Letter to the Editor

Intraoperative electroencephalographic burst suppression may help to identify patients at risk for long-term adverse outcome: Findings from a case of homozygous twins

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Dear editor

Postoperative cognitive dysfunction (POCD) is a serious risk factor after general anaesthesia, especially for elderly or cognitively impaired patients.

In order to develop preventing strategies, intraoperative electroencephalographic (EEG) monitoring could prove to be helpful [1]. Prevention of very low EEG-based monitoring indices, such as bispectral index (BIS, Covidien, Boulder CO) and burst suppression (BSupp) patterns represents an especially promising approach, even if their linkage with postoperative cognitive disorders is still a matter of controversial discussion [2–4].

In addition, inadequate anaesthesia depth could trigger intraoperative awareness events[5] that could also lead to long-term neurocognitive decline because of post-traumatic consequences [6].

Here is presented the case of 68-year old homozygous twins (S1 and S2), with similar lifestyle, weight and height (73 kg and 174 cm, and 76 kg and 175 cm respectively), same 5 years of schooling and comorbidities (essential hypertension well controlled with beta-blockers) who underwent in the same day the same total thyroidectomy procedure (first general anaesthesia for both) with similar duration (77 and 84 minutes respectively), stable intraoperative haemodynamic parameters and simultaneous 3-day hospital discharge.

Anaesthetic regimen was also superimposable: neither received premedication, and anaesthesia was induced with fentanyl 150 mcg and propofol 2 mg kg^{-1}. For neuromuscular blockade (NMB), we delivered 1 mg kg^{-1} of rocuronium. After orotracheal intubation, anaesthesia was maintained with desflurane at a minimum alveolar concentration (MAC) of 0.8 (5.4% vaporiser setting on the Dräger Zeus® Infinity® Empowered anaesthesia machine). Fentanyl boluses were further administered: 150 mcg just before skin incision and 100 mcg 40 minutes later. Rocuronium boluses of 0.15 mg kg^{-1} were also administered to maintain a deep NMB, defined as absence of first twitch at a train-of-four monitoring using the TOF-watch SX (Organon, Ireland). Thirty minutes before the end of surgery, patients received paracetamol 1000 mg, ketoprofen 160 mg, and ondansetron 4 mg for pain, nausea and vomiting prophylaxis. At the end of surgery, we reversed the deep NMB with sugammadex (4 mg kg^{-1}) and discontinued desflurane delivery.

Anaesthesia deep monitoring consisted in (a) BIS monitor by applying a BIS Quatro Sensor to the forehead, displaying both the index and the raw EEG allowing visual inspection for intraoperative BSupp episodes and (b) isolated forearm technique (IFT) to detect connected consciousness [5].

Before anaesthesia induction, BIS values were 97 for S1 and 98 for S2 (Table 1). Mean BIS values during maintenance were 35 for S1 and 42 for S2. Furthermore, we visually identified two episodes of BSupp in patient S1: after skin incision, lasting 12 minutes, and approximately 40 minutes after, lasting 8 minutes. No BSupp was observed for S2.

Table 1 Neurocognitive test results and intraoperative monitoring values.

alt-text: Table 1

Twin	Preoperative neurocognitive test				
	MoCA (c)	TMT-A (c)	TMT-B (c)	FAB (c) [z-score]	DST Forward (c) & DST Backward (c)
T1	22 (23)	59 (35)	124 (37)	12 (13) [–1,38]	4 (4,5) & 2 (2)
T2	23 (24)	57 (33)	128 (41)	12 (13)[–1,38]	4 (4,5) & 2 (2)

	Intraoperative period					
	Induction phase		Induction-Incision phase		Surgical phase	
	Mean BIS (*n*)	IFT responses (n)	Mean BIS (*n*)	IFT responses (*n*)	Mean BIS (*n*)	IFT responses (*n*)
T1	32	0	40	0	33	0
T2	39	0	46	0	42	0

	Discharge neurocognitive tests				
	MoCA (c)	TMT-A (c)	TMT-B (c)	FAB (c) [z-score]	DST Forward (c) & DST Backward (c)
T1	20 (21)	62 (38)	125 (38)	10 (11) [–2,92]	4 (4,5) & 2 (2)
T2	19 (20)	60 (36)	130 (43)	11 (12) [–2,15]	4 (4,5) & 2 (2)

	12-month follow-up neurocognitive tests				
	MoCA (c)	TMT-A (c)	TMT-B (c)	FAB (c) [z-score]	DST Forward (c) & DST Backward (c)
T1	12 (13)	94 (70)	Unable (-)	6 (7) [–6]	2 (2,5)& 1 (1)
T2	22 (23)	61 (37)	135 (48)	11 (12) [–15]	4 (4,5) & 2 (2)

BIS: bispectral index; DST: Digit Span Test; FAB: Frontal Assessment Battery; IFT: isolated forearm technique; MoCA: Montreal Cognitive Assessment; TMT: Trail Making Test. Neurocognitive results in parentheses (c) represent age- and schooling-corrected values.

Neither patient exhibited a positive IFT response during surgery.

About neurocognitive assessment, both twins underwent the same neurocognitive tests (Montreal Cognitive Assessment [MoCA], Trail Making Test A [TMT-A] and B [TMT-B], Forward and Backward Digit Span Tests [DST], and the Frontal Assessment Battery [FAB]) the day before surgery (T0), at hospital discharge (T1), and 12 months after surgery (follow-up).

Preoperatively, scores obtained at MoCA, FAB tests and Backward DST fulfilled the definition of (mild) cognitive decline for both twins (Table 1). At discharge, all test scores were worse compared to the preoperative tests in both twins, except for the Forward and Backward DST scores, which remained the same. The scores were similar between the brothers for these assessments. At the 12-month follow-up, the neurocognitive test results for S2 were similar to his postoperative results. S1, in contrast, performed worse in all tests. All scores fulfilled or almost fulfilled (TMT-A score was at the cut-off value) the definition of neurocognitive dysfunction.

Since TSH values seem related to mild cognitive decline and dementia [7], we recorded also the TSH levels trend: these values, similar in the preoperative period, differed between patients at follow-up with S1 having a TSH of 0.10 mIU l^{-1} and S2 of 0.58 mIU l^{-1}.

Briefly analysing our data, the only perioperative observable difference between the twins was lower BIS values and episodes of BSupp in S1, but not in S2.

However, this report of (only) one pair of twins cannot strengthen the hypothesis that BSupp fosters the development of POCD as suggested by some authors. Our finding case describes that BSupp at a normal anaesthesia concentration and without artery hypotension (that would have made our case a “triple low” case [3]) occurred in combination with follow-up POCD. It may thus have presented as a predictor of a frail brain. What makes this case intriguing is that both twins performed in a similar fashion in the neurocognitive tests before surgery and three days after surgery, and that they did not show postoperative delirium or discharge POCD.

In our opinion indeed, given that these two homozygous twins underwent the same surgical procedure and anaesthesia protocol, the fact that only the one with BSupp had a worse 12-month outcome may suggest that his brain was more susceptible to anaesthetic drugs than the other's brain. This could mean that the generation of BSupp may have unmasked the more fragile brain of S1, even if there was no development of cognitive impairment at the first days following general anaesthesia.

Hence, our result may also point towards the necessity of longer follow-up periods for patients at risk.

Of course, our observation is just a report and is significantly limited by the lack of additional neuropsychological follow-up evaluations in the postoperative period closer to surgery as well as later on. However, 18 months after surgery, S2 has continued living at home while S1 had to be transferred to a long-term-stay hospital for elderly.

In conclusion, we would like to state that our observation shows the potential of intraoperative BSupp identification in helping to unmask a frail brain at risk for (long-term) cognitive impairments. With our single case we only can describe our observation, but it may help to motivate other anaesthesiologists to repeat our approach when they have the opportunity.

Authors’ contributions

Study design FL, EM, PZ, MC.

Data collection: FL, EM, MC.

Data analysis: FL, MK, PZ, MC.

Interpretation of data: all authors.

Drafting of the manuscript: FL, PZ, MC.

Revision of the manuscript: all authors.

Approval of the final version of the manuscript: all authors.

Disclosurr of interest

The authors declare that they have no competing interest.

Funding

The authors are supported only by departmental funds.

Acknowledgments

Authors would thank Edoardo Rosellini, MD and AnnaPaola Mazzarolo, PsyD, for supporting the collection of data during this study.

References

[1] M.T. Chan, B.C. Cheng, T.M. Lee and T. Gin, CODA Trial Group. BIS-guided Anesthesia Decreases Postoperative Delirium and Cognitive Decline, *J Neurosurg Anesthesiol* **25**, 2013, 33–42.

[2] J. Steinmetz, K.S. Funder, B.T. Dahl and L.S. Rasmussen, Depth of anaesthesia and post-operative cognitive dysfunction, *Acta Anaesthesiol Scand* **54**, 2010, 162–168.

[3] S. Hesse, M. Kreuzer, D. Hight, A. Gaskell, P. Devari, D. Singh, et al., Association of electroencephalogram trajectories during emergence from anesthesia with delirium in the postanesthesia care unit: an early sign of postoperative complications, *BJA* **122**, 2019, 622–634.

[4] B.A. Fritz, P.L. Kalarickal, H.R. Maybrier, M.R. Muench, D. Dearth, Y. Chen, et al., Intraoperative electroencephalogram suppression predicts postoperative delirium, *Anesth Analg* **122**, 2016, 234–242.

[5] F. Linassi, P. Zanatta, P. Tellaroli, C. Ori and M. Carron, Isolated forearm technique: a meta-analysis of connected consciousness during different general anaesthesia regimens, *Br J Anesth* **121**, 2018, 198–209.

[6] J.E. Osterman, J. Hopper, W.J. Heran, T.M. Keane and B.A. van der Kolk, Awareness under anesthesia and the development of posttraumatic stress disorder, *Gen Hosp Psychiatry* **23**, 2001, 198–204.

[7] R. Hou, H. Wang, L. Chen, Y. Qiu and S. Li, POCD in patients receiving total knee replacement under deep vs light anesthesia: A randomized controlled trial, *Brain Behav* **30**, 2018, e00910.

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