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Clinical and Genetic Overview of Neurofibromatosis Type 2 (NF2)

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Neurofibromatosis type 2 (NF2) is an autosomal dominant disease characterized by bilateral vestibular schwannomas and other central nervous tumors such as meningiomas and spinal ependymomas. Symptoms vary according to the age at diagnosis and the location of these tumors. The diagnostic criteria of NF2 have been regularly revised and recently updated in 2022 with a new nomenclature "NF2-related schwannomatosis" to differentiate NF2 from other schwannoma predisposing disorders, such as SMARCB1 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1)-, LZTR1 (leucine zipper-like transcription regulator 1)-, and 22q-related schwannomatosis. Addition to the clinical features, genetic testing for pathogenic variants in these genes became an important essence to support diagnosis of NF2 and other schwannomatosis, including mosaic conditions.

Key Words : Neurofibromatosis 2 · Schwannomatosis · Mosaicism · Genetic testing.

INTRODUCTION

Neurofibromatosis type 2 (NF2) is an autosomal dominant disease caused by a pathogenic variant of the NF2 tumor suppressor gene on chromosome 22q12 (OMIM 101000)[6]. The birth incidence rate and population prevalence are estimated as 1 in 25000–33000 livebirths and 1 in 50500–60000 individuals, respectively[2,6,9,15]. NF2 patients usually develop bilateral vestibular schwannomas (VSs) but sometimes with other multiple tumors, such as meningiomas, non-VSs, and spinal ependymomas in the central nervous system (CNS) (Fig. 1). Children with NF2 rather present cataracts, optic nerve sheath meningiomas, retinal hamartomas, and dermal schwannomas[2]. Therefore, symptoms can vary according to the age and location of these tumors, which are bilateral/unilateral hearing loss, tinnitus, cerebellar dysfunction, facial nerve palsy, speech dysfunction, vision loss, hemiparesis and spinal dysfunctions.

The term "NF2" is now renewed as "NF2-related schwannomatosis" according to the new criteria updated in 2022[16]. "Schwannomatosis (SWN)" became an umbrella term for conditions that predispose to schwannomas. Previously, SWN due to identified genes known as SMARCB1 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1) and LZTR1 (leucine zipper-like transcription regulator 1) were difficult to differentiate from NF2 because of their overlapping clinical features, which are now definitely classified via genetic testing for pathogenic variants in these genes. Genetic analysis has become an important pro-

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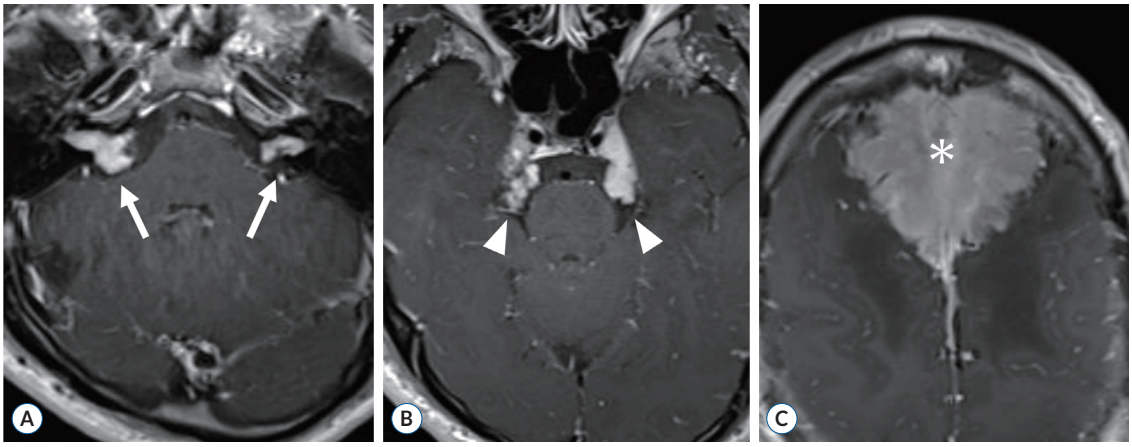

Fig. 1. A 24-year-old male who came with seizures. The patient had past histories of neurofibromatosis (no details of the type) diagnosed by a biopsy of skin granules and a cervical spinal ependymoma removed at the age of 12 years. Axial T1-weighted contrast-enhanced brain-MRI presented bilateral vestibular schwannomas (arrows) (A), bilateral trigeminal schwannomas (arrowheads) (B), and a frontal parasagittal sinus meningioma (asterisk) (C). The meningioma was totally removed via surgery, whereas the bilateral schwannomas were periodically observed by MRI. MRI : magnetic resonance imaging.

cess not only for diagnosis but also understanding the whole disease. However, because these dramatic changes in disease classification and nomenclature might not be familiar to many clinicians, we would like to use "NF2" rather than "NF2-related SWN" in this review to denote the tumor-prone syndrome caused by germline alteration of the NF2 gene.

DIAGNOSTIC CRITERIA

The diagnostic criteria for NF2 have been regularly revised to distinguish NF2 from other neurofibromatosis syndromes; neurofibromatosis type 1 (NF1) and SWN. Despite the confusion between NF1 and NF2 in the 19th and 20th centuries, NF2 has now established its character against NF1 based on the high prevalence of bilateral VS and low rates (less than 1%) of ≥6 *café-au-lait* macules or other criteria of NF1. The National Institutes of Health (NIH) Consensus Conference formulated the first criteria for NF2 in 1987 with clinical and genetic consensuses of having bilateral VS and/or family history of NF2 with either unilateral VS or any one or two other tumors associated with NF2 (e.g., neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacity) (Fig. 2). The sensitivity of diagnosis then improved by the Manchester criteria in 1992 and by the National Neurofibromatosis Foundation criteria in 1997 as by including NF2 patients who did not reach the NIH criteria before, that is, the patients without bilateral VS

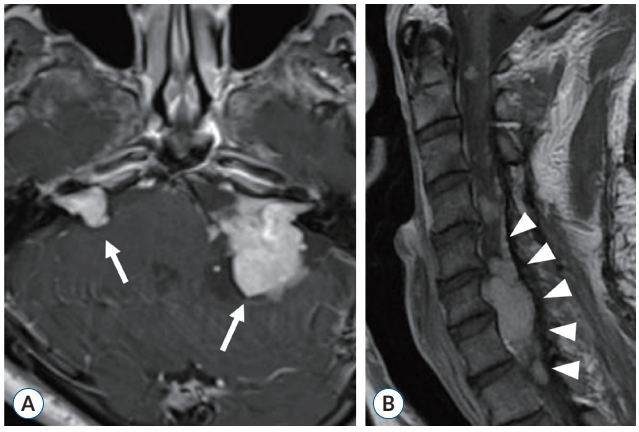

Fig. 2. A 32-year-old male whose father, sister and brother were diagnosed with NF2 showed up with headache and pain on his neck, left arm, and right leg. Axial T1-weighted contrast-enhanced brain-MRI presented bilateral vestibular schwannomas (arrows), although the patient did not suffer for hearing loss or tinnitus until the age of 50 years (A). However, the pains were caused by an intradural-extramedullary tumor (non-vestibular schwannoma) in the cervical canal at level C4-6 (arrowheads), shown in a sagittal T1-weighted cervical spine MRI (B). NF2 : neurofibromatosis type 2, MRI : magnetic resonance imaging.

or a family history of NF2 but diagnosed with multiple schwannomas and/or meningiomas. In 2011, the Baser criteria further improved the sensitivity up to 79% while maintaining high specificity of 100%. The most widely used criteria were the revised Manchester criteria published in 2019 which have replaced "glioma" with "ependymoma", removed "neurofibroma",

Table 1. Diagnostic criteria for neurofibromatosis type 2 (NF2)-related schwannomatosis

A diagnosis of NF2-related schwannomatosis can be made when a patient has one of the following : 1) bilateral vestibular schwannomas; 2) an identical NF2 pathogenic variant in at least 2 anatomically distinct NF2-related tumors (schwannoma, meningioma, and/or ependymoma); and 3) either two major or one major and two minor criteria are present as follows. Major criteria : 1) unilateral vestibular schwannoma; 2) first-degree relative other than a sibling with NF2-related schwannomatosis; 3) two or more meningiomas; and 4) NF2 pathogenic variant in an unaffected tissue such as blood or saliva*. Minor criteria : 1) can count more than once of each type : ependymoma; schwannoma† (e.g., 2 distinct schwannomas count as 2 minor criteria) and 2) can count only once : juvenile subcapsular or cortical cataract; retinal hamartoma; meningioma‡; epiretinal membrane in a person aged less than 40 years (e.g., two cataracts count as 1 minor criteria)
Mosaicism is confirmed for NF2-related schwannomatosis by either of the following : 1) clearly less than 50% pathogenic variant allele fraction in blood or saliva and 2) pathogenic variant not detected in clinically unaffected tissue but shared pathogenic variant in two or more anatomically unrelated tumors

*If the variant allele fraction is clearly less than 50%, the diagnosis is mosaic NF2-related schwannomatosis. †If the major criterion is "unilateral vestibular schwannoma", at least one schwannoma must be dermal in location. ‡Multiple meningiomas qualify as a major criterion. Meningioma cannot be used as both a major and minor criterion

created an age limit of 70 years for development of VS, and introduced molecular criteria. However, it was still difficult for clinicians to separate NF2 from other SWN with these criteria because of the overlapping clinical features, such as development of both VS and meningiomas. An international panel of experts have updated the diagnostic criteria of NF2 in 2022 and revised the terminology to "NF2-related schwannomatosis". Incorporation of genetic criteria to supplement clinical criteria has been made to help standardize the diagnosis process (Table 1). Schwannoma predisposing syndromes are now classified by specific genes that harbor a pathogenic variant. This update also allowed addition of other types of SWN when and if new genes are identified[13].

CLINICAL PRESENTATION

Clinical features

The first description of bilateral VS with multiple intracranial tumors, subsequently known as NF2, was reported by Wishart in 1822[19]. A patient showed up with bilateral hearing loss that gradually worsened from several weeks ago, however, eventually expired 1 year later at the age of 21 with pain attacks and swallowing disability. Two centuries later with further research, the mean age at diagnosis of NF2 patients is reported as 24–28 years, mostly presenting with bilateral/unilateral hearing loss, tinnitus, and imbalance[14,15]. Bilateral VS and other CNS tumors are frequently found via computed tomography (CT) scans or magnetic resonance imaging (MRI). However, the mean age at onset of initial symptoms associated with NF2 is reported as 17–20 years, which is 7–8 years earlier than the age at diagnosis[14,15]. Initial symptoms include painful or growing skin tumors, vision loss, muscle weakness, headaches, and seizures, mostly caused by other CNS tumors rather than VS[15]. These manifestations should be carefully evaluated in patients who might be at risk for NF2 but without VS yet in CT scans or MRI.

Pediatric patients with NF2

As stated above, NF2 is commonly presented among young adults. However, 61 of 334 (18.2%) NF2 patients were younger than 15 years according to a research based on the UK database of NF2[7]. Another research reported that 25 of 80 (31.2%) individuals diagnosed as NF2 were before the age of 18 years old[4]. Almost half of these patients are sporadic cases without family history of NF2. Symptoms in pediatric NF2 patients are usually caused by non-VS CNS tumors. Ophthalmic changes are rather typical to pediatric NF2 patients due to early onset cataracts, retinal hamartoma or optic sheath meningiomas[1]. Some patients present with facial palsy secondary to facial nerve schwannomas[4]. Only 20–32% of pediatric NF2 patients have hearing problems at the initial presentation[4,5].

Phenotypes of NF2

There are two major phenotypes of NF2 previously described. Patients with severe clinical course are classified as the "Wishart type" who usually present symptoms before the age of 25 years with rapid progression of bilateral VS and/or other CNS tumors. The other phenotype is the "Gardner type" that appears later in life following a benign course with small number of CNS tumors. However, it is not easy to perfectly fit every patient to either type because of the substantial variation of clinical courses[20].

Another phenotype, rather minor, is "congenital NF2" which is defined as "NF2 with onset before the age of 1 year"[18,20]. Natural history is described differently from that of typical NF2

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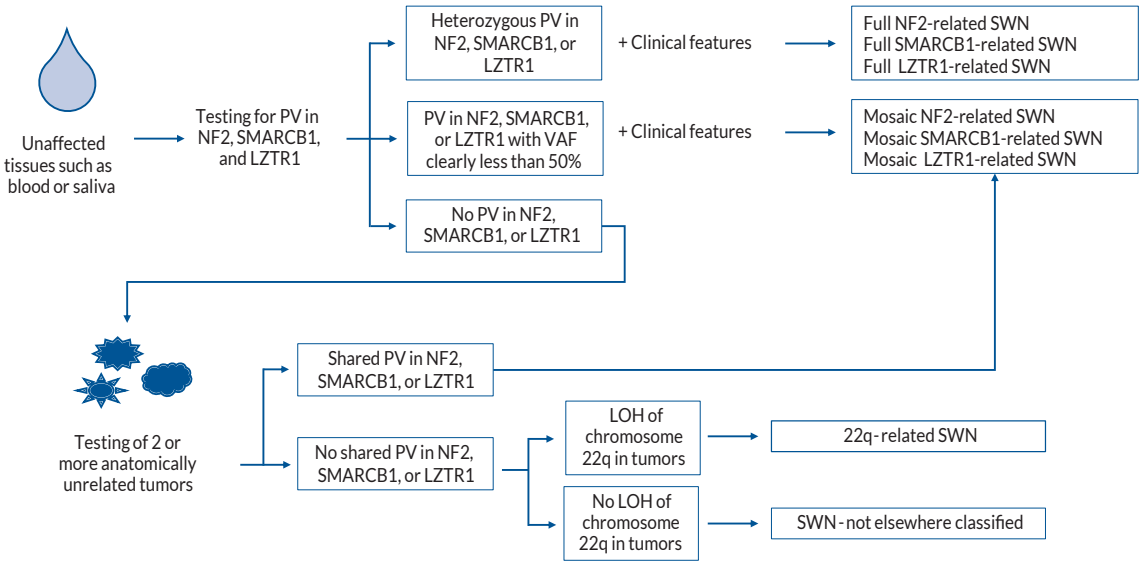

Fig. 3. Flow chart of genetic testing for NF2 and SWN[16]. SMARCB1 : SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1, LZTR1 : leucine zipper-like transcription regulator 1, PV : pathogenic variant, NF2 : neurofibromatosis type 2, VAF : variant allele fraction, SWN : schwannomatosis, LOH : loss of heterozygosity.

patients where small bilateral VSs (<1 cm) are detected as early as the first months of life via incidental MRI findings. Small bilateral VSs stay stable or asymptomatic for one to two decades until sudden and rapid (<12 months) progression at the age of 11–15 years. Congenital NF2 is also associated with other CNS tumors (e.g., meningiomas, ependymomas) and exhibits large numbers of skin NF2 plaques in atypical locations (e.g., face, hands, legs and knees) which revert to normal skin appearance at the time of VS progression. Asymptomatic diffuse high signal lesions in the periventricular regions surrounded with calcification are known as typical signs in MRI findings.

Mosaic NF2 is an alternative form of NF2 caused by postzygotic somatic mutations of the NF2 gene[20]. Patients with mosaic NF2 usually present mild symptoms with unilateral VS associated with ipsilateral meningiomas, or multiple schwannomas localized to one part of the peripheral nervous system. A recent study of 1055 *de novo* NF2 patients estimated that approximately 60% of these cases were mosaic patients[8]. Mosaic NF2 is diagnosed according to the latest criteria (Table 1) via genetic testing (Fig. 3).

Survival rates

At least two studies have reported survival rates of NF2[10,14]. Evans et al.[10] estimated a median survival time of approximately 15 years after diagnosis. More than 40% of NF2 patients were expected to pass away by the age of 50 years, whereas all patients would die by 70 years. According to Otsuka et al.[14], the overall survival rates at 5, 10, and 20 years in NF2 patients were 85%, 67%, and 38%, respectively. However, early ages at symptom onset showed poor survival. The survival rates at 5, 10, and 20 years in patients younger than 25 years were 80%, 60%, and 28%, respectively, whereas the rates were 100%, 87%, and 62% in patients older than 25 years, respectively. More than 60% had died before reaching 44 years. They also reported that the size of VS at diagnosis showed correlation to survival rates. Small VS (≤2 cm) showed better survival than those with medium-sized tumors (>2 cm and ≤4 cm), although patient's sex, positive family history of NF2, and presence of other CNS tumors or dermal abnormalities did not affect their survival. The most frequent causes of death are tumor burden, peri-operative complications, and malignancy from NF2 related tumors[20].

GENETIC FEATURES

NF2 tumor suppressor gene

The NF2 gene was identified in 1993 revealing 17 exons on chromosome 22q12 which encoded for a protein called merlin (moesin-ezrin-radixin-like protein) or schwannomin[2,17,23]. Merlin is a protein product similar to the ERM (ezrin, radixin,

moesin) protein family members and regulates cell proliferation and functions in cell-to-cell adhesion and transmembrane signaling. Following the Knudson's two-hit model of tumorigenesis, schwannomas and meningiomas occur when both alleles of the NF2 gene are inactivated due to germline mutations, somatic mutations, or both of them happened one by one[2,12]. Pathogenic NF2 alterations penetrate nearly 100%, which means that individuals who carry the same pathogenic variant on the NF2 gene as their affected parent will develop the same clinical disorders in the future[16].

Correlation between NF2 gene alterations and clinical phenotypes

Molecular genetic studies have indicated that the type of mutation in the NF2 gene might be related to its clinical severity[14]. Generally, frameshift deletions/insertions and nonsense mutations that create truncated proteins are the most frequent germline mutations that cause the severe conditions, whereas missense mutations and splice-site mutations demonstrate milder clinical courses[3]. The Wishart type, which is typically associated with truncating alterations, show poor outcomes followed by younger age at diagnosis, higher incidence of meningiomas, spinal tumors, and non-VSs[21]. In contrast, the Gardner type has lower risk of mortality with fewer meningiomas than the Wishart phenotype due to its association with missense mutations or splice-site mutations[2,22].

Genetic testing for NF2 and other SWN

The flow of genetic testing for NF2 and SWN is shown in Fig. 3. First, pathogenic variants in NF2, SMARCB1 and LZTR1 are tested from unaffected tissues such as blood or saliva. Results with heterozygous pathogenic variants in each gene with clinical features are classified as full NF2-, SMARCB1-, or LZTR1-related SWN. Mosaic NF2-, SMARCB1-, or LZTR1-related SWN will be diagnosed when the pathogenic variants in each gene exhibit a variant allele fraction clearly less than 50% with clinical features. If there were no pathogenic variants in NF2, SMARCB1 or LZTR1, additional testing from two or more anatomically unrelated tumors is required. The individual will be classified as mosaic NF2-, SMARCB1-, or LZTR1-related SWN when the tumors shared pathogenic variants in NF2, SMARCB1 or LZTR1. Another testing for loss of heterozygosity of chromosome 22q is considered when tumors do not share pathogenic variants in these genes. The result finally classifies the patient either to 22q-related SWN or "SWN-not elsewhere classified".

Genetic testing is a certain method to make diagnosis of NF2, although it is not necessary if the patient meets the characteristic clinical features. It plays a supporting role when young individuals have not exhibited any symptoms yet even though with high suspicion of NF2 according to the presence of first-, second- or third-degree relatives that are diagnosed with NF2. Presymptomatic genetic testing gives benefit to the family that the parents can survey the chance of NF2 in their children and perhaps to provide early care intervention[2]. It is also useful for confirmation of NF2 when the individual has no clinical features of NF2 but incidentally identified a pathogenic variant of NF2 in the blood via genetic sequencing for another disease[22]. However, this situation also gives caution to us not to easily diagnose NF2 or other SWN with the presence of pathogenic variants alone. In response to the increasing number of panel testing and wide analysis for underlying genetic conditions among various diseases nowadays, pathogenic variants of NF2, SMARCB1 or LZTR1 have been frequently identified in some asymptomatic individuals who had no suspicion of NF2 and other SWN[11,16]. The diagnosis of NF2 should be prudently done with consideration of the patient's clinical features and background altogether.

CONCLUSION

NF2 is a life-threatening disorder which gives various symptoms according to the patient's age and location of CNS tumors. Previous diagnostic criteria have been regularly revised to screen out every NF2 patient, however, diagnosis among pediatric NF2 patients, mosaic NF2 patients, and other SWN patients remained confusing. The formerly known NF2 became "NF2-related SWN" in the latest criteria by adding genetic criteria, which indicates that genetic testing is an essential process when making diagnosis of schwannoma predisposition syndromes. However, careful assessments are needed with the test's result in case not to mislead diagnosis of other disorders to NF2.

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AUTHOR'S DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Author contributions

Conceptualization : TKK; Data curation : TKK; Methodology : TKK; Visualization : TKK; Writing - original draft : TKK; Writing - review & editing : TKK, YSP, IN

Data sharing

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