Neuro-Oncology
23(6), 1035–1036, 2021 | doi:10.1093/neuonc/noab048 | Advance Access date 17 March 2021

Letter to the Editor

Prevalence of medulloblastoma in basal cell nevus syndrome patients with a *PTCH1* mutation

Patients with basal cell nevus syndrome (BCNS) are at risk of developing a medulloblastoma (MB) in childhood, which usually develops before the age of 3.[1,2] The incidence of MB seems to differ between *PTCH1* and *SUFU* heterozygotes. Knowledge of the prevalence of MB is important to guide screening, which is performed by MRI. In the consensus statement of the international colloquium on BCNS published in 2011, yearly MRI screening is advised in all BCNS children.[1] However, more recently, a British cohort showed a MB prevalence of 33.3% in 9 *SUFU* heterozygotes and 2.4% in 126 *PTCH1* heterozygotes.[3] Based on this study, a recent guideline on cancer surveillance in patients with BCNS advised not to screen in *PTCH1* heterozygotes and screen *SUFU* heterozygotes more frequently (ie, every 4 months during the first 3 years and half-yearly till the age of 5).[4] For more robust evidence on the low incidence of MB among *PTCH1* heterozygotes, we determined the prevalence of MB in a Dutch cohort.

A retrospective cohort study was conducted at the VU University Medical Center (VUMC) and the Maastricht University Medical Center+ (MUMC+) in the Netherlands.[5] Between April 1999 and December 2015, the laboratories of those two hospitals processed all clinical requests for *PTCH1* mutation analysis in the Netherlands and various foreign hospitals. Analysis was done by standard *PTCH1* mutation analysis (Sanger sequencing) and multiplex ligation-dependent probe amplification (MLPA). After a search for *PTCH1* analysis requests in the electronic genetic medical record system of the VUMC and MUMC+, patients with a pathogenic *PTCH1* mutation were selected. Foreign patients were excluded due to practical difficulties. Information about MB presence was retrieved from the medical records from October 2015 until December 2016.[5] The medical records of all patients aged <8 years at initial data assessment were reassessed between May 2020 and August 2020 to exclude MB development. Clinical data were available for 83 patients (from 77 families) with a pathogenic *PTCH1* mutation. Two further cases were excluded because of intrauterine fetal death. One patient was 4 years old at the time of data collection, all other patients were ≥8 years.

Of the 81 found mutations, 27 (33.3%) were nonsense, 25 (30.9%) frameshift, 11 (13.6%) splicing, 10 (12.3%) missense, 5 (6.2%) in-frame duplications and deletions, and 3 (3.7%) whole *PTCH1* gene deletions.

Only 1 of the 81 (1.2%) *PTCH1* patients was diagnosed with a MB at the age of 11 months. The patient had a germline *PTCH1* nonsense mutation in exon 12, c.1691T>G, which results in a stop at position 564 (p.Leu564*). He suffered from many other congenital anomalies, not all typical for BCNS.

Guidelines for patients with BCNS advise screening for MB with MRI.[1,4] However, screening with MRI often requires general anesthesia in young children which can be stressful for parents and children. Moreover, the developmental risk of general anesthesia at young age is still under debate and high-frequency general anesthesia should therefore be performed only with caution.[6] In this nationwide retrospective cohort study, we found a MB prevalence of 1.2% in *PTCH1* heterozygotes. Taking into account the disadvantages of MRI and the low MB prevalence in two *PTCH1* cohorts, high-frequency routine neuroimaging for MB in children with BCNS with an underlying *PTCH1* mutation is debatable. We advocate to perform MRI in *PTCH1* heterozygotes only when clinical symptoms are present. With this strategy, it is essential to monitor the development and skull growth of children twice per year during the first years of life.

Funding

None declared.

Conflict of interest statement. The authors have no conflict of interest to declare.

Authorship statement. All authors have seen and approved the manuscript.

Babette J. A. Verkouteren, Betül Cosgun, R. Jeroen Vermeulen, Marie G. H. C. Reinders, Michel van Geel, Johan J. P. Gille, and Klara Mosterd

Department of Dermatology, Maastricht University Medical Center, Maastricht, the Netherlands (B.J.A.V., B.C., M.G.H.C.R., M.V.G., K.M.); GROW School for Oncology and Developmental Biology, Maastricht University, Maastricht, the Netherlands (B.J.A.V., B.C., M.G.H.C.R., M.V.G., K.M.); Department of Neurology, Maastricht University Medical Center, Maastricht, the Netherlands (R.J.V.); Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, the Netherlands (M.V.G.); Department of Clinical Genetics, VU University Medical Center, Amsterdam, the Netherlands (J.J.P.G.)

Corresponding Author: Babette J. A. Verkouteren, MD, Department of Dermatology, Maastricht University Medical Center, P. Debyelaan 25, 6229 HX Maastricht, the Netherlands (babette.verkouteren@mumc.nl).

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