Spinal and para-spinal plexiform neurofibromas in NF1 patients, a clinical-radiological correlation study

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Aims and objectives

Neurofibromatosis 1 (NF1) is a common autosomal dominant tumor pre-disposition syndrome. NF1 affects approximately 1:4,000 people world-wide [1]. In Israel the prevalence is estimated to be 1:1000 [2]. The syndrome is characterized by a combination of clinical traits: Café au lait spots, lisch nodules (iris hamartomas), neurofibromas (cutaneous, sub cutaneous, plexiform), optic pathway gliomas and bone dysplasia [1].

The hallmark of the disease, and a major cause for morbidity and mortality, are plexiform neurofibromas (PN). PN are benign tumors of peripheral nerve sheath (WHO grade I) affecting 30-50% of NF1 patients, and leading to symptoms in 50-70% of affected patients. PN can be massive, and may undergo transformation into malignant peripheral nerve sheath tumor (10% lifetime risk). Symptoms (pain, neurological deficit) may be attributed to local mass effect, or neuropathy. PN vary widely in size, number and location from patient to patient. Figure 1 demonstrates an exemplary case of a complex spinal involvement in an NF1 patient. The largest series dealing with spinal PN, described a group of 149 patients and spinal involvement was classified into types according to their anatomical location in the spinal canal and foramina [3]. Despite the large cohort, in this study, only 12 patients had NF1, in addition, no conclusions regarding this special population were made. Two studies looked into incidence and variety of spinal tumors in NF patients specifically, but clinical correlation between the tumor burden and clinical outcome was not discussed [4, 5]. To date, clinical-radiological association was found in NF patients, only in the cervical region [6] or specific for intramedullary involvement [7]. Our aim in this study was to characterize the radiological presentation of spinal and para-spinal involvement in NF1 patients, and to correlate it with clinical presentation, as manifested in pain and neurological deficits. We also attempted to create a radiologically based risk score for clinical deterioration.
Fig. 1: Complex spinal manifestation in a NF1 patient. MRI of a 36 years old NF1 patient with spinal involvement that was a-symptomatic at presentation, he underwent a thoracic CT scan due to a non-related complain (pneumothorax). Sagittal T1 with gadolinium of the cervical region. Note that the tumors involve all the neuro-foramina in this segment (A). Axial T1 with gadolinium demonstrates massive para-spinal involvement of the thoracic region (B). Sagittal T2 of the lumbar region demonstrate multiple tumors in the neuro-foramina and in the pelvis (C).

References: radiology, Tel Aviv Sourasky Medical Center - Tel-Aviv/IL
Methods and materials

We retrospectively reviewed the records of all adult NF1 patients treated in our institution between the years 2008-2014 that had spinal manifestation of the disease. All patients with MRI studies of the spine were assessed clinically, and their imaging studies were revised. Patients were classified according to their clinical presentation: asymptomatic, suffering from pain or suffering from neurological deficit due to their spinal manifestations.

Radiologically, the spinal region was divided into segments (cervical, thoracic, and lumbo-sacral). We simplified classification of the spinal involvement in NF1 into:

1. Para-spinal tumors - tumors that had an associated large soft tissue component outside the spinal canal.

2. Tumors involving the nerve roots in neuro-foramina. (Fig.1 and 2).

3. "Kissing" PN- bilateral, foraminal tumors approximated each other at the same level, to less than 1-2 mm with significant compression of the cord or thecal sac. (fig.2B).

4. Intra medullary - tumors raising exclusively from the cord itself.

The number of each subtype of PN was documented for each spinal segment, see figure 2A for schematic summary of our classification. In order to identify possible radiological risk factors that may predict a dismal clinical outcome, we conducted a series of logistic regressions for each segment and for each tumor subtype. A radiological score for increased risk of neurological deficit was calculated according to significant (p<0.05) or trending (p<0.08) risk factors. In order to verify the accuracy of the risk score we used independent sample t-test to compare the means of the different groups.
Fig. 2: Schematic representation of our novel classification of PN subtypes and spinal involvement in NF1 [A]. Green ellipse represent para-spinal involvement (type 1). Red circle represent tumors within neuro-foramina (type 2). Blue circles represent bilateral tumors within neuro-foramina (kissing neurofibromas, type 3), and purple ellipse represents an intra-medullary lesion (type 4). B. T2 coronal MRI of the lumbar region of NF1 patient, in the yellow rectangle an example of two pairs of bilateral tumors in which the tumors approximated each other at the same level, to less than 1-2 mm with significant compression of the thecal sac, ("kissing" PN), note the large para-spinal component in this lumbar region (type 1).

References: radiology, Tel Aviv Sourasky Medical Center - Tel-Aviv/IL
Results

Out of 257 adult NF1 patients followed in our institution, 41 had spinal involvement. Thirty-four had sufficient data to be included in this study. At presentation, 12 patients were asymptomatic, 15 had pain and 13 had a neurological deficit. In our group, there was no correlation between pain and tumor burden in each segment (Fig.3 and 4). Three independent factors were found to be associated with increased risk for neurological deficit. The first is bilateral tumors that approximated each other at the same level, "kissing", in the cervical region, the second is para-spinal tumors in the lumbar region and the third is intra-medullary lesions (Fig. 5) with respective OR of 1.7 (p=0.07), 3.7 (p=0.08) and 4.2 (p=0.039). For pain, no risk factors were found to be significant. Based on these values we calculated a risk score for neurological deficit for each patient. Patients with neurological deficit were found to have a significantly higher risk score with an average of 9+/-8.3, while patients not suffering from neurological deficit had a score of 2.5+/-2.9 (p<0.05). For pain, no difference was found in the risk score.

Fig. 3: Asymptomatic vs. symptomatic patients. The only difference in tumor distribution was more cervical kissing PN in the symptomatic group.

References: radiology, Tel Aviv Sourasky Medical Center - Tel-Aviv/IL
Fig. 4: Patients suffering from pain vs. patients without pain. Pain was not associated with difference in tumor distribution or subtypes.

References: radiology, Tel Aviv Sourasky Medical Center - Tel-Aviv/IL

Fig. 5: Patient suffering from neurological deficit vs. patient that are not suffering from neurological deficit. Patients with neurological deficit had more para-spinal tumors.
in the cervical region (type 1) and had more "kissing" NF (type 3) in the cervical and lumbar region than patients that are not suffer from neurological deficit.

References: radiology, Tel Aviv Sourasky Medical Center - Tel-Aviv/IL
Conclusion

In our limited series, pain was not correlated with tumor burden in any of the spinal segments. Three factors were highly correlated with neurological deficit: para-spinal tumors (type 1) in the lumbar region, "kissing" neurofibromas (type 3) in the cervical region and intra-medullary lesions (type 4). Our novel radiological classification and score are significantly associated with increased neurological morbidity. These, may aid in identifying patients that have increased risk for neurological deterioration, and the need for future surgery, according to their imaging at presentation.
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References


