Schwannomatosis

Schwannomatosis is a dominantly inherited condition predisposing to schwannomas of mainly spinal nerve and peripheral nerves.

Multiple schwannomas in a patient are referred to as schwannomatosis. Schwannomatosis is usually indicative of an underlying tumor predisposition syndrome, such as neurofibromatosis [1].

Among schwannoma patients, 3–4% has multiple tumors (schwannomatosis) [2].

Earlier findings suggest that schwannomatosis is a disease that is distinct from non-syndromic schwannomas, both genetically and clinically [3].

Schwannomatosis and neurofibromatosis type 2 (NF2) are both characterized by the development of multiple schwannomas but represent different genetic entities. Whereas NF2 is caused by mutations of the NF2 gene, schwannomatosis is associated with germline mutations of SMARCB1 or LZTR1.

Kehrer-Sawatzki et al., from Ulm, Germany studied 15 sporadic patients with multiple non-intradermal schwannomas, but lacking vestibular schwannomas and ophthalmological abnormalities, who fulfilled the clinical diagnostic criteria for schwannomatosis. None of them harboured germline NF2 or SMARCB1 mutations as determined by the analysis of blood samples but seven had germline LZTR1 variants predicted to be pathogenic. At least two independent schwannomas from each patient were subjected to NF2 mutation testing. In five of the 15 patients, identical somatic NF2 mutations were identified (33%). If only those patients without germline LZTR1 variants are considered (n = 8), three of them (37.5%) had mosaic NF2 as concluded from identical NF2 mutations identified in independent schwannomas from the same patient. These findings imply that a sizeable proportion of patients who fulfil the diagnostic criteria for schwannomatosis, are actually examples of mosaic NF2. Hence, the molecular characterization of tumours in patients with a clinical diagnosis of schwannomatosis is very important. Remarkably, two of the patients with germline LZTR1 variants also had identical NF2 mutations in independent schwannomas from each patient which renders differential diagnosis of LZTR1-associated schwannomatosis versus mosaic NF2 in these patients very difficult [4].

The underlying epidemiology is poorly understood.

Evans et al., present the birth incidence and prevalence allowing for overlap with NF2.

Schwannomatosis and NF2 cases were ascertained from the Manchester region of England (population=4.8 million) and from across the UK. Point prevalence and birth incidence were calculated from regional birth statistics. Genetic analysis was also performed on NF2, LZTR1 and SMARCB1 on blood and tumour DNA samples when available.

Regional prevalence for schwannomatosis and NF2 were 1 in 126 315 and 50 500, respectively, with calculated birth incidences of 1 in 68 956 and 1 in 27 956. Mosaic NF2 causes a substantial overlap with schwannomatosis resulting in the misdiagnosis of at least 9% of schwannomatosis cases. LZTR1-associated schwannomatosis also causes a small number of cases that are misdiagnosed with NF2 (1%-2%), due to the occurrence of a unilateral vestibular schwannoma. Patients with

schwannomatosis had lower numbers of non-vestibular cranial schwannomas, but more peripheral and spinal nerve schwannomas with pain as a predominant presenting symptom. Life expectancy was significantly better in schwannomatosis (mean age at death 76.9) compared with NF2 (mean age at death 66.2; p=0.004).

Within the highly ascertained North-West England population, schwannomatosis has less than half the birth incidence and prevalence of NF2 [5].

1)
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