Spectrum of burden of disease in patients with neurofibromatosis type 2 under the updated diagnostic criteria

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INTRODUCTION

- Neurofibromatosis type 2 (NF2) is a genetic tumor predisposition syndrome that is most classically associated with bilateral vestibular schwannomas (VS), but can also cause a myriad of other tumor types.
- Genetically, it is defined as the de novo or inherited loss of the *NF2* tumor suppressor gene on chromosome 22q, followed by a somatic loss of heterogeneity (LOH) of the second *NF2* copy.
- In 2022, a panel of experts released the updated consensus criteria for the diagnosis of NF2 and schwannomatosis (SWN), which updated both the clinical and molecular criteria to distinguish these syndromes given their overlapping phenoptypes.[1]

Objective: to assess the spectrum of disease burden specifically in NF2 patients identified under these more precise diagnostic criteria.

METHODS

- Study Design: Retrospective review under IRB approval.
- Data Source: Medical records from our institution's NF2 clinic.
- Statistical Analysis: Conducted in R, with numerical variables scaled for clustering analysis.

RESULTS

- **71 NF2 patients** met the updated **2022 diagnostic criteria**.
- **Demographicss:**
  - **Mean age at diagnosis:** 23 years (SD 15, range 1–65).
  - **Time since diagnosis:** Median **11.8 years** (IQR 5.2–19.1).
  - **Gender: 57.7% female**.
- **Genetic testing or family history available (n=67):**
  - **Familial NF2:** 18 patients
  - **De novo mosaicism:** 6 patients
  - **De novo mutation:** 43 patients

RESULTS

Tumor Burden & Clinical Features

- **Vestibular Schwannomas (VS):** 100% of patients had at least one VS, with **88.7% (n=63) having bilateral VS**.
- **Intracranial Meningiomas: 60.6% (n=43)**.
- **Other Cranial Nerve Schwannomas: 7% (n=5)**.
- **Spinal Tumors:**
  - **IDEM (Intradural Extramedullary): 6.8% (n=53)**
  - **IDIM (Intradural Intramedullary): 41.4% (n=29)**
- Number of **intracranial and spinal tumors** were positively correlated (**Pearson R=0.05, p<0.001**).
- **Hearing Preservation:** 11.3% (n=8) of patients with bilateral VS had normal audiometry.

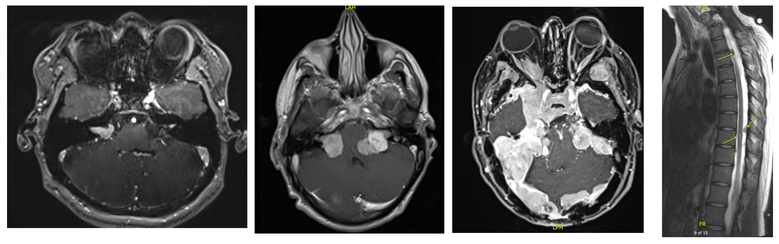

Fig 1. *Spectrum of disease on MRI imaging*. Left to right: **A**. Pt with mosaic de novo NF2, R VS and L VN enhancement. **B** Pt with familial NF2 with bilateral VS, also has olfactory groove meningioma and small falcine meningiomas (not seen here) **C** Pt w de novo NF2, diffuse meningiomatosis and collision with VS **D** Spine MRI in patient with de novo NF2, thoracic ependymoma and multiple spinal meningioma

Treatment Modalities

- **Surgical intervention: 75.7% (n=53)** had at least one surgery (**median 1, range 1–14**).
- **Radiation therapy: 35.7% (n=25)** received radiation for one or more lesions.
- **Medical therapies:**
  - **Bevacizumab:** 27 patients
  - **Tyrosine kinase inhibitors:** 6 patients
  - **Everolimus:** 6 patients
  - Some patients received combination or sequential therapies.

RESULTS

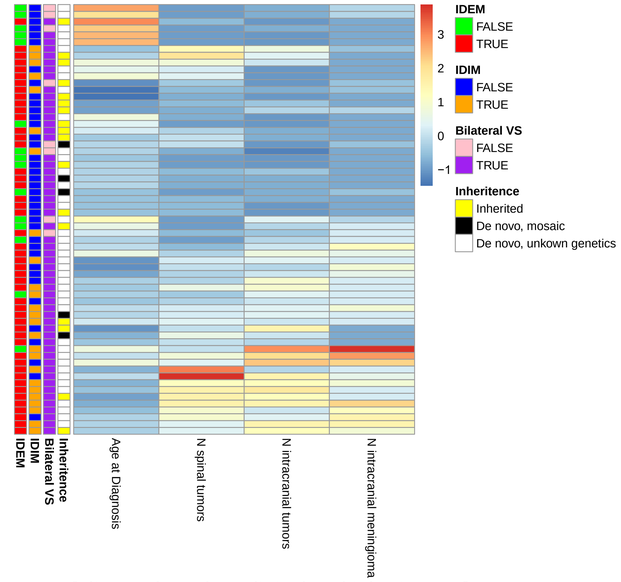

Fig 2. *Spectrum of disease based on clinical and inheritance features*

Genotype-Phenotype Associations

- **Mosaic NF2 patients** tended to have a **lower tumor burden** compared to **inherited mutations**, which in turn had **less severe disease** than **de novo NF2 mutations (Fig 2)**
- **This aligns with the higher prevalence of truncating mutations in de novo NF2.**

Conclusions

- **NF2 syndrome has a highly variable disease burden** despite its complete penetrance.
- The **updated 2022 NF2 diagnostic criteria** help refine classification, but **phenotypic variability remains significant**.
- **Genetic testing, including germline vs. mosaic status, remains crucial** for prognosis and patient counseling.

References

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