been documented in adults, and the majority of reported cases provide no formal cognitive data. The most frequently described impairments relate to orofacial apraxia (Dailey et al. 1995; Afshar-Oromich et al. 2010), memory problems (Moore 1969; Afshar-Oromich et al. 2010; De Smet and Mariën 2012; Mariën et al. 2013a), concentration deficits (Afshar-Oromich et al. 2010; Mariën et al. 2013a), executive and attentional deficits (De Smet and Mariën 2012; Mariën et al. 2013a), a decrease in IQ (De Smet and Mariën 2012; Mariën et al., 2013a), and anomia (Afshar-Oromich et al. 2010; Mariën et al. 2013a). Depicted behavioral-affective symptoms included lethargy and confusion (Moore 1969), depressed mood (Afshar-Oromich et al. 2010), childish behavior (Mariën et al., 2013a), emotional lability (Coplin et al. 1997; Afshar-Oromich et al. 2010; Idiaquez et al. 2011; Mariën et al., 2013a), aspontaneity (Caner et al. 1999; Afshar-Oromich et al. 2010), and apathy (De Smet and Mariën, 2012; Mariën et al. 2013a). Frontal-like symptoms were mentioned by Manzano-Gonzalez Lopez et al. (2015). Mariën et al. (2013a) also observed agitation, anxiety, restlessness, pseudo-bulbar-like crying and laughter, shouting behavior, and withdrawal.

2.3. Preoperative neurocognitive assessments

Preoperative cognitive, behavioral, and affective symptoms have not systematically been investigated in the pediatric or adult patient population. This nevertheless seems fundamental in order to interpret post-operative neurocognitive test results. Mariën et al. (2013a), for instance, showed that cognitive, behavioral, and affective abnormalities may already exist in the preoperative phase. They conducted cognitive assessments and behavioral observations in an adult patient before posterior fossa tumor surgery took place. A range of discrete but clinically significant deficits were objectified. First, from

conversations with the patient's husband and family, it appeared that a progressive decrease of motivation and initiative, unconcern, social withdrawal, incidences of verbal aggression, and inappropriate verbal remarks had taken place over several months. A general attitude of unconcern, and flattened affect were observed during admission, and disinhibited verbal and inappropriate, prefrontal-like behavioral reactions frequently occurred. No indications for a depressive disorder were found. In-depth neurocognitive investigations carried out two days before surgery revealed disrupted working memory span, significantly depressed recent memory, impaired attention, and distorted frontal problem-solving and planning skills. These preoperative cognitive, behavioral, and affective symptoms closely resemble CCAS (Schmahmann and Sherman 1998), reflecting a functional disruption of the cerebello-cerebral network. A quantitative SPECT study conducted in the preoperative phase revealed a pattern of perfusion changes indicating functional disruption of the cerebello-cerebral network crucially involved in the regulation of cognitive, behavioral and affective processes.

To the best of our knowledge, preoperative posterior fossa mutism in adults has only been reported once in an unusual case of fourth ventricle vagus nerve schwannoma (Muthappan et al. 2012).

In children, Walker et al. (2014) also emphasized the paramountcy of obtaining preoperative data via pre-surgery assessments or via parental and educational reports, in order to gain an insight into the pre-surgical functioning of the patients. In this respect, at the communicative, emotional, and behavioral level, Beckwitt-Turkel et al. (2012) identified depression, apathy, irritability, dysphoria, and even mutism in ≥ 21% of 14 children before posterior fossa surgery.

Di Rocco et al. (2011) found a relation between pre-surgical language impairment (PLI) and POPCMS in children diagnosed with a posterior fossa tumor. Two groups of

children were identified in their prospective study: children with PLI (anomia, reduced verbal fluency, verbal adynamia, apraxia of speech) (n = 11) and children without PLI (n = 23). Only children belonging to the PLI group (7/11, 63%) developed mutism after surgery. The authors consequently assumed that PLI may represent a subclinical state of cerebellar mutism in some children with posterior fossa tumor. These findings clearly demonstrate the need for thorough pre- and postoperative neurocognitive investigations in children with posterior fossa tumor.

3. Risk factors for POPCMS

Several risk factors for the development of POPCMS have been identified. Catsman-Berrevoets et al. (1999) found a clear interaction between type and size of the tumor, in that POPCMS is most likely to occur after resection of a medulloblastoma with a lesion diameter exceeding 5 cm (see also Pols et al. 2017). However, since POPCMS may also be associated with other tumor types and in patients with medulloblastomas not exceeding 5 cm, additional risk factors have been considered to play a possible causative role in the genesis of the syndrome in tumoral cases. These include: vermis split and length of vermian incision (Dailey et al. 1995), midline tumor location (Pollack et al. 1995; Ozgur et al. 2006; Robertson et al. 2006), tumor location adjacent to the fourth ventricle and post-surgical edema of the pontine tegmentum (Van Dongen et al. 1994), tumor infiltration into or compression of the brainstem (McMillan et al. 2009; Tamburrini et al. 2015), postoperative hydrocephalus or meningitis (Humphreys 1989; Ferrante et al. 1990; Salvati et al. 1996; Robertson et al. 2006), lesions to the deep nuclei of the cerebellum (Pollack et al. 1995; Richter et al. 2005), and multiple bilateral injuries to the proximal dentate-thalamo-cortical pathways (Morris et al. 2009). In addition, besides

tumor type and size, Law et al. (2012) suggested that also pre-surgical left-handedness plays a role in the development of POPCMS.

Whereas tumor type, tumor location in the vermis, and tumor invasion or compression of the brainstem appear to be the most consistent risk factors for developing POPCMS, recent reviews of the literature (Reed-Berendt et al. 2014; Tamburrini et al. 2015; Catsman-Berrevoets 2017) disclosed conflicting results for tumor size as an independent risk factor, vermal incision and surgical technique, degree of resection or presence of residual tumor, pre- and/or postsurgical hydrocephalus, edema in various locations, and age at diagnosis (Pols et al. 2017).

Interestingly, based upon a multiple regression analysis, Pols et al (2017) found that besides tumor size and tumor infiltration into or compression of the brainstem, a 0.5°C increase in mean body temperature in the first four days after surgery was an independent and highly significant predictor for POPCMS, amplifying the odds ratio for its development almost 5-fold. The authors explained this significant risk factor for POPCMS as resulting from changing neuronal metabolic rates, which decrease under anesthesia, and increase again once it wears off. Pols et al. (2017) postulated that a higher mean body temperature in the first days post-surgery might amplify metabolic stress to such a degree that the oxygen demands in the vicinity of the site of surgery are insufficiently answered, especially when the surrounding brain tissues are in an already critical metabolic state. Pols et al. (2017) argued that their findings were consonant with data collected in stroke patients, in whom hyperthermia is associated with relatively large infarction volumes and poorer outcome.

4. Pathophysiological explanations and hypotheses

Despite the growing interest in (POP)CMS, its pathophysiology is still unclear. Several hypotheses have been put forward to account for its pathophysiological mechanisms: (1) postoperative vasospasm of the arteries supplying the cerebellum and the brainstem, leading to ischemia and subsequent edema (Ferrante et al. 1990; Nagatani et al. 1991; Balasubramaniam et al. 1993; Turgut 1998; Ildan et al. 2002; Maffei et al. 2005); (2) transient dysfunction of the A9 and A10 mesencephalic dopaminergic cell groups and ascending activating reticular system (Catsman-Berrevoets et al. 1992); (3) transient dysregulation of neurotransmitter release originating from the tumor removal and the alleviation of long-lasting compression of the brainstem by the tumor (Caner et al. 1999); (4) bilateral surgical damage to the dentate and interpositus nuclei (Dietze and Mickle, 1990-91; Pollack et al. 1995; Van Calenbergh et al. 1995; Kusano et al. 2006; Puget et al. 2009) or to the afferent and/or efferent pathways passing through these nuclei (Crutchfield et al. 1994; Ersahin et al. 1996; Turgut 1998; Ojemann et al. 2013; Patay 2015).

Consistent with the latter hypothesis, Morris et al. (2009) concluded from a cohort study of 26 pediatric patients operated upon for a posterior fossa tumor, of whom 13 presented with post-surgical mutism, that: (1) bilateral injury to the proximal dentato-thalamo-cortical pathway may predispose patients to develop POPCMS, (2) functional disruption of the white matter bundles containing efferent axons within the superior cerebellar peduncles is a critical underlying pathophysiological component of POPCMS, and (3) decreased fractional anisotropy in the fornices and cerebral cortex may be related to the abnormal neurobehavioral symptoms of POPCMS. More recently, using diffusion tensor imaging, Ojemann et al. (2013) confirmed the bilateral involvement of the dentato-thalamo-cortical tracts –specifically in the superior cerebellar peduncles– in the emergence of POPCMS. In this respect, Patay et al. (2014), Patay (2015), and Avula et

al. (2016) showed that bilateral hypertrophic olivary degeneration of the inferior olivary nucleus –a component of the Guillain-Mollaret triangle of which the proximal structures of the dentato-thalamo-cortical pathway are a part– is significantly associated with the presence of POPCMS.

Based upon functional neuroimaging studies, there is increasing evidence that the linguistic, cognitive, behavioral, and affective impairments associated with (POP)CMS may result –by means of crossed cerebello-cerebral diaschisis (Sönmezoglu et al. 1993)[5]– from a cerebellar-induced decrease or loss of transmission of excitatory impulses from the deep cerebellar nuclei via the dentato-thalamo-cortical pathway to the anatomically and functionally connected supratentorial associative cortices. This view is supported by numerous (^{99m}Tc-HMPAO or ^{99m}Tc-ECD) SPECT studies revealing perfusion defects in distant, structurally undamaged supratentorial regions involved in cognition, behavior, and affect that paralleled the clinical course of cognitively and/or behaviorally disabled cerebellar patients (e.g., Van Mourik et al. 1996; Germano et al. 1998; Sagiuchi et al. 2001; Mariën et al. 2001, 2003, 2008, 2009, 2010, 2013a,b; Baillieux et al. 2010; De Smet et al. 2009; Catsman-Berrevoets and Aarsen 2010; Miller et al. 2010; De Smet et al. 2011; Nicita et al. 2017). For instance, Mariën et al. (2001, 2003) reported a 5-year-old patient with a posterior fossa medulloblastoma who already presented with mild dysexecutive symptoms in the preoperative phase as reflected on ^{99m}Tc-HMPAO SPECT by perfusion changes in the anatomoclinically suspected but structurally intact prefrontal brain regions. After surgical resection of the posterior fossa medulloblastoma, full-blown POPCMS was associated with a significant aggravation and extension of the preoperative supratentorial perfusion deficits on repeat SPECT. When mutism resolved, and

[5] Patay (2015) defines diaschisis as follows: "a sudden suspension or inhibition of function in one area of the brain after damage to another distant region that normally provides input to the former".

behavioral and affective symptoms started to ameliorate after a 5-week period, a marked improvement of regional cerebral blood flow was found bilaterally in the prefrontal areas. By sharp contrast, no pre- and postoperative supratentorial perfusion alterations were observed in a child who did not develop POPCMS after posterior fossa astrocytoma resection (Mariën et al. 2003). Based upon a close parallelism between the development and course of neurobehavioral symptoms and perfusion changes on SPECT in the anatomoclinically suspected supratentorial brain regions, Mariën et al. (2001, 2003) concluded that crossed cerebello-cerebral diaschisis might be intrinsically implicated in the pathophysiology of CMS.

Further evidence of a close parallelism between the emergence and clinical course of POPCMS and the changing crossed metabolic demands in cerebellum and cerebrum, was recently provided by an ^{18}F-FDG PET scan study showing right cerebellar and left frontal lobe hypometabolism during the mute phase, which returned to normal levels after the resolution of the mutism (Gedik et al. 2017).

5. Functional lateralization of the cerebellum: evidence from CMS

In agreement with the hypothesis of a topographically organized and functionally lateralized cerebellum (Schmahmann 2000; Mariën et al. 2001; Stoodley and Schmahmann, 2010), Riva and Giorgi (2000), Scott et al. (2001), and Siffert et al. (2004) correlated distinct patterns of postoperative neurocognitive symptoms with the lateralization of tumor location in the cerebellum. In the majority of patients, the disruption of linguistic processes resulted from surgical resection of tumors infiltrating the right cerebellar hemisphere, whereas deficits in non-verbal, spatial cognition were consistently found after tumor resection in the left cerebellar hemisphere. Vermal lesions

were generally associated with behavioral-affective disturbances (Levisohn et al. 2000; Schmahmann, 2004).

6. Treatment and rehabilitation

As yet, no systematic attempts have been undertaken to treat the neurobehavioral symptoms of CMS by means of pharmacological agents or specifically designed neurorehabilitation strategies. There are only a few anecdotal reports in which patients received drug treatment to improve their condition. Daly and Love (1958), for instance, administered 40 mg of methylphenidate hydrochloride intravenously and recorded a beneficial effect of this general central nervous stimulant on the patient's behavioral condition in terms of alertness and responsiveness. After this improvement, oral administration of the drug in a total daily dose of 100 mg (divided in 5 doses of 20 mg each) was stated to sharply accelerate the rate of recovery. Although the patient remained mute, he slept less, showed more spontaneous movements, and attempted to walk without help. Several attempts to discontinue analeptic drug treatment during follow-up were unsuccessful. Whenever the treatment was stopped for longer than a day, the patient became apathetic and somnolent again. Normal alertness was achieved by resuming treatment.

Since dopamine agonists (primarily bromocriptine) proved useful to treat akinetic mutism of various etiologies (e.g., Messert et al. 1966; Rose and Stewart 1981; Catsman-Berrevoets and van Harskamp 1988; Echiverri et al. 1988), similar attempts at treating CMS with bromocriptine were undertaken, though with inconsistent effect. Using treatment doses varying between 2.5 mg and 20 mg per day, Caner et al. (1999), Adachi et al. (2005), and Mateo-Sierra et al. (2005) reported a dramatic improvement in their patients' communicative and behavioral status. Ersahin et al. (1997), however,

discontinued bromocriptine therapy (doses unknown) in a 9-year-old girl because of lack of improvement after one month. Other dopamine agonists were equally used in the treatment of CMS. Mariën et al. (2013a), for instance, described a complete remission of mutism, and a substantial improvement in responsiveness and alertness after administration of ropinirole hydrochloride in a 38-year-old woman presenting with postoperative CMS. However, although an improvement in mental speed, language dynamics, behavior, and affect was found as well, a wide range of invalidating cognitive, behavioral, and affective abnormalities persisted. Treatment had to be discontinued because the patient developed psychotic symptoms.

Interestingly, other approaches in the pharmacological treatment of CMS have also been adopted. El-Nabbout and DeLong (2002) treated two patients with fluoxetine after posterior fossa surgery, based on a parallelism they observed between POPCMS patients and patients with autism, in whom language disturbance is related to decreased serotonin production after disruption to the dentato-thalamo-cortical pathways. Both patients started speaking three days after treatment was initiated. Akhaddar et al. (2012) administrated fluoxetine in a 13-year-old boy, after an initial trial with corticosteroids and simultaneous speech therapy failed to hasten recovery from POPCMS. Three to 4 days later, the patient's mutism slowly resolved and disappeared completely about 4 weeks after drug initiation. The authors admitted that the mechanism by which fluoxetine might ameliorate speech inhibition is unknown.

Shyu et al. (2011) reported on a positive outcome in a 4-year-old girl with a vermian medulloblastoma and a secondary left cerebellar nodule, who developed POPCMS on the second day post-surgery. The authors treated the patient with 2.5 mg zolpidem, and noted that she was more animated after the drug was administered, and that speech resumed 14 days later.

A recent study by Nicita et al. (2017) unveiled a spectacular effect of benzodiazepine treatment (midazolam) in a 17-year-old boy who underwent posterior fossa surgery for choroid plexus papilloma of the fourth ventricle. Four days post-surgery, he became dysarthric and less responsive. He was administered 5 mg intravenous midazolam to be sedated for a repeat MRI. Two minutes after drug administration, he started to speak well and respond adequately. About 3 hours after midazolam injection, he became akinetic, with no response to verbal or painful stimuli, without spontaneous activity such as coughing or yawning. Midazolam was administered again with the same effect: 2 minutes after injection, the patient was able to speak, move, recognize his parents, and remember events of the past. Again, after about 3 hours, he turned back into the akinetic state. Three days later, with the patient still mute and akinetic, a SPECT was performed after intravenous infusion of midazolam 5 mg. The patient showed the same sudden clinical resolution of POPCMS. In addition to clinical improvement, post-midazolam SPECT also demonstrated amelioration of –crossed– cerebellar and cerebral perfusion compared to a previous SPECT without sedation during the mute state.

As to (cognitive) rehabilitation, highly individualized approaches combining physical, occupational, and speech/language therapy are recognized to be essential to help restore basic motor function and communication (Morgan et al. 2011; Walker et al. 2014). Cognitive rehabilitation needs to address several interrelated aspects of neurocognitive functioning that encompass memory, intentional and attentional processes, executive functions, visuo-spatial and visuo-perceptual skills, and (non) verbal communication (Walker et al. 2014). Moreover, as emphasized by Walker et al. (2014), it is unreasonable to disengage cognitive rehabilitation from behavioral and emotional difficulties, or from the familial and environmental context which has been

proven to be greatly predictive of recovery from acquired brain damage.

Designing specific nursing strategies for the patients and their families is also of topmost importance (Turkel et al. 2004; Mortimer 2011; Parent and Scott. 2011). These entail managing acute symptoms and supporting the family through a period of distress; coordinating the efforts of different actors, such as physicians, (neuro) psychologists, speech/language therapists, physio- and occupational therapists; and providing information to educational services and community representatives (Gudrunardottir et al. 2016a).

7. Concluding remarks

More than 50 years of clinical research has brought to the fore that "transient cerebellar mutism" does not constitute an unambiguously distinct neurobehavioral entity following acute damage to cerebellar structures. Indeed, most studies of children and adults who developed cerebellar mutism after etiologically heterogeneous neurological disorders predominantly affecting the cerebellum, have shown that cerebellar-induced speechlessness does not occur in isolation but rather as an intrinsic part of a complex of associated neurological, neurolinguistic, neuropsychological, and neuropsychiatric phenomena. This complex of symptoms, generally denoted as CMS, affects children far more often than adults and occurs in the vast majority of reported cases after a short and relatively symptom-free interval following posterior fossa tumor surgery. Although the recent definition of POPCMS (Gudrunardottir et al. 2016b) seems suitable to describe a large proportion of these pediatric CMS patients, further discussion should focus on how to include other etiological variants and populations which are not incorporated in the current definition.

Since mounting evidence suggests that there is considerable variability in the

semiological expression of CMS –with different degrees of severity and symptom duration– it may be argued that CMS should be placed on a continuum with CCAS, the latter representing the milder form of the disorder. Several studies have suggested a possible link between the two cerebellar syndromes (Levisohn et al. 2000; Ronning et al. 2005), and CCAS may be viewed as a long-term consequence of CMS (De Smet et al. 2009; Gudrunardottir et al. 2016a). CMS and CCAS do not only share overt semiological resemblances (basically differing in extent and severity of symptoms), but possibly also a common pathophysiological substrate, as suggested by a consistent parallelism between functional neuroimaging findings and clinical observations. Both CMS and CCAS seem to reflect functional disruption of the cerebello-cerebral circuitry crucially involved in the regulation of cognitive, behavioral, and affective processes.

Many questions about the intriguing onset and evolution of the semiological characteristics of CMS, its pathophysiological substrate, its treatment, and its longitudinal outcome remain to be solved (Wibroe et al. 2017). In addition, a systematic lack of in-depth preoperative investigations and the absence of formal neurocognitive and behavioral assessments in patients without postoperative cerebellar mutism makes it likely that a number of clinically relevant symptoms have remained unnoticed and still need to be discovered.

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