Aids to diagnosis of nasopharyngeal carcinoma

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Summary

Nasopharyngeal Carcinoma (NPC) is one of the major cancer problems for large populations in South East Asia, South China, Taiwan and Hong Kong. NPC if dectected early and treated adequately carries a relatively good prognosis. Rapid and reliable screening methods for NPC is essential. This study evaluates the validity of C.T. scan and the serological test for IgA antibody to Epstein-Barr virus capsid antigen (VCA), separately and jointly, as aids to the diagnosis of NPC, in suspected cases. The sensitivity of IgA/VCA test and C.T. scan was 96.3% when considered separately. The specificity was 100% for IgA/VCA test and 76% for C.T.scan. Combination of these two tests in series gave a sensitivity and specificity of 100% with a predictive value of 100% for positive or negative tests. The implications of these findings are discussed.

Introduction

Nasopharyngeal Carcinoma (NPC) has been known for its late diagnosis. Problems of early diagnosis in the past were largely due to delay in seeking treatment on the part of the patients and due to the lack of awareness about this disease on the part of the general medical practitioners.[1] While there has been considerable improvement in both these aspects and more and more of NPC

patients are being diagnosed at a relatively earlier stage of the disease, not infrequently Ear, Nose and Throat surgeons face difficulty in establishing the diagnosis early, sometimes even in the presence of obvious clinical features suggesting NPC. This is often due to inability to visualise the tumour, deep in the fossa of Rosenmuller (FOR) from where all the NPC arise[2,3,4] and to obtain representative biopsy specimen for histopathological confirmation. These difficulties have to a great extent been overcome by the introduction of computerized axial tomography as an additional radio-diagnostic tool and nasopharyngofibrescope and telescope as instruments for direct visualisation of the nasopharynx as well as for taking biopsy from the depth of FOR. However, not all patients with abnormal CT scan findings do have NPC (the benign lesion in the nasopharynx can do the same). Another diagnostic aid in the form of Epstein-Barr virus (EBV) antibodies study, particularly estimation of titre of IgA against the viral capsid antigen (IgA/VCA) has remained of value to the clinicians although in a small percentage of NPC patients the titre is not significantly raised.[5,6,7]

On taking into consideration, the C.T. scan findings together with the result of IgA/VCA test, it was felt that the diagnosis of NPC could be made with fair amount of certainty. The confirmation of diagnosis had to be made on histopathological examination of the biopsy specimen from the nasopharynx. The purpose of this study was to evaluate the validity of C.T. scan and IgA/VCA titre, separately and jointly, as aids to the diagnosis of NPC in suspected cases.

Materials and Method

Selection of Subjects:

100 consecutive patients, who were subjected to C.T. scanning of nasopharynx as per record of the Department of Radiology, University Hospital, Kuala Lumpur, and for whom the IgA/VCA titre and histopathological diagnosis were available, were taken for study. These patients had earlier attended the ENT clinic of this hospital, where all patients suspected of NPC were sent for radiological examination. The provisional diagnosis of NPC was made in all these cases based on
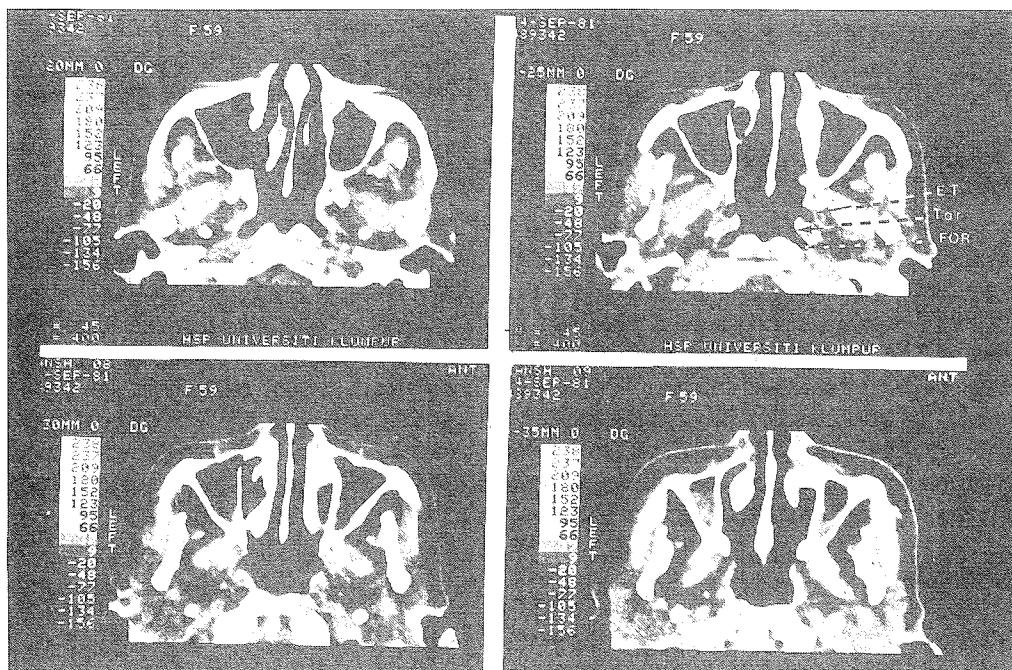

Figure 1
C.T. scan showing normal FOR, normal Torus Tubarius (TOR) and normal Eustachian tube (ET) on both sides.
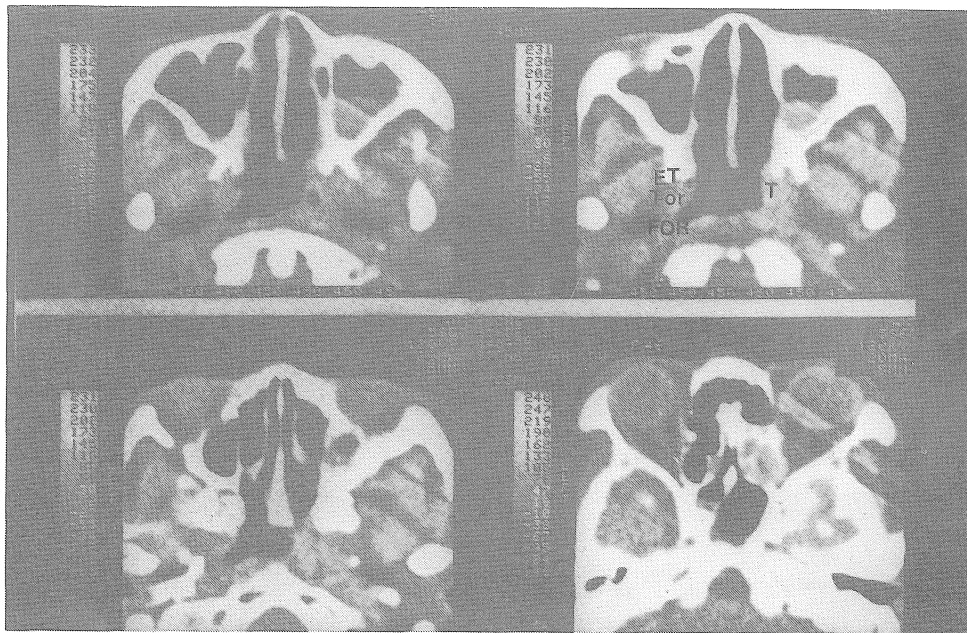
Figure 2

C.T. scan showing normal FOR, Torus Tubarius (TOR) and normal Eustachian tube (ET) on left side but these are abnormal on right side. Tumour (NPC) mass (T) filling FOR on right side with Torus taken up and the tube blocked.

clinical assessment which comprised of two parts – (a) Patient's symptoms (which are well established[8]) and (b) Examiner's finding of either a definite tumour mass in the nasopharynx or irregularity of the mucosa covering FOR or just fullness of FOR. At times even in the absence of any lesion in the nasopharynx, the NPC was suspected if the symptoms suggested so, particularly in a mid age Chinese.

C.T. Scan

Serial axial views of the nasopharynx, at 5mm cut, using high resolution Pfizer fast scanner with contrast enhancement in suitable cases, were examined in detail. Abnormalities ranging from minimal distortion of the shape of the FOR to massive lesion causing bony erosion were noted. For the purpose of data evaluation using computer following scores were designated based on the findings.

0 = Scans which did not show any abnormality (Fig. 1).

1 = Scans in which there was soft tissue mass limited to FOR (Fig. 2).

2 = Those in which soft tissue mass was beyond FOR but there was no bony erosion (Fig. 3).

3 = Scans with bony erosion (Fig. 4).

9 = Scans which were considered as doubtful (although there was no definite lesion seen, yet could not be considered as normal).

E.B.V. Serology

Titres of IgA/VCA were determined by indirect immunoflorescence technique and were scored as <5, 5, 10, 20, 40, 80, 160 and 320. Titre of <5 was considered negative and titre of 5 or over was considered positive.

Histopathological Diagnosis

Based on histopathological examination of biopsy material obtained from the nasopharynx,
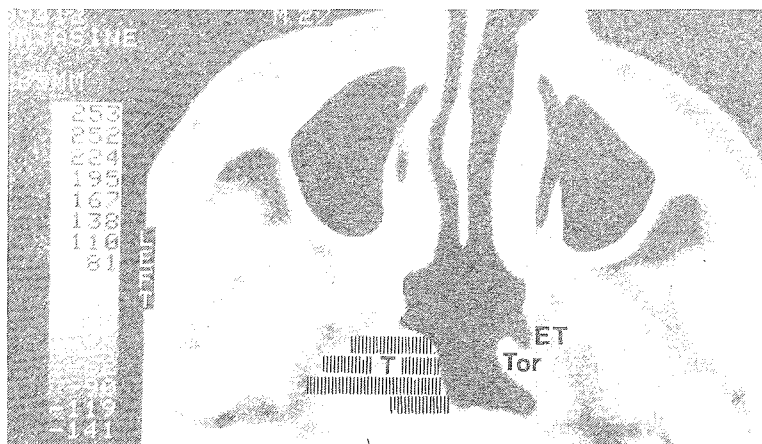
Figure 3
C.T. scan showing normal FOR, Torus and Tube on right side and tumour (NPC) mass (T) on left side which is filling part of nasopharynx beyond FOR.
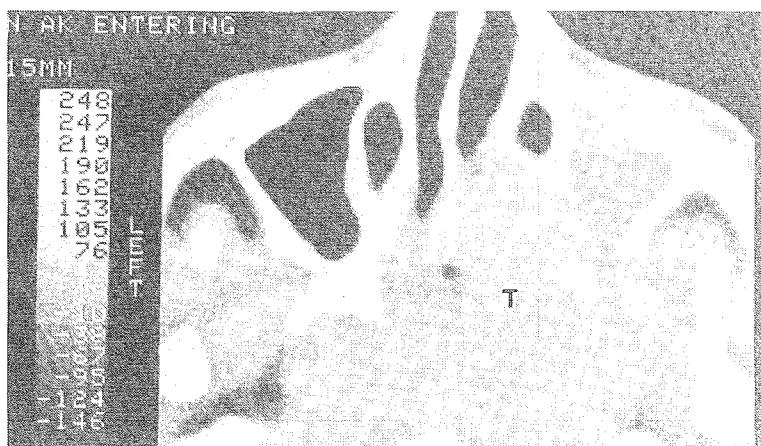

Figure 4
Massive tumour (T) mass causing extensive bony destruction.

confirmed NPC cases were divided into three categories (according to WHO classification[9]) and scored accordingly for computation purpose.

1 – For WHO I
2 = For WHO II
3 = For WHO III

The non-NPC patients were allocated either 0 (for those where there was no lesion of any kind) or 8 (for those with benign lesion).

Among the 100 subjects, there were 5 who had received radiotherapy treatment earlier, as such, were not considered suitable for analysis. The outcome variable in this study was NPC. The other variables were IgA/VCA titre, C.T. scan of the nasopharynx and the histopathological examination result of biopsy specimen. While histopathological examination confirmed the clinical status, the IgA/VCA titre and C.T. scanning were evaluated for their validity and/or reliability as prescriptive screening tests for NPC separately and jointly. Prescriptive screening is the detection of disease or precursors of disease, as a guide to the medical care of the patient. The measurements of sensitivity and specificity were utilised for evaluating the validity of these tests.

The validity of these tests were examined separately (Table IV and Table V) and then in combination. In evaluating the combination of IgA/VCA and CT scan in series the subject was

Table I

Distribution of subjects by age and sex

Age (Years)	Male (n)	Female (n)
< 20	6	1
20 - 29	11	3
30 - 39	15	6
40 - 49	24	6
50 - 59	9	6
60 - 69	3	0
70 and above	4	1
Total	**72**	**23**

Mean Age for Males: **40.7** years.
Mean Age for Females: **42.2** years.

Table II

Distribution of subjects by EBV-IgA levels and histopathological results

Score of Histopath Results of Biopsy	EBV - IgA-VCA Titre Levels								Total
	<5	5	10	20	40	80	160	320	
0	8	0	0	0	0	0	0	0	8
1	1	5	9	1	5	7	0	0	28
2	0	0	2	0	0	0	0	0	2
3	2	0	14	9	11	13	2	1	52
8	5	0	0	0	0	0	0	0	5
Total	**16**	**5**	**25**	**10**	**16**	**20**	**2**	**1**	**95**

considered positive to the test in series only if he was positive to both the tests and negative if the results were negative to any of the two tests.

Results

Table I shows the distribution of the subjects by age and sex. Out of the 95 subjects 72 (75.8%) were males. The age of the male subject ranged from 17 years to 75 years as compared to the females whose age ranged from 17 to 70 years. The mean age of the males was 40.7 years as compared to 42.2 years in the females. The table also shows that 68.4% of the 95 subjects were between the ages of 20-49 years.

Table II shows the distribution of subjects by IgA/VCA titre levels and histopathological biopsy

Table III

Distribution of subjects by C.T. scan and histopathological type

Scores of Histopathological Results	Score of C.T. Scan					Total
	0	1	2	3	9	
0	7	0	0	0	1	8
1	0	11	10	6	1	28
2	0	1	0	1	0	2
3	0	9	25	16	2	52
8	2	0	3	0	0	5
Total	9	21	38	23	4	95

Table IV

Validity of EBV-VCA-IgA Test in NPC

	BIOPSY RESULTS		
Test for IgA/VCA	NPC	Non-NPC	Total
Positive	79	0	79
Negative	3	13	16
Total	82	13	95

Table V

Validity of C.T. scan in NPC diagnosis

	Biopsy Results		
C.T. Scan	NPC	Non-NPC	Total
Positive	79	3	82
Negative	3	10	13
Total	82	13	95

results. The results indicate that out of the 95 subjects, 13 (13.7%) subjects had either no lesion or had benign lesion on histopathological examination. Out of the remaining 82 subjects, 28 (34.1%) were WHO Type I, 2 (2.5%) were WHO Type II and 52 (63.4%) were WHO Type III.

Out of the 16 subjects who had IgA/VCA titre levels less than five, 13 (18.2%) had no lesion or benign lesion. All (100%) of the 79 subjects who had VCA/IgA titre levels five or higher, had NPC.

Table III shows the distributions of subjects by C.T. scan and histopathological type of NPC. The Table shows that out of the nine subjects who showed no abnormality on C.T. scan, seven (77.8%)

Table VI

Validity of combination of C.T. Scan and
EBV-VCA-IgA in series in NPC Diagnosis

Results of IgA/VCA & C.T. Scan	BIOPSY RESULTS		
	NPC	Non-NPC	Total
Positive	76	0	76
Negative	0	10	10
Total	**76**	**10**	**86**

showed no lesion on histopathological examination and the remaining 2 (22.2%) showed a benign lesion pattern. Out of the 21 subjects with C.T. scan showing soft tissue mass limited to FOR, all showed malignant lesions on histopathology. Out of the 38 subjects with C.T. scan showing soft tissue mass beyond FOR but without any bony erosion, 35 (92.1%) showed malignant lesion. While the remaining three (7.9%) in the group showed benigh lesions on histopathological examination.

Out of the 23 subjects with C.T. scan showing bony erosion, all had NPC on histopathological examinations. Out of the four subjects whose C.T. scans were considered as doubtful, one (25%) showed no pathological lesions of any kind on histopathological examinations, while three (75%) were confirmed to be NPC.

Table IV shows that using IgA/VCA test alone, the sensitivity (the ability to identify correctly those who have the disease) was 96.3% and the percentage false negatives (which is complementary to sensitivity) was 3.7%. The results also showed that the specificity (the ability to identify those who do not have the disease) was 100% and the percentage of false positives (which is the complement of specificity) was 0%. In computing the predictive value of the test, the results show that the predictive value of a positive test was 100% while the predictive value of a negative test was 81%.

Table V shows that the sensitivity of C.T. scan in the diagnosis of NPC was 96.3% and the percentage of false negatives was 3.7%. The specificity of the test was 76% and the percentage of false positive was 23%. The predictive value of a positive test was 96% and the predictive value of a negative test was 76%.

Table VI shows the validity of using the combination of IgA/VCA and C.T. scan in series. The results indicate that the sensitivity and specificity of using the tests in series is 100%. There were no false positive or false negatives. The predictive value of a positive test and a negative test was 100%.

Discussion

Serological test for IgA antibody to EBV capsid antigen has been regarded as a marker for the diagnosis of NPC.[10,11] It has been used to screen high risk population for nasopharyngeal carcinoma with encouraging results.[12] When this test was applied to those patients who were highly suspected to have NPC (based on the clinical feature) its value became all the more significant. Out of 95 such cases in the present series this test was positive in 79 (83.2%) and all of them were confirmed to be NPC. Of the 82 confirmed cases of NPC, there were three who were negative for this test. Thus the sensitivity of this test was 96.3%. However, the specificity and the predictive value of a positive IgA/VCA test, was 100%, but of a negative test if was only 81%. This meant that if the clinical features suggested NPC and the IgA/VCA titre was raised, that was almost certainly a case of NPC for which a histological confirmation had to be obtained with more deligence. There would be, of

course cases of NPC for which IgA/VCA test would remain negative.

It was interesting to note from this study that the results of C.T. scan was complementary for those cases of NPC for which the serology was negative. Applying C.T. scan as an aid to NPC diagnosis in suspected cases, it was noted that the specificity and the predictive values were lower as compared to the serological test. This was so because clinical observation of a lesion in the nasopharynx was rightly suspected particularly in mid age Chinese, to be NPC and the C.T. scan could be positive as well, but on histopathological examination few of them were confirmed to be non-NPC.

The most significant result of this study was the fact that if the two parameters (IgA/VCA test and C.T. scan) were used in combination (in series) in all suspected cases of NPC not only the sensitivity and specificity became 100% but the predictive value of both the positive and negative tests was also 100%. In all those cases where IgA/VCA was positive and C.T. scan showed abnormality, examination of representative biopsy specimen obtained from the nasopharynx (sometimes repeated) established the diagnosis of NPC in each one of them. So far we have not encountered any one case where IgA/VCA and C.T. scan are positive and the patient does not have NPC.

It is thus suggested that in those situations where there is clinical suspicion of NPC and the biopsy from the nasopharynx is negative, C.T. scan of the postnasal space is examined along with the IgA/VCA titre. If the results of these two investigations are positive, the biopsy examination is repeated till the confirmation of the diagnosis of NPC.

Acknowledgement

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