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Original Article

Sensitivity and Specificity of Non-Enhanced CT-Brain: A Cross-Sectional Study

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Abstract

Aim: This study aims to determine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of non-enhanced CT (NECT) brain and contrast-enhanced computed tomography (CECT) as the reference standard in diagnosing brain abnormalities and to assess changes in diagnosis (if any) after reviewing the contrast-enhanced study. **Methods:** This is a descriptive retrospective cross-sectional study done by reviewing CT-scans performed at Universiti Kebangsaan Malaysia Medical Centre from January to December 2015. NECT and its corresponding CECT brain scans were evaluated by a radiologist and a radiology resident independently on separate occasions. The final diagnosis was categorized as normal and abnormal. The sensitivity, specificity, PPV and NPV of NECT compared to CECT were calculated. **Results:** NECT and CECT brain scans obtained in 158 patients for indications other than trauma were reviewed. 50.63% (*n*=80) and 49.37% (*n*=78) of them are male and female respectively. Both paediatric and adult patients were included in this study, with a mean age of 49.33 (range=6 months to 92 years old). The sensitivity, specificity, PPV and NPV of NECT brain were found to be 95%, 100%, 100% and 86.7% respectively. **Conclusion:** NECT brain demonstrated high sensitivity, specificity and PPV. 6 out of 158 (3.8%) NECT brain failed to identify brain abnormality which were then seen on CECT. CECT following normal NECT should be limited to patient who i) has positive neurological sign after exclusion of stroke, ii) is a known case of primary tumor, iii) has inflammatory/ infective disease *i.e* tuberculosis.

Keywords: *CT Brain; Normal and Abnormal CT Brain; Non-Enhanced CT Brain; Contrasted CT Brain*

Introduction

Computed tomography (CT) is a diagnostic imaging that utilises a combination of x-ray beam and computer technology to generate axial images of the body. CT has been used extensively for imaging of lesions in the brain in paediatric and adult patients. A CT-scan generates accurate images of many body parts, including the muscles, fat, bones and organs. The two main forms of CT scans are non- enhanced computed tomography (NECT) and contrast-enhanced computed tomography (CECT). Contrast, a substance injected intravenously, helps to enhance tissue structures, highlight blood vessels and hence helps to verify the target area of concern in CECT (Kocak, 2022).

Previous studies demonstrated that contrast enhancement is only useful when the initial unenhanced scan showed abnormalities and when there is a suspicion of intracranial abnormality suggested by persistent focal signs and symptoms (Minné *et al.*, 2014). CT-brain with the administration of intravenous contrast medium has limited benefits compared to NECT brain and incurs

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increased cost, causes patient discomfort and also increases the risk of morbidity and mortality when contrast reaction occurs. These are some of the essential factors to be considered before subjecting patients to undergo CECT. (Huckman, 1975).

A previous study by Ibrahim *et al.* (2012) conducted at our institution, Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Kuala Lumpur, identified CT as one of the radiology investigations that consumed a great amount of resources. The cost of CECT was almost double of that of NECT. In an era that emphasizes on cost-effective and evidence-based medical interventions, studies on the comparative accuracy of less costly diagnostic and imaging techniques are of paramount importance. To our knowledge, there is no previous study on the diagnostic accuracy of NECT brain done in the local setting. This retrospective study was done to determine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of NECT, by employing CECT as the reference standard, in diagnosing brain abnormalities and to assess changes in diagnosis (if any) after reviewing the CECT. We hypothesized that the sensitivity of NECT brain is relatively high and comparable to CECT brain in ruling out brain abnormalities.

Methodology

This is a descriptive retrospective cross-sectional study. Ethical approval was obtained from the Research and Ethics Committee Universiti Kebangsaan Malaysia (RECUKM) (Ethical approval code: FF-2016-423). The need for written informed consent was waived by RECUKM due to the retrospective nature of the study. All patients irrespective of age with an indication other than trauma who had NECT brain followed by CECT brain done in the same setting or within 48 hours in UKMMC Radiology Department from January to December 2015 were included in this study. Cases where only plain or contrasted CT scan was performed were excluded from the study.

Sample size

Sample size required was calculated using Cochran's equation. Sensitivity and specificity of NECT were estimated to be 94% and 100% respectively based on a similar study by Demaerel *et al* (1998). Sensitivity of 94% was utilized for sample size calculation as it resulted in larger sample size requirement compared to specificity. This study requires 87 samples at 5% precision and 95% significance level.

Imaging Analysis

The CT scans were evaluated by a radiologist and a radiology resident. Reviewers were asked to review the NECT brain while blinded from the findings of CECT brain. After reviewing all the NECT images, contrasted CT brain scans were reviewed. Reviewers were also blinded to the official report/interpretation of the scans. Images were viewed at a standard soft-tissue algorithm with a window width of 80 Hounsfield Unit (HU) and a window level of 40 HU. As per usual clinical practice, images were also viewed at multiple window levels and widths apart from the standard setting. When available, bone windows and/or bone algorithms were reviewed. Each NECT and CECT scan was assigned a unique number code. The order of the scans to be reviewed by each reviewer was randomly assigned. Each NECT and CECT scan was categorized by the reviewers as normal or abnormal. Data was collected manually by employing a data collection sheet. The f low of study procedure was summarized in Table 1.

Table 1: Flow Chart for Study Procedure

<table>
<tr><td colspan="2">Retrieval of patient case from the hospital computer system for cases which fulfill the criteria below:
i) Referred to UKMMC Radiology Department for brain CT scans for non-trauma clinical indication
ii) Both NECT and CECT brain were performed in the same setting or within 48 hours
↓</td></tr>
<tr><td>1st Reader (Radiologist)</td><td>2nd Reader (Radiology Resident)</td></tr>
</table>

Review NECT scans ↓ Review CECT scans at a separate time after all patients' NECT scans have been reviewed. ↓		Review NECT scans ↓ Review CECT scans at a separate time after all patients' NECT scans have been reviewed. ↓	
Data Collection and Result Interpretation			
Abnormalities on both NECT and CECT brain	Normal findings on both NECT and CECT brain	Abnormal on NECT but normal on CECT brain	Normal on NECT but abnormal on CECT brain
True positive (The diagnosis made at NECT was confirmed by CECT)	True negative (No further information was obtained)	False positive (The findings at CECT changed the initial diagnosis)	False negative (The findings at CECT changed the initial diagnosis)

Data Analysis

The CECT scans were used as the reference standard. With regard to each anatomic compartment evaluated, scans that showed abnormal findings on both NECT and CECT were classified as true positive. Scans with normal findings on both NECT and CECT were classified as true negative. Scans that revealed abnormal findings on NECT and normal findings on CECT were classified as false positive. Scans that were interpreted as normal on NECT but showed abnormal findings on CECT were classified as false negative. The rates of true positive, true negative, false positive, and false negative rates were utilized to calculate the sensitivity, specificity, PPV and NPV of NECT, using CECT as the reference standard.

Results

A total of 158 patients were included. Baseline characteristics of the patients are summarized in Table 2. The gender distribution was more or less equal, 50.63% (*n*=80) of the patients are male and 49.37% (*n*=78) of them are female. Both paediatric and adult patients were recruited to the study (range: 6 months-92 years old) with a mean age of 49.33 years old. They were from 6 different races, namely Malay (*n*=88, 55.7%), Chinese (*n*=55, 34.8%), Indian (*n*=10, 6.3%), Myanmar, (*n*=3, 1.9%), Somalian (*n*=1, 0.63 %) and Nigerian (*n*=1, 0.63%).

Table 2: Baseline Characteristics of the Study Population

Patient Characteristics	Frequency, n	Percentage (%)
Gender		
Male	80	50.6
Female	78	49.4
Race		
Malay	88	55.7
Chinese	55	34.8
Indian	10	6.3
Myanmar	3	1.9
Nigerian	1	0.6
Somalian	1	0.6
Age	median = 54	range = 0.5-92

There was no discrepancy in CT brain result interpretation between the two reviewers. The number of patients with normal NECT and CECT [true negative] was 39 (24.7%) and the number of patients with abnormal NECT and CECT [true positive] was 113 (71.5%). Figure 1 shows an example of the imaging of true positive results. None of the patient had abnormal NECT but normal CECT [false positive]. Frequency of true negative, true positive, false negative and false positive was summarized in Table 3.

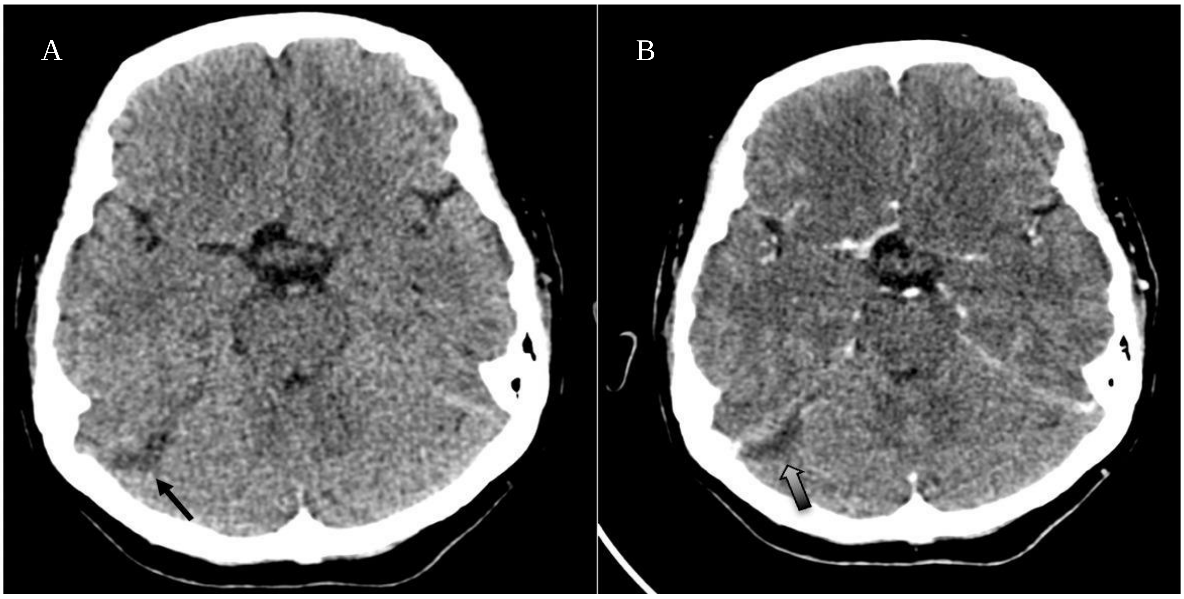

Figure 1: *An example of true positive result. NECT (A) shows subdural effusion of right tentorium cerebelli (arrow) and CECT (B) also shows subdural effusion of right tentorium cerebelli (block arrow).*

Table 3: Frequency of True Negative, True Positive, False Negative and False Positive

Finding at unenhanced CT (Initial diagnosis)	**Finding at Contrast enhanced CT (final vdiagnosis)**	**No of scans (n=158)**	**Diagnostic Status**
Normal	Normal	*n*=39, 24.7 %	True negative
Abnormal	Abnormal	*n*=113, 71.5 %	True positive
Normal	Abnormal	*n*=6, 3.8 %	False negative
Abnormal	Normal	0	False positive

In 6 out of 158 patients (3.8%) the NECT was reported as normal but CECT was reported with brain abnormality [false negative]. Among them, leptomeningeal enhancement on CECT was showed in three cases in keeping with meningitis. Nevertheless, these had no clinical impact as the diagnosis of meningitis and sign of increased intracranial pressure should be based on clinical assessment rather than imaging. An example of false negative result is shown in Figure 2. The remaining three false negative cases showed imaging findings and/or diagnosis as follow: multiple parenchymal nodules suggestive of neuro tuberculosis (Figure 3), small sphenoid wing meningioma (Figure 4) and multiple metastatic nodule (Figure 5). Abnormalities that were detected by CECT but not by the initial NECT are categorized into infective and neoplastic and are summarised in Table 4. Sensitivity, specificity, PPV and NPV of NECT were calculated as 95%, 100%, 100% and 86.7% respectively (Table 5a and Table 5b).

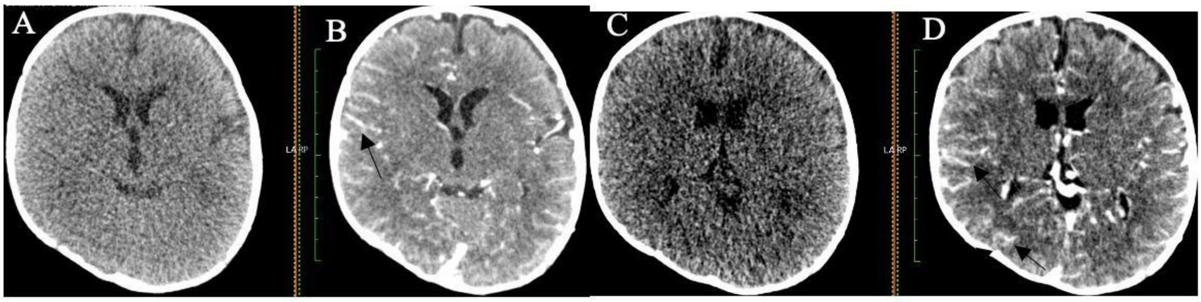

Figure 2: *An example of false negative result (Meningoencephalitis**)**. NECT (A,C) and CECT (B,D) of the brain. No abnormality is seen in the NECT scans. However, diffuse abnormal leptomeningeal enhancements are seen in the CECT scans (arrows in B, D).*

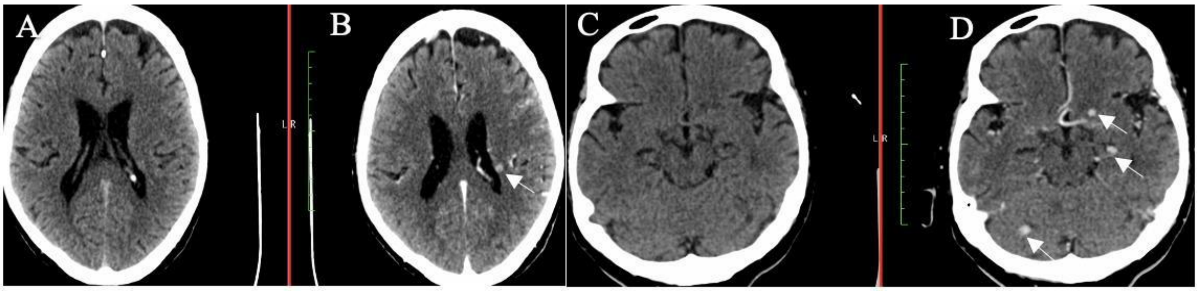

Figure 3: *False negative (Neurotuberculosis). NECT (A,C) and CECT (B,D) of the brain. No abnormality is seen in the NECT scans (A,C). However, multiple enhancing nodules are seen in the CECT scans (arrows in B, D).*

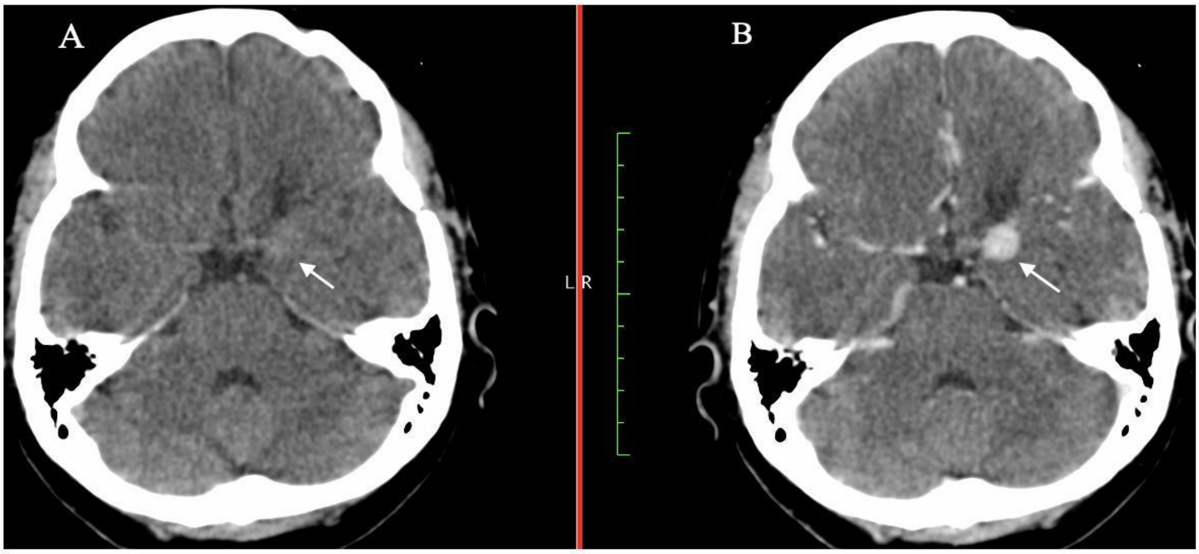

Figure 4: *False negative (Meningioma). NECT (A) and CECT (B) of the brain. No abnormality is seen in the NECT scan (arrow in A), however there is an avid enhancement extra-axial lesion in the left sphenoid wing in the CECT scan. (arrow in B).*

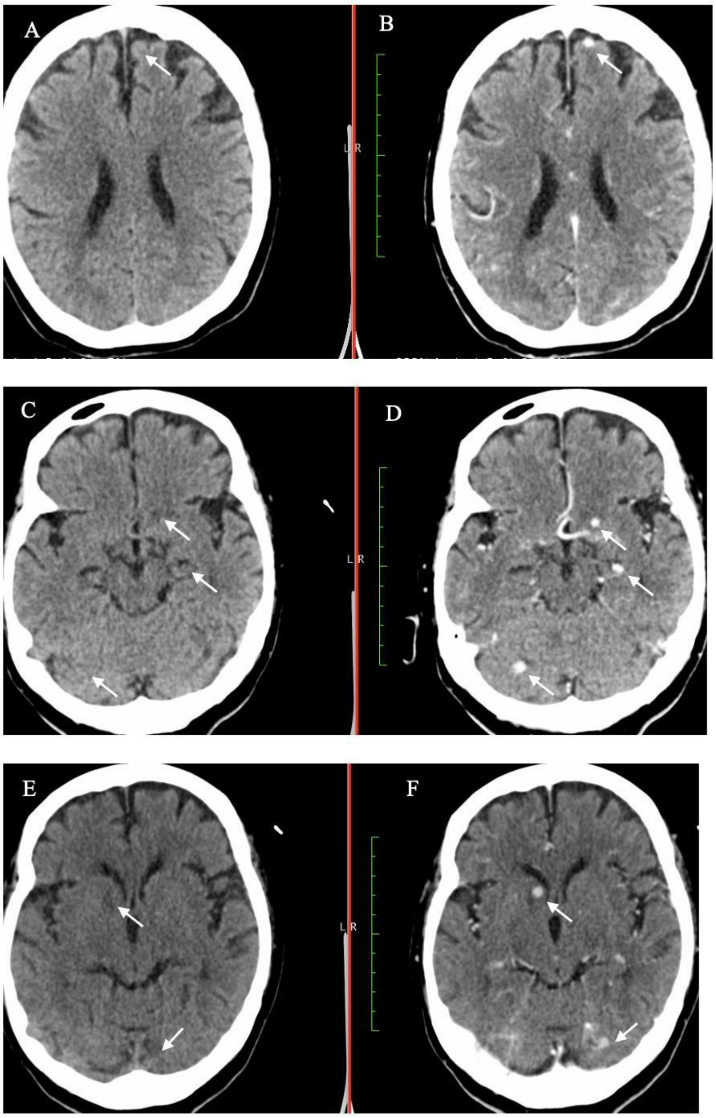

Figure 5: *False negative (Metastasis). NECT (A, C, E) and CECT (B, D, F) of the brain. No abnormality is seen in the NECT scans (arrows in A, C, E). Multiple enhanced nodules can be seen in the CECT scans (arrows in B, D, F).*

Table 4: Summary of Findings in False-Negative Cases

Classification of findings	**Presumed diagnosis based on CECT**	**Radiological features**	**Number of Cases**
Infective	Meningoencephalitis	Leptomeningeal enhancement	3
	Neurotuberculosis	Multiple enhancing parenchymal nodules	1
Neoplastic	Sphenoid wing Meningioma	Avid enhancement small extra axial mass	1
	Metastasis from a known primary	Enhancing nodules	1
Total			**6**

Table 5a: Sensitivity, Specificity, PPV and NPV of NECT

a True positive = 113 (71.5 %)	**b** False Positive =0 %
c False Negative = 6 (3.8 %)	**d** True Negative= 39 (24.7%)
Sensitivity = $\frac{TP}{TP+FN} = \frac{a}{a+c}$ $\frac{113}{113+6}$ = 95 %	**Specificity =** $\frac{TN}{TN+FP} = \frac{d}{d+b}$ $\frac{39}{39+0}$ = 100 %
Positive predictive value= $\frac{TP}{TP+FP} = \frac{a}{a+b}$ $\frac{113}{113+0}$ = 100 %	**Negative predictive value=** $\frac{TN}{TN+FN} = \frac{d}{d+c}$ $\frac{39}{39+6}$ = 86.7 %

Table 5b: Non-Enhanced and Contrast-Enhanced Cross Tabulation

			Contrast-Enhanced		Total
			Normal	Abnormal	
Non-Enhanced	Normal	Count	39	6	45
		% within NonEnhanced	**NPV 86.7%**	13.30%	100.00%
		% within ContrastEnhanced	**Specificity 100.0%**	5.00%	28.50%
		% of Total	24.70%	3.80%	28.50%
	Abnormal	Count	0	113	113
		% within NonEnhanced	0.00%	**PPV 100.0%**	100.00%
		% within ContrastEnhanced	0.00%	**Sensitivity 95.0%**	71.50%
		% of Total	0.00%	71.50%	71.50%
Total		Count	39	119	158
		% within NonEnhanced	24.70%	75.30%	100.00%
		% within ContrastEnhanced	100.00%	100.00%	100.00%

NPV=Negative predictive value, PPV=Positive predictive value

Discussion

In our study, false negative results occurred in 3.8% of the cases. The missed diagnosis on NECT may be attributable to several imaging and reviewer factors. Examples of imaging factors are the quality of the diagnostic images, the presence or absence of secondary signs and the density and size of the abnormal findings. Pathology is not visible on an NECT when there is an absence of secondary signs like oedema or mass effect and when it is isodense to the surrounding parenchyma (Minné *et al*., 2014).

On the other hand, accuracy of a radiologist's report can be influenced by interruptions, inaccurate or incomplete clinical history, unavailability of previous investigations for comparison, poor quality examination and poor viewing conditions. (European Society of Radiology, 2004; Royal College of Radiologists, 1995 and Talan *et al.,* 1989). We did not provide clinical history of each individual case to the reviewers in our study as doing so would have created an interpretive bias. NECT and CECT were reviewed at separate timing rather than one after another. This was to prevent a potential bias and to prevent the reviewers from changing their initial evaluation of the NECT.

Among the six abnormalities that were missed on NECT, three of them (50%) were diagnosed as meningitis on post contrast administration CT scan. There was no significant clinical impact in these 3 cases as the diagnosis of meningitis should not be based on imaging but rather on clinical assessment. A study by Nagra *et al.* (2011) showed that about 86%-88% of patients with meningitis showed normal CT findings and only a small number (2-4%) of these patients had abnormal CT scan leading to contraindication for lumbar puncture. In other words, normal CT results would not exclude meningitis. Instead of depending on radiological findings, the safety of conducting a lumbar puncture should be a clinical decision. As indicators of raised intracranial pressure, clinical predictors such as altered mental status, papilledema or focal neurology and the overall clinical impression are more useful compared to CT brain findings (Cabral *et al.,* 1987). A comprehensive and detailed clinical assessment done before radiological imaging is of paramount importance as the imaging finding may not be suggestive of raised intracranial pressure, resulting in false reassurance for the clinicians (Cartwright *et al*., 1992 and Strang & Pugh, 1992).

One of the six patients whom the NECT failed to detect the abnormality was diagnosed as meningioma by CECT. This was because the lesion was isodense to the brain parenchyma and there was lack of calcification on NECT. However, the lesion demonstrated avid enhancement on CECT, hence suggesting the atypical features of meningioma. Subsequent biopsy of the lesion provided a final diagnosis of angiomatous meningioma. This patient presented with multiple episodes of fitting and a history of tongue biting and ictal drowsiness as well as a Glasgow Coma Scale (GCS) of 12/15. Majority (60%) of meningioma cases would have hyperdense on plain CT, however about 40% of meningioma will demonstrate isodense to the brain parenchyma. Calcifications are seen in 20-30% of meningioma (Greenberg, Chandler and Sandler, 1999).

The other two missed NECT brain cases were namely brain metastasis and neurotuberculosis. In both cases, CECT showed multiple small intraparenchymal enhancing nodules with lack of perilesional edema. NECT failed to identify the lesions as they were isodense to the brain parenchyma and there was an absence of perilesional edema. The patient with cerebral metastasis presented with vomiting and headache and was a known case of lung adenocarcinoma with lung metastasis. The patient with neurotuberculosis presented with ataxic gait and right sided limb weakness and was a known case of miliary tuberculosis.

The results of our study were in congruence with published literature, including both retrospective and prospective studies, conducted among adult and paediatric populations. In a study by Branson *et al.* (2007), 353 CT scans of paediatric patients were reviewed and the sensitivity of NECT brain in children was reported as 97%, with 2.7% (5 of 183 cases) showed change in diagnosis after performing CECT following normal or equivocally abnormal NECT. They concluded that NECT brain in the paediatric population has high sensitivity and specificity in the diagnosis of pathologic findings. Performing CECT following NECT brain in this population did not frequently result in a change in the final diagnosis. The sensitivity (97%) and false negative rate (2.7%) of the study are comparable to our study with a corresponding value of 95% and 3.8% respectively.

A study by Chishti *et al.* (2003) demonstrated the role of intravenous iodinated contrast media in CT brain in selected patients. Among 547 cases, an abnormality was observed on the CECT exclusively but not on the NECT in 3 cases (0.5%). The initial diagnosis based on NECT was changed in 15 cases (2.7%) after reviewing the subsequent CECT. A prospective study by Bernard , Hourihan & Adams (1991) reported an important but limited role of CECT in patients with focal lesions. Therefore, in agreement with published literature, it is reasonable not to give contrast when the NECT is normal if there is a low suspicion of the presence of a lesion.

Wood *et al.* (1990) retrospectively reviewed 322 cases and evaluated the role of CECT in patients in the emergency room for non-trauma indications. Abnormalities, which were not evident on the initial NECT, were observed on the CECT 3 cases (1.25%). Similar to the findings in our study, additional information obtained from CECT did not result in a change in patient management. As such, it was concluded that if an NECT is normal in an acute setting, subsequent CECT is not necessary in most circumstances. To the best of authors' knowledge, no false positive in NECT has been reported in the literature. This is in congruence with our study result where NECT demonstrated a specificity of 100%.

In selected situations where CECT brain is recommended, several factors need to be considered. Radiation exposure is one of the most decisive factors to be taken into account as ionising radiation can lead to many adverse effects, including the induction of cancer. The cancer-inducing potential of radiation is not confined to a threshold dose. In other words, even a small dose of ionising radiation carries such a risk. The dose of contrast agent is also cumulative from each CT done. A retrospective cohort study by Pearce *et al.* (2012) demonstrated a positive correlation between the CT radiation dose received in childhood and the occurrence of brain tumours and leukemia later in life. A radiation dose of around 4 mSv (equivalent to 200 chest radiographs) is deemed necessary. Consequential NECT and CECT results in double the radiation dose and hence carry twice as much risk for cancer development. In line with the ALARA (As Low As Reasonably Achievable) principle, radiologists should limit radiation exposure to a lowest possible amount (Shah & Platt, 2008).

The types of contrast agents, their respective risks and contraindications as well as common clinical scenarios in which CECT is indicated are some of the important factors when deciding on the type CT scan to be utilized. A history of reactions to specific contrast agents, chronic or acutely worsening renal diseases, pregnancy, radioactive iodine treatment for thyroid disease and concomitant metformin use are contraindications for using contrast agents. Timely and effective communication in the multidisciplinary team, especially between physicians and radiologists is of paramount importance in performing the most suitable radiological investigation at the lowest cost and risk to the patient (Rawson & Pelletier, 2013). The use of contrast agents is also associated with a risk of adverse reactions, which can be further classified into general and organ-specific reactions resulting in nephro-, pulmonary, cardiovascular and neurotoxicity. (Namasivayam *et al*., 2006). Another important consideration is the cost of the procedure, which includes the cost of contrast media and the operational expenses of radiological imaging facilities. When only one type of investigation, either NECT or CECT, was selected and performed based on clinical indications, throughput of patients can be increased while the cost incurred to both patients and healthcare institutions can be reduced.

To sum up, owing to the risk of radiation dose and contrast reactions as well as the overall cost (including contract media and other operational cost), we would suggest limiting the utilization of CECT brain in patients with the following history: (a) positive neurological sign and symptoms in a non-obvious cerebral infarct, (b) a known case of primary tumour to look for metastasis and (c) inflammatory or infection *e.g.* tuberculosis.

The main limitation of our study was small numbers of patients who had both NECT and CECT brain at the same setting or within 48 hours. Some of our patients who had suspicious abnormality on NECT had subsequent MRI brain for further assessment of the suspected abnormality without proceeding to CECT. Some of the patients performed both NECT and CECT but beyond the timeframe of 48 hours due to logistic reasons and institutional reasons like lack of resources. Multi-centre study with larger sample size could be carried out in the future to study the need of CECT in specific clinical conditions.

Conclusion

NECT brain demonstrated very high sensitivity, specificity and PPV. NECT failed to detect abnormality in 6 out of 158 cases (3.8 %), with an impact on clinical treatment decision in 3 cases. Supplementary CECT following a normal NECT result should be limited to patients with: (i) positive neurological sign and symptoms after exclusion of cerebral infarction or ischaemia, (ii) a background history or known case of primary tumor, (iii) inflammation or infective disease *i.e* tuberculosis especially those with neurological signs.

Conflict of interest

The authors declare no conflict of interests.

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