Original article

Spontaneous cerebrospinal fluid rhinorrhoea and its association with body mass index (BMI)

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Abstract

Objective: The purpose of this study is to review the correlation of spontaneous cerebrospinal fluid rhinorrhoea (CSFR) and Body Mass Index (BMI) and describe the demographics, the surgical techniques and outcomes. ***Materials and methods*:** We performed a retrospective review of clinical data of twenty patients diagnosed with spontaneous CSFR and treated at the Malaysian National University Medical Centre from 1997 to 2015. ***Result and Discussion:*** A total of 20 patients were selected in this research (19 females,1male). The mean age was 45.5 years with nineteen females and one male patient. The mean BMI was 33.1kg/m^2.Majority of patients with spontaneous leaks are females in their forties. The bath plug technique, onlay of middle turbinate grafts, nasoseptal flaps and mucoperiosteal grafts techniques were used and three patients reported recurrences. ***Conclusion*:** Spontaneous CSFR is more common in women in their 40s with BMI>25. The most common sites of leaks are the cribriform plate followed by the sphenoid sinus. Spontaneous CSFR cases are strongly related with increased BMI.

Keywords: spontaneous cerebrospinal fluid rhinorrhoea; BMI, intrathecal fluorescein; Bath plug technique; middle turbinate grafts; nasoseptal flaps.

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Introduction

Cerebrospinal fluid (CSF) rhinorrhoea is the leakage of CSF through the nose due to a communication between the subarachnoid space and the nasal cavity. The sites of defect involve bony dehiscence in the region of the cribriform plate, sphenoid sinus and fovea ethmoidalis and rarely involve the frontal sinus [1, 2]. This breach of the dividing layers as aforementioned brings about the potential risk of ascending infection which can result in meningitis that can lead to significant mortality and morbidity for the patient[3]. Due to a significant risk of 30-40% of patients developing this complication, early endoscopic intervention is recommended[4]. However, a recent study in 2012 discovered that primary spontaneous CSF rhinorrhoea had a lower incidence and delayed onset of meningitis compared to that of a secondary cause. This could be explained by elevated intracranial pressure (ICP) hindering the ascension of bacteria[5].

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There has been much uncertainty in defining "spontaneous" CSF rhinorrhoea when trauma is not the cause. There have been previous classifications of CSF rhinorrhoea into primary and idiopathic when the cause of the CSF leak could not be found and secondary when the CSF leaks were due to either intracranial or extracranial cause [1, 6, 7]. Later publications have further classified CSF rhinorrhoea into traumatic (>90%) and non-traumatic (<10%) where spontaneous leaks account for 3-4% of all leaks in the non-traumatic group[6-10]. Ommaya 1968 has classified non-traumatic CSF leaks into high pressure and normal pressure leaks. The high pressure leaks were due to tumours and hydrocephalus whereas the normal pressure leaks due to congenital anomalies, focal atrophy and osteomyelitic lesions[7].

In 2011, Andrey SL reported 173 patients with primary CSF rhinorrhoea, 143 females and 30 males age ranging from 11months to 72 years therefore taking into account all congenital anomalies. All these patients were diagnosed from 1999[11]. Banks CA in 2008 reported 77 cases of spontaneous CSF rhinorrhoea with an average BMI of 35 which was greater than traumatic cases (BMI: 30) and congenital patients BMI: 23)[12]. This was consistent with Holzmann's study in 2003 reporting 17 cases of spontaneous CSF rhinorrhoea with an average BMI of 34.87 as compared to non-spontaneous cases (28.53)[13]. In 2013, Chaaban MR et al conducted a 5 year study and reported 46 patients having spontaneous CSF leaks where 36/46 were obese (BMI >30)[14].

To date, there is limited data on the incidence of CSF rhinorrhoea. A large majority of CSF leaks (96%) are caused by accidental or surgical trauma whereby 16% of CSF rhinorrhoea are caused by the latter. However, CSF rhinorrhoea is noted only in 2-3% out of all cases of serious head trauma with more than 50% fistulas reported at the anterior skull base, mostly at the cribriform plate. The majority of traumatic CSF leaks present within 2 days to 3 months following the traumatic event. Interestingly, most CSF fistulas caused by accidental head trauma resolve spontaneously or with conservative modalities such as lumbar drainage and bed rest. The most reliable approach to distinguish between a traumatic or neoplastic lesion and a spontaneous CSF rhinorrhoea are High-Resolution Computed Tomography (CT) and Magnetic Resonance Tomography (MRI) scans. In the case of frequent or constant leaks, CT cisternography is helpful in identifying the site of the leak. Per-operatively, the use of intrathecal sodium fluorescein is the best method for localization of the bony defect with sensitivity and specificity of 73.8% and 100%, respectively[2, 15-17].

This study was designed to increase the current understanding of spontaneous cerebrospinal fluid rhinorrhoea and to review the correlation between Body Mass Index (BMI) and spontaneous CSF rhinorrhoea.

Materials and methods

The National University of Malaysia Medical Centre (UKMMC), Kuala Lumpur is a tertiary referral centre with a busy otorhinolaryngology-head neck surgery department that receives referrals from all around Malaysia. After the ethical approval we conducted a descriptive retrospective study of all patients diagnosed with spontaneous CSF rhinorrhoea from 1997 to 2015. A standard proforma was developed, and information was collected in a systematic manner. This includes the patients' demographic data, BMI, sites of the fistula, co-morbidities, surgical technique, recurrence and the use of intrathecal fluorescein. CSF leaks due to congenital anomalies in children and arachnoid cysts were excluded.

BMI is defined as the weight in kilograms divided by the square of the height in metres (kg/m^2). According to the WHO guidelines, a person who is overweight is one who has a BMI of ≥25 but <30, obese with a BMI range of ≥30 but <40 and a morbidly obese individual with a BMI of ≥40. A literature review on the association of obesity with spontaneous CSF rhinorrhoea was performed for comparison and to analyse if different human demographics affect the said condition.

Ethical Clearance: All procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation (UKMMC Committee and the Perdana University Institutional Review Board) and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Table 1 depicts the age, demographics, BMI, and details of CSF leak repair in our patient sample. Twenty patients were included in the study, where they were 19 females and one male. The average age was 45.5 (ranging from 14-71 years). Among the female patients, one had normal body mass index (BMI range 18.5-24.9), eight were overweight (BMI range 25-29.9), six were obese (BMI range 30-39.9) and five were morbidly obese (BMI >40). The only male patient was overweight. The average BMI of the 20 patients amounted to $33.1kg/m^2$ with a median of $30kg/m^2$.

This distribution is illustrated in Figure 2. In Malaysia, the average BMI of individuals aged between 40-49.9 years is 35.8, 50-59.9 years with an average BMI of 36.4, 60-69.9 years with average BMI of 37.0, and an average BMI of 31.6 in individuals above 70 years. Figure 1 is a scatterplot illustrating the prevalence of spontaneous CSF rhinorrhoea in overweight to obese patients in their late thirties to forties.

Table 1: Demographics of patients presenting with spontaneous CSF rhinorrhoea

Patient	Age	Sex	Ethnicity	BMI (kg/m^2)	Site of leak	Procedure
CSF-R1	14	F	KADAZAN	26.6	Cribriform plate	ER (Bath plug technique)
CSF-R2	50	F	INDIAN	26.7	Sphenoid sinus	ER (Bath plug technique)
CSF-R3	37	F	INDIAN	26.8	Cribriform plate	ER (Bath plug technique)
CSF-R4	43	M	CHINESE	27.5	Sphenoid sinus	ER (Bath plug technique)
CSF-R5	52	F	INDIAN	30.2	Sphenoid sinus	ER (Onlay septal cartilage graft)
CSF-R6	35	F	INDIAN	30.4	Fovea ethmoidalis	ER(Bath plug technique)
CSF-R7	39	F	MALAY	41.8	Cribriform plate	ER (Mucoperiosteal septal graft, MT flap)
CSF-R8	37	F	MALAY	50.3	Cribriform plate	ER (Bath plug technique with free MT graft)
CSF-R9	38	F	INDIAN	43.1	Sphenoid sinus	ER (Nasoseptal flap) 2nd repair
CSF-R10	62	F	MALAY	44.8	Sphenoid sinus	ER (Nasoseptal flap)
CSF-R11	50	F	INDIAN	33.8	Cribriform plate	ER (Bath plug technique, overlay using MT graft)
CSF-R12	41	F	INDIAN	50.6	Cribriform plate	ER (Nasoseptal flap)
CSF-R13	51	F	INDIAN	28.0	Cribriform plate	ER (MT flap)
CSF-R14	54	F	CHINESE	33.3	Sphenoid sinus	ER (Bath plug technique, onlay technique with MT graft) 2nd repair
CSF-R15	42	F	INDIAN	29.8	Cribriform plate	ER (Bath plug technique, MT flap)
CSF-R16	47	F	MALAY	25.3	Cribriform plate	ER (Mucoperiosteal graft, MT graft)
CSF-R17	60	F	INDIAN	27.1	Sphenoid sinus	ER (bath plug technique)
CSF-R18	71	F	INDIAN	23.3	Cribriform plate	ER (nasal septal flap)
CSF-R19	41	F	MALAY	32.9	Cribriform plate	ER (Bath plug technique, MT flap)
CSF-R20	46	F	MALAY	30.2	Cribriform plate	ER (Bath plug, onlay MT graft, free mucoperiosteal graft) and Craniofacial repair

M=Male, F=Female, BMI=Body Mass Index, MT = Middle Turbinate, ER=Endoscopic repair

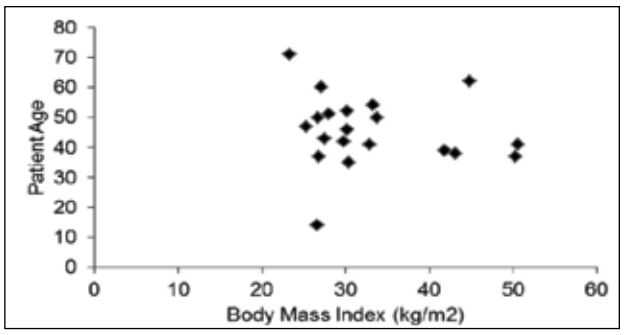

Figure 1: Age-BMI relationship

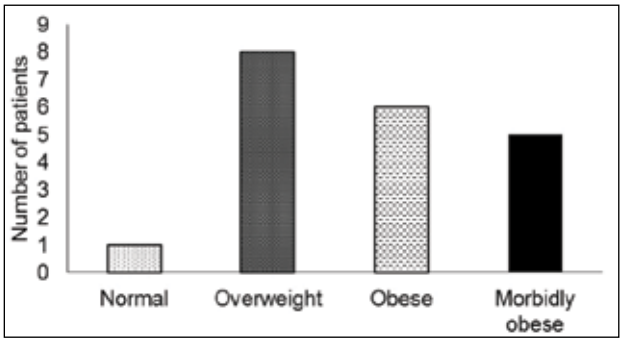

Figure 2: BMI of patients with spontaneous CSF Rhinorrhoea

Among our patient sample, eleven patients were Indian (55%), two were Chinese (10%), one Kadazan (5%) and six patients were of Malay (30%) ethnicity. This shows that among the Malaysian population, the Indian population were the most prone to have spontaneous CSF rhinorrhoea, followed by the Malays, Chinese then Kadazan which is consistent with the Malaysian statistics on the prevalence of obesity in different ethnic groups. However, a larger study has to be done including similar cases from peninsular and east Malaysia. East Malaysia has a higher population of Kadazan and other ethnicities could also be taken into account.

The presenting complain in all patients was clear, watery nasal discharge, salty in taste which could be demonstrated by stooping forwards. Three patients had an associated history of meningitis (15%). Six patients (30%) presented with headache, and two patients (10%) with blurring of vision being possible symptoms of raised intracranial pressure. One patient had underlying benign intracranial hypertension with empty sella syndrome.

β-2- transferrin test was used as a confirmatory test in two patients who tested for it using private medical facilities. For the rest of the patients, the presence of CSF was confirmed by biochemistry where we measure the CSF glucose/blood glucose ratio (normally CSF glucose is 2/3 of the blood glucose). However, it is important to take note that CSF glucose levels can increase with higher blood glucose level and decrease with bacterial meningitis. β-2- transferrin studies are performed to confirm the presence of CSF, but do not assist in the localization of the defect. The β-2- transferrin test is not available in our centre.

HRCT of 19 patients demonstrated visible defects in seven patients, three at the sphenoid sinus and four at the cribriform plate. Of the patients that went for the HRCT, three patients also underwent an MRI assessment of which two patients had identifiable defects at the cribriform plate. In addition, two other patients had negative CT cisternography (CTC). MRI cisternography and CTC were used to guide in a patient management. This is depicted in Table 2.

Table 2: Visible bony defects identified in Radiographic studies

Patient	HRCT	MRI	CT Cisternogram	SITE OF LEAK
CSF-R1	N/A	N/A	N/A	CP
CSF-R2	NEGATIVE	N/A	No bony defect but evidence of leak	SS
CSF-R3	N/A	N/A	N/A	CP
CSF-R4	POSITIVE	N/A	N/A	SS
CSF-R5	POSITIVE	N/A	N/A	SS
CSF-R6	N/A	N/A	N/A	FE
CSF-R7	N/A	N/A	N/A	CP
CSF-R8	ESS	N/A	N/A	CP
CSF-R9	POSITIVE	N/A	N/A	SS
CSF-R10	NEGATIVE	MENINGOCELE	N/A	SS
CSF-R11	NEGATIVE	N/A	N/A	CP
CSF-R12	POSITIVE	N/A	N/A	CP
CSF-R13	POSITIVE	N/A	N/A	CP
CSF-R14	N/A	N/A	No bony defect but evidence of leak	SS
CSF-R15	POSITIVE	N/A	N/A	CP
CSF-R16	NEGATIVE	N/A	N/A	CP
CSF-R17	NEGATIVE	N/A	N/A	SS
CSF-R18	NEGATIVE	POSITIVE	N/A	CP
CSF-R19	POSITIVE	POSITIVE	N/A	CP
CSF-R20	N/A	N/A	N/A	CP

CT = computed tomography, MRI = Magnetic Resonance Imaging, ESS = empty sella syndrome, CP = Cribriform Plate, SS = Sphenoid Sinus, FE = Fovea Ethmoidalis, N/A = not available

Intrathecal sodium fluorescein was used to help to identify and confirm the site of the leakage. This technique was used in 19 patients where a lumbar drain is inserted on the day of surgery and 10 per cent fluorescein (0.1ml mixed in 10ml of CSF) was given intrathecally as a slow bolus over 10 minutes to the patients. The patients are observed in the recovery area in the reverse Trendelenburg position for approximately 45 minutes to 1 hour, and are returned for general anaesthesia. CSF leak was confirmed endoscopically by looking for a bright yellow green fluid under light shone over a blue filter which demarcates the location of the fistula. If the leak was not visualized, then a Valsalva manoeuvre would be elicited to increase intracranial pressure and encourage the intrathecal sodium flourescein to leak from the fistula[6]. The intrathecal sodium fluorescein did not light up in one patient out of the 19 who underwent the procedure. One patient failed to undergo this procedure as there was a failure in lumbar drain insertion.

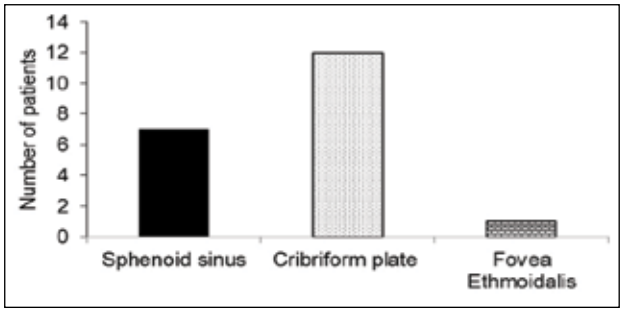

Figure 3: Site of leakage

Figure 3 illustrates the various sites of leakage and the number of patients respectively. Based on the various diagnostic modalities used, of the 20 patients, 35% of the patients had CSF leaks from the sphenoid sinus (n=7), 60% from the cribriform plate and (n=12) 5% from the fovea ethmoidalis (n=1). This is consistent with a study by Lund VJ in 2006 concluding that the commonest sites for congenital dehiscence is the cribriform niche adjacent to the vertical attachment of the middle turbinate anteriorly and the superior and lateral walls of the sphenoid posteriorly [18, 16, 19]. CT scans of 2 patients with spontaneous CSF rhinorrhoea with leaks from the right cribriform plate and the lateral recess of the sphenoid are shown in Figure 4(a) and Figure 4(b) respectively.

The size of the defects ranged from 0.3cm to 2cm. Seventeen patients had a single defect whereas two patients had two defects and one patient had three defects. The bath plug technique using abdominal fat

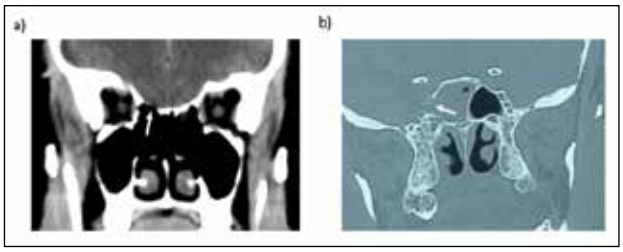

Figure 4: Representative perioperative CT scans from patients

or fat from the ear lobe was used in twelve patients (60%). A middle turbinate graft was used in nine patients (45%), nasoseptal flap in five patients (25%) and mucoperiosteal free flaps harvested from the middle turbinate in three patients (15%). A single surgical technique was used in twelve patients (60%) and two or more surgical techniques were used in eight patients (40%). This is illustrated in Table 1. Successful repair was seen in seventeen patients (85%). Three patients had recurrence of a CSF rhinorrhoea all of which had defects at the cribriform plate. In these three patients, the bath plug technique with a middle turbinate graft was used. One of these patients had benign intracranial hypertension (BIH) and empty sella syndrome (ESS) had multiple recurrences of CSF leaks. Another patient who the similar surgery had five recurring leaks over two years and had a craniofacial repair done for the fifth repair. There were no documented leaks after that.

Discussion

Spontaneous CSF rhinorrhoea is multifactorial in origin, of which increased intracranial pressure, brain pulsations which occur continuously along the skull base, degree of pneumatisation of the paranasal sinuses and the transmission of pulsations via arachnoid pits/villi causing bone erosion (the so called 4P's of spontaneous CSF rhinorrhoea) have been previously implicated[20].

A major factor in the pathogenesis of spontaneous CSF rhinorrhoea is increased ICP. Cerebrospinal fluid surrounds the brain is produced by the choroid plexus of the ventricular system. As secretion of CSF occurs at a steady state, the CSF pressure is highly dependent on the resorption at the arachnoid villi in the subarachnoid space. Bledsoe et al expanded on obstructed intracranial venous flow as a mechanism for increased ICP[21]. Large hydrostatic pressures in the venous system will prevent CSF resorption from the arachnoid villi into the venous system.

Impaired CSF absorption leads to an increased intracranial pressure. As a result, hydrostatic forces are exerted in the closed system and seek the path of least resistance such as perforations in the cribriform plate, diaphragma sellae, and other areas with significant pneumatisation and thinning of the bone[22]. This theory most likely explains how benign intracranial hypertension (BIH) leads to the development of spontaneous CSF leaks via the formation of fistulas. Benign intracranial hypertension (BIH), also known as pseudotumor cerebri is a syndrome of increased ICP with no identified cause. Whilst there may be subtle variations in the exact diagnostic classification of BIH, in principle BIH is diagnosed based on the presence of symptoms and signs of increased intracranial pressure, elevated CSF pressure of >25 cmH_2O, normal biochemical and cytological composition of CSF, and the absence of ventriculomegaly, mass, structural, or vascular lesion on radiological imaging. Empty sella syndrome (ESS) results from BIH due to the herniation of arachnoid tissue and CSF through the diaphragma sellae; partially or completely compressing the pituitary gland [3]. One patient in our series, who had BIH and ESS, underwent regular CSF drainage to control her intracranial pressures. BIH is commonly seen in obese women of childbearing age (15-44 years) with an incidence of 3.5 in 100,000 women with BMI of >30 [23, 24]. Furthermore in this study, two patients were seen to have meningoceles and one patient with arachnoid granulations protruding from the defect probably attributable to increased ICP and bony erosions. The defects in both cases may act as a pressure relief valve in cases of raised intracranial pressure that could possibly mask symptoms of raised intracranial pressure such as headache and blurring of vision.

Another key factor to note is the bony architecture of the skull base. The patency of the skull base is the deciding factor for normal pressure leaks and is a confounding factor in a high pressure leaks. Certain areas of the skull base are normally quite thin, notably the lateral lamella of the cribriform plate (LLCP). Some literature have described of a defect in the lateral sphenoid sinus forming a canal known as the lateral craniopharyngeal canal (Sternberg canal) that was thought to participate in the pathogenesis of spontaneous CSF rhinorrhoea.[9, 25]. However, there are a number of controversies regarding the location of this anatomical entity. A study had previously reported that the Sternberg canal was located at the posterior part of the lateral sphenoid sinus wall, lateral and inferior to the maxillary nerve and arose due to an incomplete fusion[26]. However, another

study in the same year claimed that the Sternberg canal is located medial to the foramen rotundum and V2 of the trigeminal nerve; and the cause of the leak was associated with erosive arachnoid pits rather than congenital dehiscence[27]. The latter study also further concluded that the Sternberg canal is not as prevalent as previously reported.

In addition to the above possible causative factors, a previous report suggested that central obesity raises intra-abdominal and intra-thoracic pressure, consequently increasing cardiac filling pressure. This in turn impedes the venous return from the brain leading to increased intracranial pressure[1]. It is possible that obese patients may have decreased mobility and increased effort in performing daily activities due to their heavy weight. Hence on vigorous or stressful motion, they may experience transient hypertension characterized by increased intra-abdominal and intra-thoracic pressure. Furthermore, the act of stooping forward while trying to recover from strenuous activity may result in increased intracranial pressure. A study of eight morbidly obese women has shown that surgically induced weight loss resulted in reduced CSF pressures[28]. However, one of our patients had a normal BMI of 23.3 and was diagnosed at age 71, which contradicts this visible trend in our series. It may be possible that the patient mentioned here had significant age related bony erosion.

In addition to the previous postulated aetiologies, we postulate that continuous straining during childbirth, chronic cough, forceful sneezing may attribute to sudden extreme bouts of increased intracranial pressure, which can result in a dural tear. A dural tear accompanied with a pre-existing bony defect can result in CSF rhinorrhoea. This observation will however require further studies.

Traditionally, frontal craniotomies have been used to manage spontaneous CSF leaks with a success rate of 60-80% but this has been associated with significant morbidity such as frontal lobe retraction and anosmia. The transnasal endoscopic approach to CSF leak repair has a success rate of 76%-95% with minimal morbidity, decreased recovery time, preservation of olfaction, and the possibility of revision by the same route proving to be the treatment of choice [6, 8, 29-31]. At this centre, the technique includes the bath plug technique where fat is harvested from the ear lobe or sub-umbilical region and is introduced, with vicryl into the intradural space usually used when the defects are smaller than 15mm. The middle turbinate is used either as a graft or free flap to stabilize and reinforce the repair [19].

Looking retrospectively at the three patients who had recurrent leaks, one patient had BIH and ESS whose leak recurred after seven years, one patient had symptoms of increased intracranial pressure and another had BMI of 32.9 with no symptoms of increased ICP, both recurrences occurred within 2 years of the first surgery. From here we can postulate that the recurrences may be attributable to new leaks caused by uncontrolled ICP or further bony erosion as a result of aging. Another observation is that in the two cases of recurrence, the bath plug technique with middle turbinate grafts was used. Unfortunately, due to the limited information in the written records of the patients, we could not access the details of the revision surgeries, intracranial pressures and further findings in the case of new leaks.

Conclusion

Our study suggests that spontaneous CSF rhinorrhoea is more common in women in their 40s with BMI > 25. This observation tallies with the evidence in the current available literature. Further studies on specific demographics will be required to have a better picture on the prevalence of spontaneous leaks in our population. If radiological imaging has negative findings, intrathecal fluorescein is an effective means of confirming and localizing the site of the CSF leak. The most common sites of CSF leaks are the cribriform plate followed by the sphenoid sinus.

Declaration

There is no known conflict of interest

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Editing and approval of final draft: Y. W. Tan, B. S. Gendeh , R. A. O'Connell, S Husain,

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