Medulloblastoma (MB) is the most common malignant brain tumor in childhood. Four main distinct MB subtypes have been identified: WNT, SHH, Group 3, and Group 4. Group 4 MB (G4MB) is the most frequent (35%) but also the least understood. The early detection of the disease is essential to reduce cancer mortality and therapy-related toxicity. To date, there is no reliable marker for G4MB that could facilitate the early diagnosis and the evaluation of response to treatments. Therefore, the discovery of biomarkers as a specific G4MB patients’ signature would be extraordinarily worthwhile. MicroRNAs are single-stranded non-coding RNA strongly deregulated in several types of tumors. microRNAs are released into the bloodstream and are stably detectable. The minimally invasive liquid biopsy flank the reliability and specificity of microRNAs in cancer indicates circulating microRNAs as promising biomarkers to get early diagnosis, but also to follow treatment response and detect recurrence. Here, we report a high-throughput screening of microRNAs in G4MB plasma samples before surgery and during follow-up. Differentially expressed circulating microRNAs were detected in 4 patients and in 4 age-/sex-matched healthy donors. Baseline microRNA profiling disclosed a signature of 34 miRNAs identifying patients versus healthy children. microRNAs were validated by RT-qPCR on a wider cohort of G4MB patients (n = 8) and healthy donors (n = 8). We identified two important oncogenic microRNA clusters significantly upregulated in G4MB plasma patients. Therapy reduced the expression of these microRNAs up to healthy donors levels. In conclusion we identified a specific circulating microRNA signature in G4MB.