Clinical Neurology and Neurosurgery 146 (2016) 130–137

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Growth dynamics of intramedullary spinal tumors in patients with neurofibromatosis type 2

Anna C. Lawson McLean*, Steffen K. Rosahl

Department of Neurosurgery, HELIOS Klinikum Erfurt, Germany

ARTICLE INFO

Article history:
Received 4 February 2016
Received in revised form 9 April 2016
Accepted 3 May 2016
Available online 6 May 2016

Keywords:
Spinal tumors
Neurofibromatosis type 2
Growth dynamics
Magnetic resonance imaging

ABSTRACT

Objectives: Volumetric data on the natural growth of intramedullary tumors in patients with neurofibromatosis type 2 (NF2) are rare, but crucial for long-term disease monitoring. Our aim was to evaluate the growth rates and growth patterns of these tumors.
Patients and methods: Patient records from the regional neurofibromatosis referral center were evaluated for inclusion in this analysis. Magnetic resonance images of the spine were collected and digitized as necessary. Tumor volumes were determined by volumetric extrapolation after segmentation in datasets (iPlan Net software, BrainLAB, Munich) if the tumors met the following inclusion criteria: sagittal T2-weighted MRI scans had to be available from at least two investigations and tumors had to be visible on at least two slices. All tumors that had undergone previous therapy, such as surgery, radiation or bevacizumab treatment were excluded from this study.
Results: Suitable MR images of the spine were available from 51 patients (20 males, 31 females) with NF2. The median follow-up time per patient was 54 months (range 0–190 months). 23 patients (15 females, 11 males) of the 51 patients with spinal imaging harbored intramedullary tumors. Across this cohort, there was an aggregate of 68 tumors at baseline. Over the course of follow-up, the patients developed 19 additional tumors, resulting in a total of 87 tumors. A final set of 42 tumors from 19 patients met the inclusion criteria and was included in the growth analysis. The median follow-up time per tumor was 44 months (range 9–122 months). 23 of the tumors were located in the cervical spine; 19 of them were located in the thoracic spine. The median tumor size ± standard deviation (SD) after 5 years was 136 ± 71.0% compared to baseline. The median time to ≥20% tumor growth was 24 months. Overall, 30 tumors (71.4%) grew, 8 (19.1%) remained stable and 4 (9.52%) decreased in size. The most common growth pattern was saltatory growth.
Conclusion: Intramedullary spinal cord tumors are present in about half of patients with NF2. The majority of these tumors grow over time, albeit slowly. Given the confines of the spinal medulla and the limited scope for functional recovery after symptomatic tumor expansion, NF2 patients should be under continual surveillance in order to rapidly identify intramedullary spinal tumors that may require microsurgical resection.

1. Introduction

Neurofibromatosis type 2 is an autosomal-dominant disorder, which is characterized by the development of multiple neoplasms of the central and peripheral nervous system. NF2 has an incidence of 1 in 25,000 live births and a prevalence of 1 in 100,000 [10].

The cause of NF2 is a defect of the NF2 gene on locus 22q12, which codes the protein merlin (moesin-ezrin-radixin-like protein). Within the cell, merlin functions as a link between the cell membrane and the cytoskeleton. It connects to several cellular pathways and plays a key role in cell proliferation and migration [25].

In addition to intracranial neoplasms, skin lesions and ocular impairment, some of the patients with NF2 are prone to develop tumors located in the spinal medulla. The majority of these tumors are ependymomas or astrocytomas [17,18,20], and are most commonly found in the cervical spine, followed by the thoracic spine. Intramedullary tumors rarely occur in the lumbar spine [1,9,20,24]. They can cause variable symptoms such as motor deficits, sensory

Abbreviations: MRI, magnet resonance imaging; NF2, neurofibromatosis type 2; SD, standard deviation; WHO, World Health Organisation.

* Corresponding author at: Department of Neurosurgery, HELIOS Klinikum Erfurt, Nordhäuser Str. 74, 99089 Erfurt, Germany.
E-mail address: anna.lawsonmclean@gmail.com (A.C. Lawson McLean).

http://dx.doi.org/10.1016/j.clineuro.2016.05.006
0303-8467/

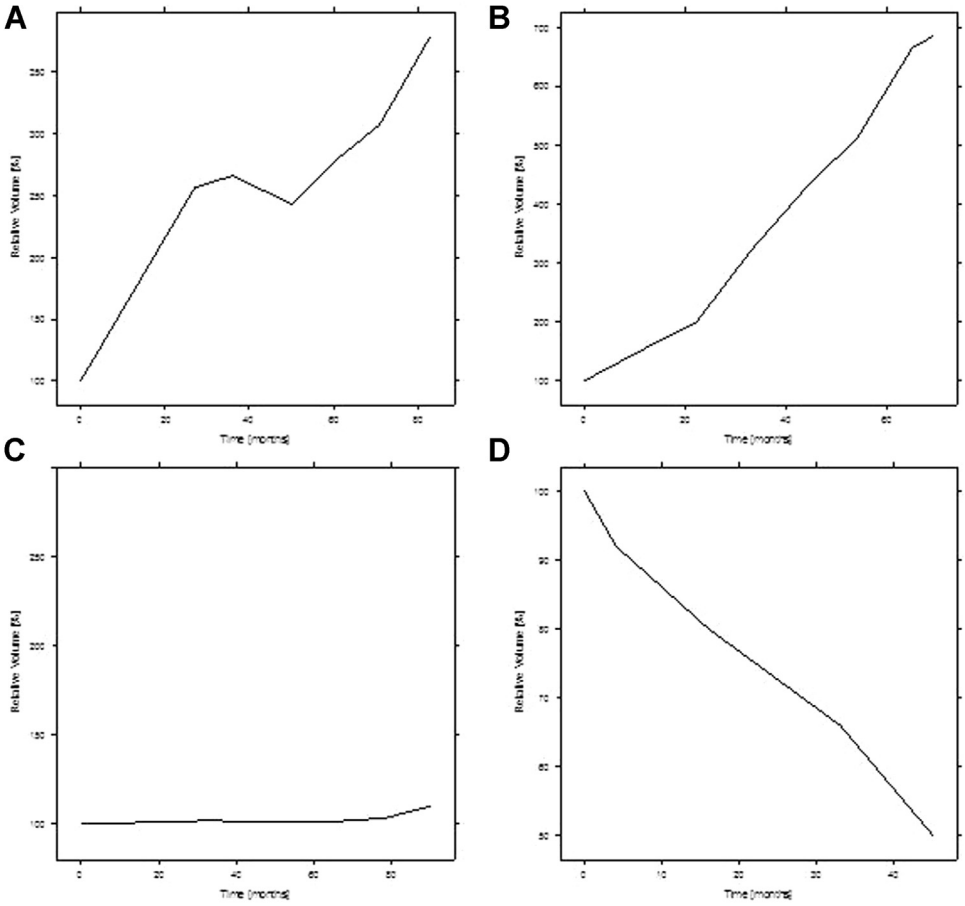

Fig. 1. Examples of possible growth patterns of intramedullary spinal tumors: (A) saltatory growth; (B) linear growth; (C) stable in size; and (D) decreasing in size.

disturbance, pain, or dysfunction of the bowel or bladder [6,13]. Since these tumors can have a severe impact on patients' quality of life, it is important to have an understanding of their growth dynamics to inform treatment decisions and the timing of any therapeutic intervention.

Thus far, data on natural growth of intramedullary spinal tumors are rare [1,9,24]. No quantitative volumetric study on this topic is known to the authors. The aim of this study was to evaluate the growth rates and behavior of these tumors.

2. Patients and methods

This study on retrospective data has been registered with and approved by with the Ethics Committee of the State Chamber of Medicine in Thuringia. Patient records from all patients with definite NF2 attending the regional neurofibromatosis referral center were obtained and screened for demographic data and information on previous therapy. Imaging of the spine at 2-year intervals forms part of the standard follow-up protocol for patients with NF2 at our institution. All available MRI datasets of the spine were collected and digitized as necessary.

The number of distinct intramedullary spinal tumors per patient was quantified. Tumors were then measured by semi-automated volumetric quantification if they met the following inclusion criteria:

1. Only intramedullary tumors that were visible on native T2-weighted images were included.
2. Tumors had to be visible on datasets from two investigations that had been performed no more than 36 months apart from one other.
3. Tumors had to be visible on at least two MRI slices.
4. Tumors must not have undergone previous treatment, including radiotherapy, medical therapy and/or surgery.

Criterion 2 was selected to introduce a maximum time interval and to reduce loss-to-follow-up bias.

iPlan Net software (BrainLAB, Munich) was used for volumetric measurements. Datasets were uploaded into the program and tumors were outlined on each slice using semi-automated segmentation. Volumes were automatically calculated from the selected areas.

All tumors were measured on sagittal datasets by the same rater. A smaller slice thickness was preferred. The slice thickness varied from 3.0 to 4.0 mm.

R software (R Development Core Team, 2015) was utilized for statistical analysis.

Tumor volumes at the time of first-available investigation were considered the baseline and consecutive volumes were grouped according to when the scans were performed: Volumes measured from MR images obtained within the first year (12 months) after the first investigation were analyzed as one group, as were volumes on datasets recorded within the second year after baseline, and so on. For each year, median tumor volume compared to baseline was determined.

The Peña-Strawderman-Hollander model for recurrent survival analysis as described by Baethge et al. [2] was used for determination of latency to tumor growth. This method is a derivative of