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Tailoring neurofibromatosis type 1 care to Singapore: From consensus to implementation

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Rare diseases are easily overlooked in health systems, which are typically built around common diseases, and neurofibromatosis type 1 (NF1) is no exception. In this issue of the *Annals*, Fong et al. present one of the first Singapore-specific consensus guidelines on the diagnosis, surveillance, and management of NF1.[1] Their work deserves recognition. It cannot be stressed enough how important local guidelines are for NF1. It is not sufficient simply to adopt guidelines from other countries or continents, because referral pathways, imaging capacity, access to drugs, and possibly the ancestry-related spectrum of disease might differ, and recommendations that do not account for the local context are of little use to patients.

The authors started with a documented literature search on NF1 diagnosis, surveillance, and management using specific inclusion and exclusion criteria. They used the extracted data to draft a panel of recommendations (133 close-ended statements). A multidisciplinary panel of geneticists, dermatologists, neurologists, neurosurgeons, and oncologists rated these anonymously. Nineteen of 24 invited experts completed the first round. After a virtual meeting, 17 completed the second round. With consensus set at three-quarters agreement, 113 reached consensus after round 1. Twenty statements failed to achieve consensus, were adjusted in response to comments, and together with a new statement were submitted to a second round of the Delphi process. Nine of the 21 reached consensus after round 2. This led to the current "evidence-informed consensus-based" set of guidelines spanning genetic testing, surveillance in childhood, transition and adulthood, and management of complications. These recommendations are not evidence-based but are based on expert consensus because, for many rare diseases, such as NF1, there are very few randomised controlled trials available in the literature. The results of this endeavour are clearly presented by Fong et al. and will be particularly useful for all healthcare workers involved in the care of individuals with NF1 in Singapore.

The panel recommends surgery as an option for symptomatic plexiform neurofibromas when feasible, mirroring the international view that complete resection is seldom achievable and carries morbidity.[2] The choice between surgical and pharmacological therapy rests with a multidisciplinary board. Radiotherapy is discouraged because of the risks of secondary malignancy and vasculopathy. Mitogen-activated protein kinase kinase (MEK) inhibitors are endorsed for symptomatic, inoperable, or incompletely resected plexiform neurofibromas in children and adults. In children, an objective response, measured as a volume reduction of the plexiform neurofibroma of 20% or more, was seen in 70%.[3] In adults, the evidence shows an objective response, measured as a volume reduction of 20% or more of the plexiform neurofibroma, in about 1 in 5 patients versus 1 in 20 on placebo.[4] Pain and quality of life did not improve significantly. This is the only randomised placebo-controlled, double-blind phase 3 study of treatment with a MEK inhibitor in NF1 available at the moment. This represents a genuine but modest benefit, so patient selection, cost, and access will shape uptake. Other trials in adults were single-arm.[5,6] Selumetinib, a MEK inhibitor is covered in Singapore by the Rare Disease Fund for children with NF1 aged 2 years or older who have a symptomatic and inoperable plexiform neurofibroma. Applications for adults are not standard but are not excluded, and the fund might cover treatment of plexiform neurofibromas in adults with NF1.[7] Time will tell how many treatments in adults will be covered. The absence of consensus on tipifarnib and mechanistic target of rapamycin inhibitors honestly reflects equivocal trial results.

The stakes are high because life expectancy in NF1 is shortened by malignancy and vascular disease.[8,9,10] Malignant peripheral nerve sheath tumour (MPNST) is a leading cause of cancer-related death. However, the lifetime risk of 8–16%[8,9] is an average across a heterogeneous population in which some individuals harbour many plexiform neurofibromas and others none, and the risk carried by any single lesion remains unknown. MPNSTs typically arise in pre-existing plexiform neurofibromas, often through premalignant atypical neurofibromatous neoplasms of uncertain biological potential (ANNUBP), which carry a considerably higher risk of progression.[11] ANNUBP is diagnosed

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when at least 2 of 4 histopathological criteria are met: (1) cytological atypia, (2) loss of neurofibroma architecture, (3) hypercellularity, and (4) mitotic index > 1/50 high-power fields (HPF) and < 3/10 HPF. In the presence of a heterozygous inactivation of *CDKN2A* in the tumour, only 1 of 4 histopathological criteria is needed for diagnosis. The presence of a homozygous *CDKN2A* inactivation is sufficient for the diagnosis of ANNUBP, even in the absence of histopathological criteria.[12] The practical corollary is that imaging is valuable because it identifies which individuals and which lesions warrant closer attention, not because it can predict malignant change in a given tumour. The panel's handling of whole-body magnetic resonance imaging (MRI) at transition illustrates this reasoning. In line with the ERN GENTURIS guidelines,[2] a single whole-body scan between the ages of 16 and 20 years is suggested to map internal tumour burden. Where no internal plexiform neurofibromas are found, routine repeat whole-body imaging is not advised, whereas a high burden justifies continued surveillance. Evidence that surveillance improves outcomes is emerging. In a retrospective cohort of adolescents and adults followed with whole-body diffusion-weighted MRI and clinical review, timely nerve-sparing removal of atypical neurofibromas was associated with a lower incidence of MPNST than predicted.[13] However, reliance on historical controls limits that conclusion, and prospective validation is needed, including measurements of harm and cost. The data supports moving away from the surveillance concentrated in childhood that was customary a few decades ago, towards structured follow-up across the lifespan.

Aside from increased oncological risks, NF1 is associated with potential problems in a multitude of other areas such as growth and development, cognitive and behavioural functioning, the skeletal system, the cardiovascular system, the skin, and psychosocial well-being. The guidelines address the monitoring and management of pain, café-au-lait macules, hypertension, learning difficulties, attention-deficit/hyperactivity disorder, speech and language development, scoliosis, and osteoporosis. The guidelines recommend adding a psychologist to the multidisciplinary team, which could make an enormous difference to the quality of life of individuals with NF1.

The greatest practical challenge is retaining people in care. Many adults with NF1 drift away from specialist follow-up once paediatric services end. A recent study in Singapore of children and adults with cancer predisposition syndromes for whom whole-body MRI was recommended, showed an uptake of 57%, leaving room for improvement.[14] A formal transition programme and a national registry of individuals with NF1 and their complications would allow Singapore to measure whether recommendations are followed and whether outcomes improve. Incidence of certain complications could vary by region and/or ethnic group, as was recently reported for optic pathway glioma in children.[15,16] Region-specific incidence rates are important for building the next generation of guidelines.

Guidelines are living documents. These guidelines already address most of the unmet needs in Singapore's patients (optimised multidisciplinary NF1 care, management of neurological symptoms, management of cutaneous lesions, financial coverage for NF1, early NF1 screening, local awareness, and support groups), as was recently published.[17] The items that fell short of consensus, including surgery for bone dystrophic changes, the role of radiotherapy and targeted therapy in MPNST, and imaging for scoliosis, offer a ready research agenda. Guidelines need periodic updates, and, as Fong et al. mentioned in their publication, it might be relevant to include patient representatives in the process of updating the guidelines. Cascade testing and reproductive counselling, acknowledged by the authors as beyond the scope of this exercise, merit a consensus of their own. Fong et al. have delivered a pragmatic foundation. The task now is to implement, audit, and refine it.

Keywords: *Delphi consensus, neurofibromatosis type 1, peripheral nerve sheath tumour, surveillance*

Ethics statement

Not applicable, as no participants were recruited.

Declaration

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