

Screening of nasopharyngeal cancer in high-risk familial cohort: A practical approach using a screening algorithm

Dear Editor,

In Singapore, nasopharyngeal cancer (NPC) is among the top 3 cancers afflicting middle-aged males (30–49 years old).¹ Unfortunately, patients with early-stage NPC are often asymptomatic, and most patients (approx. 70%) are diagnosed with advanced disease with adversely reduced survival. First-degree relatives of NPC patients have about 4 to 10 times increased risk of developing NPC,² and strategies for reducing NPC-specific mortality among this high-risk group are feasible. Herein, a working group from the Chapter Board of Otorhinolaryngologists Singapore proposed a screening algorithm for these high-risk individuals of NPC based on existing available evidence.

Our algorithm expands on the existing Ministry of Health (MOH) guidelines, which recommend family history-positive individuals to be screened with Epstein-Barr virus (EBV) serology against viral capsid antigen (VCA-IgA), early antigen (EA-IgA) and Epstein-Barr nuclear antigen (EBNA1-IgA), supplemented with clinical examination including a flexible nasoendoscopy.³

We recommend screening of individuals with ≥ 1 first-degree relative with NPC, especially among middle-aged adults from 30–70 years old. We propose EBV IgA serology (anti-IgA VCA and anti-IgA EA) as a screening tool because of numerous evidence supporting its role in the risk stratification of NPC risk among familial cohorts.⁴ When available, anti-EBNA1-IgA can also be incorporated. We recommend a detection threshold of EBV EA-IgA titre of $\geq 1:10$ and VCA-IgA titre of $\geq 1:160$ (measured via immunofluorescence assay [IFA]) as sufficiently raised for further review and follow up.⁵ Screening should be combined with nasoendoscopy, which is conveniently available in Singapore and can identify subtle masses arising from clefts of the fossa of Rosenmuller. Whenever possible, photo-documentation may be performed to pick up subtle changes on interval endoscopies. In some cases, a trans-palatal endoscopic visualisation can offer a panoramic view of the Rosenmuller clefts when viewed from an inferior perspective (Fig. 2).

Cohort 1: Negative EBV serology with normal nasopharyngeal examination. For family history-positive individuals with negative EBV serologies, studies have demonstrated a much lower risk of developing NPC.⁶ Presently, there is insufficient data to guide the duration of follow-up. If there are no lesions detected on nasopharyngeal

endoscopic examination, a follow-up in the primary care setting with a 12–18 monthly repeat EBV serology can be feasible. If the titres become positive, or the patient develops symptoms, a referral to the ENT specialist should be made. We recommend follow-up till 70 years of age as the prevalence of NPC wanes after this age.

Cohort 2: Positive EBV serology with normal nasopharyngeal examination. If positive EBV serology is encountered with no obvious endoscopic masses, the next steps to detect NPC are not well established. The available options are: (1) continue surveillance with repeat endoscopy and EBV serology in 6–12 months; (2) perform an upfront Magnetic Resonance Imaging (MRI) post-nasal space (PNS) to detect subclinical NPC (up to 10%); and (3) perform a plasma EBV-DNA to select patients for MRI PNS. Options (2) and (3) may be recommended for patients concerned of an occult primary nasopharyngeal carcinoma that cannot be confidently excluded on endoscopic examination.

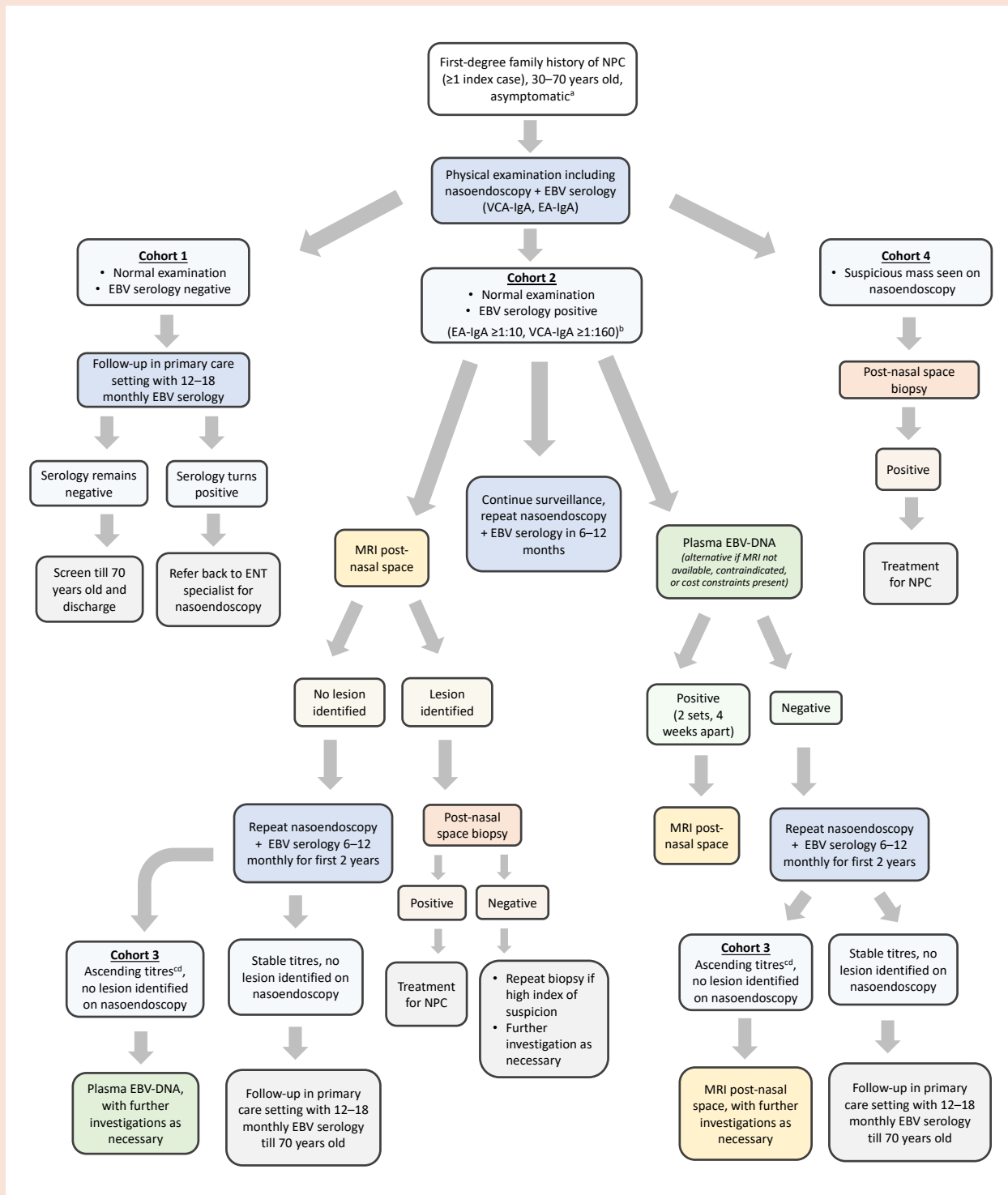
There are existing cost-effective and short MRI protocols for screening that could be performed with high sensitivity and specificity.⁷ When a suspicious lesion is detected on MRI, a targeted PNS biopsy should be performed. However, these short screening protocols are not available and a standard contrast enhanced MRI is usually performed.

There is increasing evidence that plasma EBV-DNA (targeting the BamHI-W fragment) can exclude the presence of NPC with a high negative predictive value (approx. 99%).⁸ Individuals with persistently positive EBV-DNA are more likely to develop NPC (relative risks of 16.8), compared to individuals initially negative for EBV-DNA.⁸ A 2-time point-testing approach set 4 weeks apart is recommended to reduce the rate of false positives (up to 8%).⁹ If the EBV-DNA is negative, close monitoring of 6–12 monthly with repeat nasoendoscopy for the first 2 years can be performed, especially if a baseline MRI scan was not obtained.

Nasoendoscopy and EBV serology should be performed 6–12 monthly for the first 2 years, as studies have shown that new NPC cases are commonly identified within this period.¹⁰

Cohort 3: Persistent raised or rising EBV serology titres with normal nasopharyngeal examination. Individuals with persistently raised EBV serology, especially up-trending titres should

Fig. 1. Proposed screening algorithm for high-risk familial cohort in Singapore.



EA: early antigen; EBV: Epstein-Barr virus; ENT: otorhinolaryngologist; MRI: magnetic resonance imaging; NPC: nasopharyngeal carcinoma; VCA-IgA: viral capsid antigen

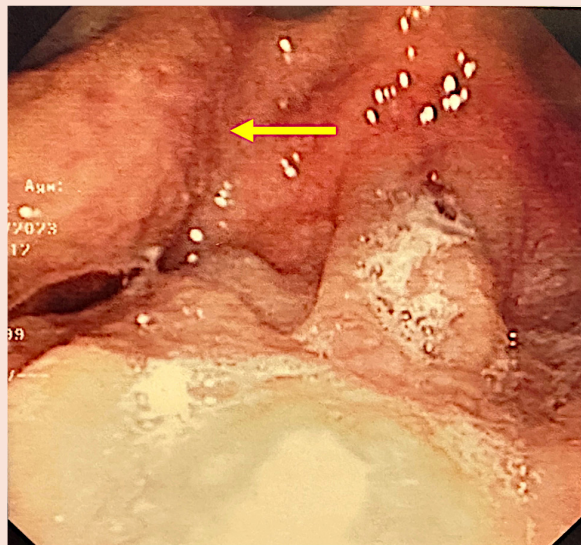
^a Risk of NPC further increased in ≥2 affected first-degree relatives; Positive family history in sibling (especially in sister); Male; Middle age. To further encourage screening in these groups.

^b Studies demonstrate the best test profile with highest sensitivity, specificity, PPV and NPV with EA-IgA ≥1:10 and VCA-IgA ≥1:160.

^c Ascending titres of VCA-IgA more significant than EA-IgA.

^d If continually ascending titres with negative MRI PNS, consider non-NPC-related malignancy.

Fig. 2. Trans-palatal endoscopic visualisation demonstrating a panoramic view of the Rosenmuller cleft (yellow arrow).



undergo regular repeat nasoendoscopy in 6–12 months. Studies demonstrate that ascending VCA-IgA titres, compared to other serology markers, may signify a relative higher risk of developing NPC (hazard ratio of 21.3 for ascending titres, compared to 6.2 for stable titres).¹¹ However, the mechanistic explanation of fluctuations of EBV serology in NPC development is unknown. Should no tumour be identified on follow-up, further evaluation can be performed using MRI PNS or plasma EBV-DNA to exclude occult NPC as previously discussed.

As EBV is also associated with other non-nasopharyngeal malignancies (e.g. NK-T cell lymphoma and gastric cancer), a positron emission tomography computed tomography scan can also be considered in cases of persistently positive plasma EBV-DNA and with normal nasal endoscopic findings.

Cohort 4: Positive EBV serology with a mass on nasopharyngeal examination. When a post-nasal mass is encountered, a biopsy should be performed to confirm diagnosis and appropriate treatment instituted.

A cost-effectiveness analysis study compiled by the World Health Organization (WHO) showed that screening was associated with a median 10-year reduction in NPC mortality of 52.9%.¹² Nevertheless, a prospective cost effectiveness analysis of this workflow should be performed in our local setting. Currently, our algorithm proposes IFA for the evaluation of EBV serology, but future

studies should be done to validate use of EBV serology measured using ELISA technique as this method is more commonly available. Additionally, the current follow-up recommendations are based on extrapolated data, and more long-term longitudinal real-world follow-up data needs to be obtained to determine an optimal duration of follow-up. Future studies should also be done to evaluate the impact of this proposed NPC screening programme on the incidence, stage distribution and overall morbidity and mortality reduction of NPC.

In conclusion, NPC screening of individuals with family history is recommended, especially among middle-aged males. Screening should consist of a full head and neck examination, and detailed endoscopy with complete visualisation of the nasopharynx. EBV serology should also be performed, preferably using IFA with same laboratory standards for harmonisation and serial interpretation. A raised EBV serology increases the risk of developing NPC in the future, and close follow-up should be performed, especially within the first 2 years. MRI PNS is a useful tool to look for occult NPC, and may be performed for further evaluation, especially in those with increasing IgA serology assays or persistently raised plasma EBV-DNA. Plasma EBV-DNA is useful as an auxiliary test because of its high negative predictive value.

Declaration

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