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"Handle a book as a bee does a flower, extract its sweetness but do not damage it."

John Muir (1838 – 1914)
American environmentalist

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Editorial

The End of Acquired Immunodeficiency Syndrome (AIDS) in Singapore – Are We There Yet?

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World AIDS (acquired immunodeficiency syndrome) Day was first commemorated in 1988. It has since taken place on 1 December annually, and is a reminder of the ongoing challenges faced by persons living with human immunodeficiency virus (HIV) and their care providers. Over the years, the landscape of HIV worldwide has changed dramatically with the availability of effective antiretroviral therapy (ART) and widespread use of evidence-based preventative measures. Today, the diagnosis of HIV is no longer the death sentence that it was once thought to be, as persons living with HIV on effective ART who are virologically suppressed have a life expectancy comparable to those without the virus.[1]

In 2014, the United Nations proposed an ambitious 90-90-90 treatment target—that by the year 2020, 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained ART, and 90% of all people receiving ART will have complete viral suppression.[2] This has galvanised considerable political will and roused communities into action in the quest to end AIDS. At the most recent 9th International AIDS Society Conference on HIV Science, Joint United Nations Programme on HIV and AIDS (UNAIDS) Executive Director Michel Sidibé reported strong progress globally with more than half of all persons living with HIV on treatment.[3] The state of HIV epidemic in Singapore is not so clear despite outstanding HIV care in our public and private healthcare institutions and the widespread availability of almost the entire range of state-of-the-art testing and treatment options.

The first case of HIV reported in Singapore was in 1985. Since then, the number of reported HIV diagnoses initially rapidly increased, only plateauing over the recent decade.[4] The Ministry of Health (MOH) reported that in 2016, there were 408 new cases reported—a reduction in number compared to previous years.[5] Despite this reassuring statistic, what remains troubling is that 40% of these patients had late-stage HIV infection, and the majority of these infections were diagnosed in heterosexual men in the course of medical provision—in other words when they were already ill with opportunistic infections.[5] The same report noted that only 5% of heterosexual men with HIV were detected through voluntary HIV screening programmes. Typically, patients infected with HIV take up to 8 to 10 years to present with symptoms of opportunistic infections. Recently, it was found that older age, lower socioeconomic income status and having sex workers and social escorts as sexual partners were epidemiological risk factors for late-stage HIV diagnosis in Singapore.[6] This group is hard to reach with voluntary screening programmes. Thus, the reported figures for HIV infections in heterosexuals in Singapore may actually represent only the tip of the iceberg of the current HIV epidemic in heterosexuals.

This possibility is supported by data on the rate of undiagnosed HIV in Singapore from seroprevalence studies. Locally, 2 sentinel populations have been monitored through unlinked anonymous testing. Discarded blood from patients with sexually transmitted infections (STIs) attending the Department of STI Control clinic and from inpatients at a tertiary restructured hospital (not known to be infected) were tested anonymously for HIV. Comparing data from 2014 and 2015, the HIV seroprevalence among STI attendees had risen from 1.2% to 1.5%,[4]—both figures are considerably higher than the 1.0% figure reported at the beginning of the millennium. The corresponding figures for adult inpatients were 0.9% in 2014 and 0.5% in 2015, again both higher than the 0.2% in 2000. These figures are a reminder of the importance of increasing testing to better understand the state of the epidemic here and improve care for our patients.

The benefit of early initiation of ART, regardless of immune status (i.e. CD4 count) is now universally accepted and part of all World Health Organization (WHO) recommendations to improve patient outcomes. The effectiveness of ART in preventing transmission of the virus, where "undetectable equals untransmittable",[7] also highlights the critical importance of early diagnosis and ART initiation if we are to end the HIV epidemic. We can only achieve this through increased awareness of individuals at risk, improving access to testing, and public education on the natural history of disease. We have to remind the

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public that persons may be asymptomatic in early stages of the illness, and also that if they are treated when they are still asymptomatic, they may actually never become symptomatic and live normal lives.

The stigma and discrimination faced by persons living with HIV are often cited as reasons for fear of coming forward for testing. Anonymous testing has mitigated some of this stigma, and is currently available at several healthcare providers regulated by the MOH locally. Action for AIDS, a pioneer in the field of anonymous testing in Singapore, even has mobile vans which bring testing to the community on a regular basis. Despite greater access to testing, at the moment no ART are included in any of the MOH standard drugs lists. This means that patients with HIV who are financially needy are required to undergo means testing for medication assistance fund subsidies and Medifund assistance. This is unique for any class of drugs on the WHO's standard drug lists. This is in contrast to other countries such as Denmark and Taiwan with universal healthcare models, in which citizens are given free access to ART, that has contributed to the control of the HIV epidemic.[8,9] It will take greater advocacy for policies to change in order to be able to treat more and test more.

Understanding socio-behavioural factors driving the epidemic locally is also going to be critical. In recent years, young men who have sex with men (MSM) have come into the spotlight as key drivers of the HIV epidemic worldwide. In Asia and the Pacific region, HIV prevalence among MSM in 2015 was higher than 5% in 9 of the 19 countries that reported data.[10] The ease of travel between countries in the region given our geographic interconnectivity and socioeconomic intimacy provides fertile ground for the HIV infection to cross borders. In 2014, a molecular epidemiological study that investigated the outbreak of a novel strain of HIV among MSM in Malaysia was traced back to a heterosexual Malaysian living in Singapore.[11] This underscores the fact that greater collaborative effort with our regional counterparts is crucial if we want to make the end of AIDS a reality in Singapore.

How have we done well? The local climate of fear towards HIV has improved somewhat. Healthcare workers (HCWs) infected with blood-borne viruses, including HIV, were once restricted from all patient contact for fear of risk of transmission. Under the latest MOH regulations, these HCWs may now be offered employment or specialty training positions, as long as they do not perform exposure-prone procedures that could result in patient exposure to the HCW's blood or body fluids.[12] The quiet lifting of the travel ban on foreigners with HIV entering Singapore on short-term visit passes is a small but significant move towards removing the discrimination that persons with HIV face.[13] There is still some way to go in creating a more inclusive society that will remove any apprehension that persons with HIV may have in seeking treatment. In a world without AIDS, there will be widespread acknowledgement that persons living with HIV are indeed our fellow residents with the same dreams, aspirations and rights as the rest of the population.

The struggle towards the end of the HIV epidemic in Singapore is clearly not won and despite the considerable successes that have been notched up by both public health and infectious diseases practitioners over the years, there is still much work to be done. Hopefully there will be a time in the not too distant future, when we may speak with our children about how we used to commemorate the 1st of December, as AIDS would have become a disease of the past.

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Original Article

Malignant Hyperthermia and *Ryanodine Receptor Type 1* Gene (*RyR1*) Mutation in a Family in Singapore

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Abstract

Introduction: Sporadic clinical episodes of malignant hyperthermia (MH) that develop during general anaesthesia (GA) have been reported in Singapore. However, there is no published local report of a confirmed case of MH susceptibility (MHS) by skeletal muscle contracture tests and/or molecular tests. Materials and Methods: We report 2 patients from an extended family who developed signs of clinical MH while under GA. The MH episodes were successfully treated with intravenous dantrolene sodium. Sequence analysis of the entire *Ryanodine Receptor Type 1* (*RyR1*) coding gene was carried out in an index patient. Results: The index patient was found to carry a c.7373G>A (p.Arg2458His) mutation in exon 46. This particular mutation satisfies the criteria for a MHS causative mutation. Hence, the index patient was considered to be MHS and did not need to undergo further muscle contracture testing. The same mutation was also found in 3 other members of his extended family. Conclusion: This is the first report of a Singaporean family with at least 4 members carrying a MH-causative mutation in *RyR1* gene. This report serves to highlight the existence of the putative gene for MH in Singapore, and the need for clinical vigilance during anaesthesia involving the use of triggering agents.

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Key words: Dantrolene, Inhalational agent, Suxamethonium

Malignant hyperthermia susceptibility (MHS) is a pharmacogenetic disorder, which usually develops during or immediately after the application of general anaesthesia (GA) involving volatile agents (e.g. halothane, isoflurane, sevoflurane, desflurane, and enflurane) and/or the depolarising muscle relaxant suxamethonium. The classic malignant hyperthermia (MH) crisis consists of a hyper-metabolic state caused primarily by continued activation of the skeletal muscles, which leads to massive carbon dioxide (CO_2) production, skeletal muscle rigidity, tachyarrhythmias, unstable haemodynamics, respiratory acidosis, cyanosis, hyperkalaemia, lactic acidosis, fever, and eventual (if untreated) death.[1] The estimated incidence of MHS ranges from 1 in 3000 anaesthetics to 1 in 50,000 anaesthetics, with most estimating an incidence in children of about 1 in 10,000 anaesthetics and in adults of 1 in 50,000 anaesthetics.[2] The incidence of MHS varies depending on the routine use of triggering anaesthetics, as well as the prevalence of susceptibility mutations in the population. For example, Monnier et al and Ibarra et al's analyses of individuals with homozygous or compound heterozygous mutations yielded an estimated MHS prevalence as high as 1 in 2000 to 3000 in the French and Japanese populations, respectively.[3,4]

The incidence of MHS in Singapore is unknown, although sporadic clinical MH cases have been reported.[5,6] The standard diagnostic test for MHS has been the in vitro measurement of contracture response of freshly biopsied muscle to graded concentrations of caffeine and the anaesthetic halothane. The test is referred to as the caffeine/halothane contracture test (CHCT) in North America[7] and the in vitro contracture test (IVCT) in Europe.[8] The test is currently not available in Singapore.

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MHS is an autosomal dominant myopathy; its pathophysiology has been attributed to calcium (Ca^{2+}) dysregulation within the myofibrils. To date, mutation in two genes predisposing to MHS have been identified; the *ryanodine receptor type 1* gene (*RyR1*), encoding the skeletal muscle isoform of the Ca^{2+} release channel of the sarcoplasmic reticulum;[9] and the *voltage-gated calcium channel subunit alpha1 S* (*CACNA1S*), encoding the α1 subunit of the L-type Ca^{2+} channel isoform of the sarcolemma (dihydropyridine receptor).[10] Pathogenic variants in *RyR1* have been identified in up to 70%-80% of individuals with confirmed MHS,[11,12] while pathogenic variants in *CACNA1S* account for only 1% of all MHS.[13] Although more than 200 *RyR1* variants have been associated with MHS, only 35 have been shown to have functional effects consistent with MH pathogenicity.[14]

We report a Singaporean family with 4 members carrying a MH-causative mutation in *RyR1*; 2 of them had developed a clinical MH episode each. Prior to clinical assessment and genetic testing, written informed consent was obtained from the index patient (proband), and members of his family.

Case Report 1

Our index patient is a 20-year-old healthy Chinese male (American Society of Anesthesiologists physical status I) who was a full-time National Service personnel. He was admitted for open reduction and internal fixation of a fracture of his left lower radius following a motorcycle accident. Preoperative assessment revealed no physical abnormalities and he was serving combat duty in his army unit. The index patient was unaware of any significant medical history among his family members, and he opted for general anaesthesia (GA). General anaesthetics consisting of intravenous (IV) propofol and fentanyl for induction, followed by desflurane in an oxygen-air mixture were administered via a laryngeal mask airway (LMA) (Proseal®) for maintenance. The patient's lungs were mechanically ventilated to keep the end-tidal carbon dioxide (CO_2) between 35 to 45 mmHg. The patient also received 2 grams of IV cefazolin for prophylaxis prior to the start of surgery.

Monitoring during GA included electrocardiogram (lead II), non-invasive blood pressure monitor, pulse oximetry, end-tidal CO_2 ($ETCO_2$), and an esophageal temperature probe. The patient's $ETCO_2$ was noted to be gradually increasing about 40 minutes into the surgical procedure (from 36 to 90 mmHg). The set respiratory rate of the mechanical ventilator was increased, and the breathing circuit (circle system) and the CO_2 absorber were checked to exclude machine malfunction or exhaustion of the CO_2 absorber. There was no increase in the temperature (36.5°C) and he was haemodynamically stable. The warm air administrating device was switched off. An arterial blood gas was obtained and this confirmed hypercapnia and respiratory acidosis (pH 7.14, $PaCO_2$ 87.8 mmHg, BE-3, bicarbonate 28.9 mmol/L). A provisional diagnosis of clinical MH was made and the surgeon was informed to abort the surgical procedure, and to complete the wound closure as soon as possible.

MH treatment protocol was activated. This included asking for help and the MH cart. One person was designated to dilute dantrolene sodium (Dantrium® DSM Pharmaceuticals), and arrangements were made to bring in a stand-by anaesthesia machine and to commence surface cooling with ice packs. The $ETCO_2$ and $PaCO_2$ decreased within 10 to 15 minutes after the administration of IV dantrolene (2.5 mg/kg). Blood samples were dispatched for electrolytes, creatine kinase (CK), and thyroid screening panel. The bladder was catheterised to monitor urine output and a urine sample was also sent for myoglobin. All the blood results were within normal limits including repeated CK levels over the next 2 days (293→317→291 [normal range 30-350 U/L]).

The patient was monitored in the surgical intensive care unit (ICU) for the first 24 hours and subsequently in the high dependency unit for the next 24 hours before being discharged to the general ward. He was discharged on the fifth postoperative day and was reviewed by one of the authors (LTL) a week later. The patient was well apart from complaining of a feeling of general weakness as well as a heavy feeling in his head.

The patient was readmitted 4 weeks later to complete the surgery under a brachial plexus block. He made an uneventful recovery from the anaesthesia and surgery—no dantrolene prophylaxis was given for the second operation. Arrangements were made for the patient to be registered with the 'Medik Awas' programme (a local medical alert registry) with the Singapore Medical Association. A letter was issued to the patient and the Ministry of Defence was also notified.

Case Report 2

While the patient was being monitored in the ICU, he was visited by his mother who told us that the patient's paternal grandmother had an "anaesthetic reaction" some years ago while undergoing surgery and anaesthesia in another hospital. We interviewed the patient's grandmother and obtained written informed consent to trace her medical records.

The patient's grandmother had an uneventful coronary bypass surgery (CABG) performed for triple vessel coronary artery disease in 2009. Isoflurane was administered as part of the GA for about 1 hour (end-tidal [ET] concentration

ranged from 0.3%-1.15%) before the patient was put on cardiopulmonary bypass (CPB) for about 30 minutes. After the CPB, the patient's ET concentration ranged from 0.4%-0.45%. Her postoperative recovery following the CABG procedure was uneventful. The patient subsequently underwent an elective surgery for left eye strabismus under GA in 2011. Sevoflurane in an oxygen-air mixture was administered via an endotracheal tube and the patient's $ETCO_2$ was noted to rise about 30 minutes after induction of GA from 40 to 90 mmHg. There was no mention of temperature monitoring in the chart. The operation was aborted and the patient was also given IV dantrolene sodium (3 mg/kg). She made an uneventful recovery. She was given a letter by the Department of Anaesthesia to alert her healthcare providers to avoid giving her volatile agents or depolarising muscle relaxant. Her blood CK levels done during the clinical MH episode were mildly raised (212→221→253 U/L [normal 40-200 U/L]), and myoglobin was detected in her urine (113→73.4→47.1→49 µg/L [normal <21 µg/L]). A repeat CK level performed 5 months after the MH episode was reported as 400 U/L.

Identification of *RyR1* Mutation

As muscle contracture tests are not available in Singapore, and the patient was unwilling to undergo the test in an overseas centre at his own expense, we proceeded to perform *RyR1* full gene sequencing after obtaining written informed consent from our index patient. The genetic test was carried out at the Emory Genetic Laboratory in Georgia, United States of America (USA). Sequence analysis of the entire *RyR1* coding gene identified a c.7373G>A (p.Arg2458His) mutation in exon 46. This mutation has been previously reported in patients with MHS.[15-18] This missense mutation, involving a substitution of arginine to histidine, is predicted to be deleterious or possibly damaging to protein function by computational tools (SIFT score 0 and PolyPhen2 score 0.987). This gain-of-function mutation (c.7373G>A p.Arg2458His), as well as other mutations located in the similar hotspot Region II of the *RyR1* gene, have been shown to cause aberrations in *RyR1* channel function (such as hyper-activation of the channel by, and hyper-sensitisation of the channel to, various physiological and pharmacological agonists, resulting in a leaky Ca^{2+} channel).[18-20] After obtaining written informed consents, blood tests for the same *RyR1* mutation were carried out for his father and paternal grandmother by the same laboratory, which also turned out to be positive. The grandmother's daughter and siblings were interviewed by 2 of the authors (DWYL and LTL), and the same mutation (c.7373G>A [p.Arg2458His]) was also found in one of the proband's paternal grand aunt (Fig.1). The rest of the family members

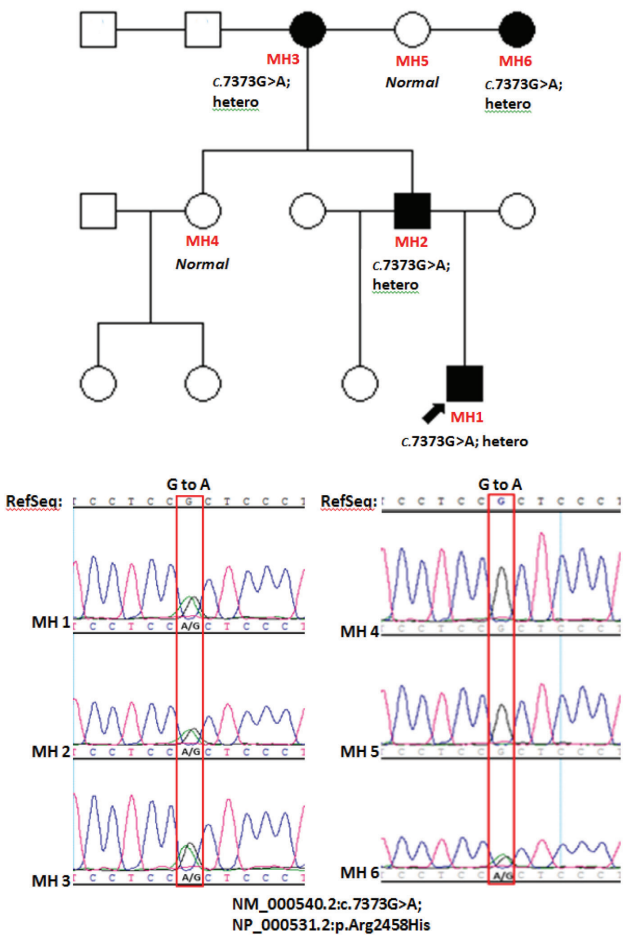

Fig. 1. Family pedigree and *RyR1* mutation analysis. Female and male individuals are represented by round and square symbols respectively. The index patient (proband) is indicated with an arrow. Individual with *RyR1* causal mutation is represented by a full black symbol.

were not willing to undergo the genetic testing. Tests for the specific *RyR1* mutation for 3 family members were carried out at the Human Genetics Laboratory of the Department of Paediatrics at the National University of Singapore.

Discussion

This is the first reported case of MH with a causative *RyR1* mutation, and the first report of multiple members within the same family carrying the same mutated *RyR1* in Singapore.

MHS is a potentially fatal pharmacogenetic disorder; therefore confirmation of the diagnosis is important to prevent the patient and any affected family members from any future exposure to triggering agents. A confirmed diagnosis will also facilitate genetic counselling and may also affect career choices. For example, the military service

of the USA does not enlist individuals with MHS.[21] Cases of "awake" MH episodes during exertion, heat challenge, and febrile illness in the absence of triggering drugs have been reported.[22-24] These reports show that non-anaesthetic awake episodes induced by heat stress and MH share some clinical (muscle hypermetabolism) and biological (positive in vitro contracture test) features, however, the underlying molecular cause of non-anaesthetic awake MH is not fully established, although novel mutations in the *RyR1* have recently been identified in 2 unrelated children who experienced fatal, non-anaesthetic awake episodes associated heat stress, and in 13% of a military cohort who had a well documented exertional heat stroke crisis.[25,26] Our index patient (Case 1) was still serving his national service commitment in the army when the MH event occurred. However, he had been coping well with his military training.

Although MHS is considered a form of myopathy, except for a few congenital myopathies with a strong association with MH (e.g. King-Denboroug syndrome, and central core disease), the majority of the MHS patients display no symptoms/signs of myopathy until they are exposed to triggering agents (Cases 1 and 2). MHS is a pharmacogenetic disorder of autosomal dominant inheritance (as illustrated in this family, Fig. 1) with incomplete penetrance and variable expressivity (e.g. Case 2). The variability in clinical MH responses can be attributed to some as yet unidentified environmental factors, and the different *RyR1* variants present in the affected individual.[16] The moderate hypothermia (28°C) used as part of the CPB procedure during the CABG surgery could have masked/aborted the MH reaction in Case 2. It is worth noting that our index patient is a young male and therefore has a bigger muscle mass compared to his grandmother. However, his CK levels were not elevated during and after the MH episode, while his grandmother's CK levels were only mildly elevated. The lack of a significant rise in CK levels could be attributed to the early detection and early administration of dantrolene. In addition, it has been shown that different *RyR1* variants are associated with quantitative differences in MH phenotype including the CK levels.[16] It is fortunate that both cases were identified at an early stage when the $ETCO_2$ levels were rapidly rising due to hyper-metabolism, and were successfully treated with adequate doses of dantrolene. It has been shown that the likelihood of any complication increased 2.9 times per 2°C increase in maximum temperature and 1.6 times per 30-minute delay in dantrolene use.[27]

In addition to exposure to GA, situations in which a MHS patient is likely to receive a MH triggering agent would include the emergency room or ICU, where clinicians may use the depolarising muscle relaxant suxamethonium to facilitate tracheal intubation during emergent airway management. Suxamethonium should be avoided in favour of a non-depolarising muscle relaxant such as rocuronium in a MHS patient. Clinicians who use suxamethonium in their clinical practice should be familiar with the early signs of MH, MH crisis management protocol, and ensure the availability of dantrolene to treat MH crisis. Current literature does not support the use of dantrolene prophylaxis to prevent MH crisis.

As many early signs of MH episodes present in a variable manner, a clinical grading scale (CGS) has been developed to address concerns for objectivity evaluation of the clinical MH episode.[28] However, this scale lacks sensitivity because incomplete recording of necessary data or early termination of the crisis (e.g. Cases 1 and 2) would not yield scores indicative of MH, even in the presence of a true MH episode. The CGS was not intended to be a clinical guide in the operating room but to assist MH researchers in classifying adverse events and help to identify those subjects with the most convincing episodes of MH for subsequent evaluation of the sensitivity of the diagnostic tests.[28] The CGS calculated retrospectively for our index patient (Case 1) was 20 points, based on an inappropriate rise in the $ETCO_2$ (15 points), and a rapid reversal of the respiratory acidosis with IV dantrolene (5 points). A raw score of 20 points will yield a MH rank of 4 (i.e. the qualitative likelihood of MH is somewhat greater than likely).

In vitro muscle contracture test is currently considered the gold standard to establish the diagnosis of MHS. A sensitivity of 97% and specificity of 78% are reported for the North America Malignant Hyperthermia Group (NAMHG) protocol while figures of 99% sensitivity and 94 % specificity are obtained with the European Malignant Hyperthermia Group (EMHG) protocol.[7,8] In addition to cost, the individual must be physically present at an overseas MH diagnostic centre as the test involves a muscle biopsy usually from the vastus muscle group, and has to be carried out within 5 hours of harvesting. It is usually carried out 3 to 6 months after the clinical MH episode depending on the degree of rhabdomyolysis, and hence may not be suitable for someone who is waiting for an urgent surgery (e.g. fracture).

Since the identification of the 2 MH causative genes (*RyR1* and *CACNA1S*),[9,10] deoxyribonucleic acid (DNA) analysis offers an alternative to the muscle contracture test. Both the NAMHG and EMHG currently consider DNA screening to be a viable alternative primary diagnostic approach to the muscle contracture test, although limited to a positive diagnosis and to those few mutations that have been functionally characterised.[29,30] It is important to note that because of the heterogeneity of the disorder, as well as discordance within families, a negative DNA result cannot be used to rule out MHS and a muscle contracture test is recommended where a DNA test is negative for a familial mutation.[29,30] The test requires only a blood specimen, which

can be sent to an accredited diagnostic laboratory, and it can be performed on patients of all age groups. When a causative mutation is found on *RyR1* sequence analysis, first-degree relatives can be tested for the identified mutation with reduced cost. Our index patient was found to have a causative *RyR1* mutation (c.7373G>A [p.Arg2458His]). As this particular mutation (1 of the 35 causative mutations published to-date) satisfies the criteria for a MHS causative mutation,[14-16] our index patient is considered to be MHS and he did not need to undergo any further muscle contracture testing. The same causative *RyR1* mutation was subsequently found in 3 other members of his extended family (Fig. 1), therefore, these 3 family members are also considered MHS without any need for IVCT/CHCT.

We counselled the family members to encourage their first-degree relatives to test for the familial causative *RyR1* variant. If an individual does not have the familial *RyR1* variant, the entire *RyR1* should be examined and IVCT/CHCT performed in an overseas MH diagnostic biopsy centre to rule out MHS. This is because more than one gene is associated with MHS, and not all are known. Furthermore, the IVCT/CHCT is the only test that can produce a true negative diagnosis. MH diagnostic biopsy centres will also provide professional genetic counsellors to better advise patients on their test results.[31-33] In the meantime, relatives who have tested negative for the familial variant or who are unwilling to be tested are advised to inform their doctors and anaesthetists that their MHS status is unknown, and it would be best to avoid administering triggering agents to these patients.

The incidence of MHS in Singapore is unknown. An e-mail survey conducted by one of the authors (LTL) with Heads of Department/Clinical Directors of all the Department of Anaesthesia in Singapore (excluding private practice) gave an estimate of approximately 1 clinical MH episode per 100,000 general anaesthetics, which is lower than what is generally quoted in anaesthetic literature. The low incidence will hamper the setting up of a local MH registry and MH diagnostic centre, however, we can explore the possibility of establishing an Asian MH referral centre in the future. At the moment, suspected clinical MH cases will need to be referred to an overseas MH diagnostic centre for the muscle contracture test. The low incidence of the condition could partly be due to under-diagnosis arising from lack of awareness and lack of availability of local testing facilities. Although genetic testing is less invasive than a muscle contracture test, clinical testing currently has to be sent overseas due to a lack of accredited local laboratories offering such services. Diagnostic testing for this condition using DNA screening also has its limitations—bearing in mind that the sensitivity of detecting a *RyR1* causative mutation is only about 40% in someone without a prior positive muscle contracture test.[34] This report serves to remind clinicians of the existence of this uncommon and potentially fatal condition within our community. Anaesthetists should remain vigilant and be trained to recognise this clinical condition early and to treat the condition in a timely manner.

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Original Article

Reliability and Validity of the English-, Chinese- and Malay-Language Versions of the World Health Organization Quality of Life (WHOQOL-BREF) Questionnaire in Singapore

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Abstract

Introduction: The World Health Organization Quality of Life (WHOQOL-BREF) questionnaire is a 26-item questionnaire that evaluates 4 domains of quality of life (QoL), namely Physical, Psychological, Social Relationships and Environment. This study aimed to evaluate the validity and reliability of the WHOQOL-BREF among Singapore residents aged 21 and above. Materials and Methods: We recruited participants from the general population by using multistage cluster sampling and participants from 2 hospitals by using convenience sampling. Participants completed either English, Chinese or Malay versions of the WHOQOL-BREF and the EuroQoL 5 Dimension 5 Levels (EQ-5D-5L) questionnaires. Confirmatory factor analysis, known-group validity, internal consistency (Cronbach's alpha) and test-retest reliability using the intraclass correlation coefficient (ICC) were performed. Results: Data from 1316 participants were analysed (Chinese: 46.9%, Malay: 41.0% and Indian: 11.7%; 57.5% men, mean standard deviation [SD, range] age: 51.9 [15.68, 24 to 90] years); 154 participants took part in the retest in various languages (English: 60, Chinese: 49 and Malay: 45). Tucker-Lewis Index (TLI) was 0.919, 0.913 and 0.909 for the English, Chinese and Malay versions, respectively. Standardised root mean square residual (SRMR) was 0.067, 0.074 and 0.094, respectively. Cronbach's alpha exceeded 0.7 and ICC exceeded 0.4 for all domains in all language versions. Conclusion: The WHOQOL-BREF is valid and reliable for assessing QoL in Singapore. Model fit is reasonable with room for improvement.

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Key words: Health-related quality of life, Linking values, Mapping functions, Patient-reported outcomes, Preference-based measures

Introduction

Health-related quality of life (HRQoL) is a multidimensional concept that describes the aspects pertaining to health. It is generally agreed that HRQoL assesses the well-being and functioning of an individual, comprising physical and emotional aspects while opinions are divided as to whether it should also include the individual's social aspects.[1] HRQoL is increasingly recognised as an important measure of patient-reported outcomes and treatment efficacy, and requires reliable assessment tools that demonstrate reliability and validity for a specific patient population.[2]

The World Health Organization Quality of Life (WHOQOL-BREF) questionnaire—an abbreviated version of the WHOQOL-100 test—was designed for studies that require a brief assessment of quality of life (QoL), such as epidemiological studies, clinical trials and routine clinical work.[3,4] It was also designed as a cross-cultural

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questionnaire, and has since been used in a large number of countries across various continents including Africa,[5,6] South America,[7] Europe,[6,8-10] Oceania[11] and Asia.[12-16] Even though the WHOQOL-BREF was designed as a cross-cultural questionnaire, Singapore was not one of the 20 centres in 18 countries involved in its development.[3] As Singapore has a multiethnic population that uses several languages, the psychometric properties of the WHOQOL-BREF test need to be evaluated to suit the Singaporean population. The Chinese version of the WHOQOL-BREF, for instance, was tested in Mainland China, Taiwan and Hong Kong.[12,14,15] Fortunately, the factor structure of the WHOQOL-BREF was replicated in all 3 Chinese-speaking populations. However, there were previous studies which reported that the factor structure of the WHOQOL-BREF may not be replicable in some populations. For example, in a study that evaluated the factor structure of the Spanish version of the WHOQOL-BREF across 9 Spanish-speaking countries, it was reported that the model fit statistics from the confirmatory factor analysis were poor for most of the countries.[17] The WHOQOL-BREF has previously been used in Singapore,[18] on a separate sample of patients with schizophrenia and on a sample of patients with diabetes mellitus.[19] It has not been used in the general population. Furthermore, the study among patients with schizophrenia did not evaluate the psychometric properties of the WHOQOL-BREF. Hence, this study aimed to determine the validity and reliability of the WHOQOL-BREF for assessing HRQoL in 3 languages – English, Chinese, and Malay – in a multiethnic Singaporean population.

Materials and Methods

Participants and Study Design

Singapore is a multiethnic society, comprising 3 main ethnic groups – Chinese, Malays and Indians. This study encompasses participants from the general population as well as 2 clinic samples. Ethics approval for this study was obtained from the National Healthcare Group Domain Specific Review Board (Ref. 2013/00747) and the SingHealth Centralised Institutional Review Board (Ref. 2015/2041). Participants provided written informed consent. Participants from the general population were recruited based on a multistage cluster sampling method using postcodes as the primary sampling unit (PSU), followed by the selection of households and then the selection of respondents. Three call attempts (1st attempt and 2 callbacks) were made at different days and times of the week. Contacted participants of each household residing in public housing (i.e. high rise flats built by the government) were selected based on a prespecified quota for language of interviews, age and gender within each ethnic group. More than 80% of Singaporeans reside in public housing. A list of potential households was selected using a sampling frame maintained by the survey company engaged to conduct this survey. The face-to-face interviews were conducted in the participants' homes between October 2014 and January 2015. A subset of participants was revisited within 2 weeks for assessment of test-retest reliability. The interviewers were trained in survey data collection and were effectively bilingual in English and Mother Tongue (i.e. Chinese or Malay). We paired interviewers and participants by ethnicity to improve response rate. For example, Malay interviewers would be given a list of Malay households to follow-up with.

The clinic samples were chosen to enrich the dataset, such that a wider spread of health status was represented. The clinic participants were drawn from two separate studies in outpatient clinics at the National Heart Centre Singapore (NHCS) and the Division of Endocrinology at the National University Hospital (NUH). Recruitment was conducted by research assistants via convenience sampling in the clinics while patients were waiting to see the doctor. Patients with recent acute myocardial infarction (STEMI), haemodynamic instability or gestational diabetes were excluded. Interviews were carried out between March 2015 and February 2016.

In both the general population and clinic samples, an eligible participant had to be a Singapore resident aged 21 years and above who spoke English, Chinese (Mandarin) or Malay. Participants who spoke only Tamil were excluded as the questionnaires were not available in Tamil. All participants read and signed the written informed consent form prior to commencement of the interviews.

Questionnaires

The WHOQOL-BREF and EuroQoL 5 Dimension 5 Levels (EQ-5D-5L) questionnaires were used, in addition to a socioeconomic and clinical questionnaire to capture information such as age, gender, ethnicity and self-reported medical conditions. For the Chinese version of the questionnaires, simplified Chinese was used.

WHOQOL-BREF

The WHOQOL-BREF is a subjective evaluation of individuals' perceptions of their positions in life, in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[4] It is not equivalent to a health status measure such as the EQ-5D-5L. The WHOQOL-BREF is a 26-item questionnaire that includes 1 item from each of the 24 facets contained in the WHOQOL-100 and 2 additional items on overall quality of life and general health. The 24 items are organised into 4 domains, namely WHOQOL-BREF Physical (WHO-PHY), Psychological (WHO-PSY), Social Relationships (WHO-SOC) and Environment (WHO-ENV). Three negatively phrased items were

reversed scored. Domain scores were computed by taking the mean of the scores of the items that constitute the domain and multiplied by 4 so that the scores were directly comparable with those derived from WHOQOL-100. Mean substitution was performed for missing data; missing item scores were replaced with the mean of the non-missing item scores in the same domain if at least 50% of the items in the domain were non-missing. The English and Chinese versions of WHOQOL-BREF were obtained from the WHO website while the Malay (Malaysian) version was obtained from the authors of a Malay study.[20]

EQ-5D-5L

The EQ-5D-5L is a health status measure comprising 5 dimensions: mobility (EQ-MOB), self-care (EQ-SC), usual activities (EQ-UA), pain/discomfort (EQ-PN) and anxiety/depression (EQ-AD) with 5 response options for each dimension (no, slight, moderate, severe, extreme problems/unable).[21] Participants indicate their health status for the day by selecting 1 response option per dimension, giving rise to a 5-digit health profile, which is in turn linked with a utility score. We used the Japanese value set from the EuroQoL Group's crosswalk project as a Singapore dataset is not available.[13,22] The Japanese value set has a possible range of -0.111 to 1. Participants with missing data were excluded from analysis.

Statistical Analyses

We conducted confirmatory factor analysis (CFA) with ordered categorical factor indicators using a robust weighted least squares estimator (WLSMV) with a diagonal weight matrix in MPlus 8.0 (Muthén & Muthén, California, USA). The raw WHOQOL-BREF item scores were used for this purpose and items with missing responses were deleted listwise. The model structure was defined in 2 ways: first, according to the original 4-factor model and then we added a second-order factor contributed by the 4 factors. Based on the rule of thumb by Hu and Bentler,[23] we defined good model fit as a Tucker-Lewis Index (TLI) = 0.95 and standardised root mean square residual (SRMR) = 0.08.

Known-group validity was investigated with a *priori* hypotheses that differences in mean WHOQOL-BREF scale scores between individuals with and without a specific chronic medical condition will exceed half a standard deviation (SD) (rule of thumb for defining minimally important difference).[24] We limited the analyses to 5 medical conditions that had a prevalence of at least 5% across the 3 language groups: diabetes, hypertension, dyslipidaemia, heart disease and mental illness. In addition, we hypothesised that the difference in mean WHO-PHY scores between participants with and without problem on EQ-MOB as well as the difference in mean WHO-PSY scores between participants with and without problem on EQ-AD will exceed half a SD.

Two aspects of reliability were assessed: internal consistency and test-retest reliability. Internal consistency was assessed using Cronbach's alpha; test-retest reliability was assessed using intraclass correlation coefficient (ICC). Cronbach's alpha exceeding 0.7 indicates acceptable reliability for group level; 0.9 for individual level.[25] ICC was used in a subset of study participants 2 weeks after the first interview. We defined ICC <0.40 as poor; 0.40-0.59 as fair; 0.60-0.74 as good; and 0.75 and above as excellent.[26]

Results

The study included a total of 1316 participants, with 892 participants from the general population, 221 participants from NHCS and 203 participants from NUH. In terms of ethnicity, there were 617 Chinese, 539 Malays, 154 Indians and 6 Others. The English-, Chinese- and Malay-language versions were completed by 454, 443 and 419 participants, respectively.

A larger proportion of those who completed the English-language version were younger and had tertiary education compared to those who completed the Chinese- and Malay-language versions. The prevalence of high blood pressure and high cholesterol was significantly higher among those who completed the Chinese- and Malay-language versions compared to those who completed the English version, presumably because these participants were older (Table 1).

A higher proportion of participants who completed the Malay-language version lived in small (1- or 2-room) public housing. WHO-PSY scores were 3.69 points lower (P <0.001), WHO-SOC were 3.53 points lower (P <0.001) and WHO-ENV scores were 2.12 points lower (P = 0.022) for someone who completed the Chinese-language version compared to someone who completed the English-language version after adjusting for age, gender, educational level and housing type (Table 2).

We followed-up with 154 participants for retest. The number of participants analysed for the English-, Chinese- and Malay-language versions were 60, 49 and 45, respectively. Mean SD age of the participants in the retest was 39.7 years (13.51, 24.0 to 84.0), 52.7 years (13.62, 24.0 to 77.0) and 49.7 years (14.97, 24.0 to 83.0) for the English-, Chinese- and Malay-language versions, respectively. Hence, they were generally younger than those who participated in the first round of interviews.

Confirmatory Factor Analysis

In the 4-factor CFA, TLI = 0.919 and SRMR = 0.067 for the English-language version (n = 399). For the Chinese-language version (n = 367), TLI = 0.913 and SRMR =

Table 1. Characteristics of Study Participants (n = 1316)

	English Language Survey (n = 454)	Chinese Language Survey (n = 443)	Malay Language Survey (n = 419)	Pearson's Chi-Squared Statistics/ F-Statistics, Where Applicable	*P* Value
Gender, n (%)					
Male	277 (61.0)	250 (56.4)	229 (54.7)	3.89	0.143
Age group (years)					
Mean (SD, range)	49.1 (16.16, 24.0 – 90.0)	55.0 (15.33, 24.0 – 84.0)	51.8 (14.96, 24.0 – 85.0)	16.14	<0.001
21 – 29	82 (18.1)	39 (8.8)	48 (11.5)	43.44	<0.001
30 – 39	90 (19.8)	59 (13.3)	61 (14.6)		
40 – 49	80 (17.6)	76 (17.2)	82 (19.6)		
50 – 59	80 (17.6)	93 (21.0)	106 (25.3)		
60 – 69	75 (16.5)	108 (24.4)	81 (19.3)		
>70	47 (10.4)	68 (15.4)	41 (9.8)		
Ethnicity, n (%)					
Chinese	174 (38.3)	443 (100)	0 (0)		
Malay	124 (27.3)	0 (0)	415 (99.0)		
Indian	152 (33.5)	0 (0)	2 (0.5)		
Others	4 (0.9)	0 (0)	2 (0.5)		
Education, n (%)				148.54	<0.001
Primary or less	39 (8.6)	141 (31.8)	113 (27.0)		
Secondary or less	232 (51.1)	180 (40.6)	259 (61.8)		
Tertiary	183 (40.3)	122 (27.5)	47 (11.2)		
Housing, n (%)				39.93	<0.001
Smaller public	279 (61.5)	290 (65.5)	329 (78.5)		
Larger public	140 (30.8)	122 (27.5)	83 (19.8)		
Private	33 (7.3)	30 (6.8)	5 (1.2)		
Others	2 (0.4)	1 (0.2)	2 (0.5)		
Chronic medical conditions, n (%)					
Diabetes mellitus	123 (27.1)	120 (27.1)	119 (28.4)	2.87	0.580
High blood pressure	129 (28.4)	171 (38.6)	145 (34.6)	12.42	0.014
High cholesterol	84 (18.5)	118 (26.6)	94 (22.4)	8.51	0.014
Heart disease	128 (28.2)	121 (27.3)	113 (27.0)	2.08	0.721
Mental illnesses	66 (14.5)	80 (18.1)	53 (12.7)	8.40	0.078
Mean (SD, range) WHOQOL-BREF domain scores					
PHY	74.9 (15.5, 12.5 – 100)	71.7 (15.6, 7.1 – 100)	72.9 (18.0, 10.7 – 100)	4.20	0.015
PSY	72.5 (14.1, 4.2 – 100)	67.1 (15.9, 12.5 – 100)	71.0 (13.8, 16.7 – 100)	16.04	<0.001
SOC	74.0 (16.1, 0 – 100)	69.0 (13.4, 16.7 – 100)	74.1 (14.1, 33.3 – 100)	17.70	<0.001
ENV	72.0 (14.1, 18.8 – 100)	68.2 (14.6, 9.4 – 100)	69.0 (12.5, 34.4 – 100)	9.37	<0.001
Mean (SD, range) EQ-5D utility scores	0.92 (0.10, 0.25 – 1)	0.91 (0.10, 0.29 – 1)	0.91 (0.15, 0.02 – 1)	1.02	0.362

ENV: Environment; PHY: Physical; PSY: Psychological; SD: Standard deviation; SOC: Social Relationships; WHOQOL-BREF: World Health Organization Quality of Life

Table 1. Characteristics of Study Participants (n = 1316) (Cont'd)

	English Language Survey (n = 454)	Chinese Language Survey (n = 443)	Malay Language Survey (n = 419)	Pearson's Chi-Squared Statistics/ F-Statistics, Where Applicable	*P* Value
With problems on EQ-5D , n (%)					
Mobility	50 (11.0)	54 (12.2)	76 (18.1)	10.62	0.005
Self-care	11 (2.4)	4 (0.9)	20 (4.8)	12.61	0.002
Usual activities	32 (7.1)	34 (7.7)	47 (11.2)	5.53	0.063
Pain or discomfort	146 (32.2)	173 (39.1)	139 (33.2)	5.41	0.067
Anxiety or depression	108 (23.8)	111 (25.1)	73 (17.4)	8.30	0.016

ENV: Environment; PHY: Physical; PSY: Psychological; SD: Standard deviation; SOC: Social Relationships; WHOQOL-BREF: World Health Organization Quality of Life

0.074. For the Malay-language version (n = 363), TLI = 0.909 and SRMR = 0.094. In the second-order CFA, the findings were similar to those of the 4-factor CFA. That is, TLI = 0.918, 0.913 and 0.907 for the English-, Chinese- and Malay-language versions, respectively while SRMR = 0.068, 0.074 and 0.096 for the English-, Chinese- and Malay-language versions, respectively. Factor loading exceeded 0.4 for all items in the 3 language versions. For example, in the English-language version, factor loading of items ranged from 0.465 to 0.891 for WHO-PHY; from 0.543 to 0.830 for WHO-PSY; from 0.819 to 0.873 for WHO-SOC and from 0.682 to 0.798 for WHO-ENV.

Known-Group Validity

The prevalence of chronic medical conditions ranged from 14.5% (mental illness) to 28.4% (high blood pressure) among those who completed the English-language version; from 18.1% (mental illness) to 38.6% (high blood pressure) among those who completed the Chinese-language version; and 12.7% (mental illness) to 34.6% (high blood pressure) among those who completed the Malay-language version (Table 1). Apart from WHOQOL-BREF PSY (English) that did not differentiate between participants with and without heart disease (P >0.05), differences in mean scores between participants with and without a given chronic medical condition were statistically significant (Table 3).

Known-group validity of the WHOQOL-BREF domains with EQ-5D-5L was well supported with the differences in mean scores between known-groups exceeding the minimally important difference. Mean (SD) WHO-PHY score was 77.0 (13.81) for participants without problem (n = 404) versus 57.5 (17.71) for participants with any problem (n = 50) on EQ-MOB among those completing the English-language versions (P <0.001). The difference in mean scores between the two groups were 21 and 29 points with pooled standard deviations of 15.63 and 17.97 for those completing the Chinese- and Malay-language versions, respectively (P <0.001). Mean (SD) WHOQOL-BREF PSY score was 75.9 (11.69) for participants without problem (n = 346) versus 61.6 (15.48) for participants with any problem (n = 108) on EQ-AD among those completing the English-language versions (P <0.001). The difference in mean scores between the 2 groups were 17.5 and 14.4 points with pooled SD of 15.92 and 13.80 for those completing the Chinese- and Malay-language versions, respectively (P <0.001).

Table 2. WHOQOL-BREF Domain Scores after Adjusting for Age, Gender, Educational Level and Housing Type

WHOQOL-BREF Domains	Regression Coefficients (95% Confidence Interval)			
	Chinese Language	*P* Value	Malay Language	*P* Value
PHY	-0.25	0.812	0.23	0.833
PSY	-3.69	<0.001	0.14	0.894
SOC	-3.53	<0.001	1.44	0.157
ENV	-2.12	0.022	-0.92	0.337

ENV: Environment; PHY: Physical Health; PSY: Psychological; SOC: Social Relationships; WHOQOL-BREF: World Health Organization Quality of Life

Internal Consistency

For internal consistency, WHOQOL-BREF met the group-level reliability criteria (>0.7), with Cronbach's alpha values ranging from 0.82 to 0.86 across the 4 domains for the English-language version, from 0.73 to 0.85 for the Chinese-language version, and from 0.82 to 0.89 for the Malay-language version (Table 4).

Table 3. Known-Group Validity of WHOQOL-BREF Domains Based on Co-Existing Chronic Medical Conditions by Language Versions

English Language	**Has Diabetes (n = 123)**	**Has High Blood Pressure (n = 129)**	**Has High Blood Cholesterol (n = 84)**	**Has Heart Disease (n = 128)**	**Has Mental Illness (n = 66)**
WHOQOL-BREF Physical Health					
Mean (SD) domain scores	62.7 (16.87)	63.2 (16.20)	64.6 (16.14)	68.5 (15.06)	60.4 (15.60)
Mean (SE) difference	-16.6 (1.45)*§	-16.2 (1.43)*§	-12.6 (1.79)*§	-8.8 (1.57)*§	-16.8 (1.91)*§
WHOQOL-BREF Psychological					
Mean (SD) domain scores	66.4 (18.14)	65.7 (16.62)	66.6 (19.02)	71.4 (15.19)	63.6 (18.86)
Mean (SE) difference	-8.4 (1.44)‡	-9.6 (1.40)*§	-7.2 (1.67)*	-1.6 (1.47)	-10.4 (1.81)*§
WHOQOL-BREF Social Relationships					
Mean (SD) domain scores	66.2 (18.59)	65.6 (17.45)	68.4 (19.24)	70.0 (16.24)	67.4 (19.51)
Mean (SE) difference	-10.6 (1.63)*§	-11.6 (1.59)*§	-6.8 (1.92)*	-5.5 (1.67)*	-7.6 (2.12)*
WHOQOL-BREF Environment					
Mean (SD) domain scores	66.5 (16.30)	65.2 (14.54)	67.6 (17.86)	69.7 (15.34)	65.3 (16.33)
Mean (SE) difference	-7.5 (1.45)*	-9.4 (1.40)*§	-5.3 (1.70)†	-3.2 (1.47)‡	-7.7 (1.84)*
Chinese Language	**Has Diabetes (n = 120)**	**Has High Blood Pressure (n = 171)**	**Has High Blood Cholesterol (n = 118)**	**Has Heart Disease (n = 121)**	**Has Mental Illness (n = 80)**
WHOQOL-BREF Physical Health					
Mean (SD) domain scores	63.6 (14.20)	64.4 (16.35)	62.5 (15.21)	63.1 (14.49)	61.5 (16.79)
Mean (SE) difference	-11.42 (1.58)*§	-12.1 (1.41)*§	-12.6 (1.57)*§	-12.0 (1.57)*§	-12.5 (1.84)*§
WHOQOL-BREF Psychological					
Mean (SD) domain scores	60.2 (17.41)	62.2 (16.94)	60.0 (16.07)	61.5 (16.54)	62.5 (15.53)
Mean (SE) difference	-9.7 (1.63)*§	-8.2 (1.50)*§	-9.7 (1.65)*§	7.9 (1.66)*	-5.7 (1.95)†§
WHOQOL-BREF Social Relationships					
Mean (SD) domain scores	64.1 (14.896	66.2 (14.40)	64.4 (13.51)	64.5 (14.03)	66.0 (13.67)
Mean (SE) difference	-6.8 (1.39)*§	-4.6 (1.29)*	-6.3 (1.41)*	-6.3 (1.38)*	-3.6 (1.64)‡
WHOQOL-BREF Environment					
Mean (SD) domain scores	63.0 (15.13)	64.2 (15.70)	61.5 (15.18)	62.2 (15.16)	63.9 (14.27)
Mean (SE) difference	-7.4 (1.52)*	-6.7 (1.39)*§	-9.2 (1.51)*§	-8.4 (1.51)*§	-5.3 (1.79)†
Malay Language	**Has Diabetes (n = 119)**	**Has High Blood Pressure (n = 145)**	**Has High Blood Cholesterol (n = 94)**	**Has Heart Disease (n = 113)**	**Has Mental Illness (n = 53)**
WHOQOL-BREF Physical Health	108 (23.8)	111 (25.1)	73 (17.4)	8.30	0.016
Mean (SD) domain scores	58.5 (18.51)	60.0 (18.22)	56.4 (18.25)	56.9 (17.90)	54.2 (16.91)
Mean (SE) difference	-20.1 (1.68)*§	-19.7 (1.58)*§	-21.2 (1.83)*§	-21.9 (1.66)*§	-21.4 (2.43)*§
WHOQOL-BREF Psychological					
Mean (SD) domain scores	64.4 (16.58)	64.7 (14.65)	63.7 (15.34)	62.3 (15.21)	60.1 (15.14)
Mean (SE) difference	-9.3 (1.43)*§	-9.7 (1.34)*§	-9.5 (1.55)*§	-11.9 (1.40)*§	-12.5 (1.94)*§

SD: Standard deviation; SE: Standard error; WHOQOL-BREF: World Health Organization Quality of Life

*P <0.001.

†P <0.01.

‡P <0.05.

§Difference is minimally important (i.e. exceeds half a standard deviation).

Table 3. Known-Group Validity of WHOQOL-BREF Domains Based on Co-Existing Chronic Medical Conditions by Language Versions (Cont'd)

Malay Language	Has Diabetes (n = 119)	Has High Blood Pressure (n = 145)	Has High Blood Cholesterol (n = 94)	Has Heart Disease (n = 113)	Has Mental Illness (n = 53)
WHOQOL-BREF Social Relationships					
Mean (SD) domain scores	68.4 (15.75)	68.4 (13.83)	67.1 (14.87)	66.7 (14.60)	68.8 (15.92)
Mean (SE) difference	-8.0 (1.48)*	-8.7 (1.39)*§	-9.0 (1.60)*§	-10.2 (1.48)*§	-6.1 (2.06)†
WHOQOL-BREF Environment					
Mean (SD) domain scores	63.9 (13.80)	63.2 (12.66)	62.4 (12.06)	61.9 (12.05)	60.8 (12.34)
Mean (SE) difference	-7.0 (1.31)*§	-8.8 (1.21)*§	-8.5 (1.41)*§	-9.6 (1.30)*§	-9.3 (1.78)*§

SD: Standard deviation; SE: Standard error; WHOQOL-BREF: World Health Organization Quality of Life

*P <0.001.

†P <0.01.

‡P <0.05.

§Difference is minimally important (i.e. exceeds half a standard deviation).

Test-Retest Reliability

The number of participants who completed the retest in English, Chinese and Malay was 60, 49 and 45, respectively. The ICC ranged from 0.58 (fair; PSY) to 0.83 (excellent; ENV) in the English-language version (Table 4). In the Chinese-language version, ICC ranged from 0.64 (good; SR) to 0.88 (excellent; PHY). For the Malay-language version, ICC ranged from 0.58 (fair; SR) to 0.69 (good; ENV).

Discussion

This study is the first in Singapore to evaluate the WHOQOL-BREF in the English-, Chinese- and Malay-language versions. It is also one of the few studies evaluating the test-retest reliability of the WHOQOL-BREF. Two aspects of reliability were assessed: internal consistency and test-retest reliability. The WHOQOL-BREF performed well in both aspects. Where validity is concerned, the WHOQOL-BREF demonstrates known-group validity, being able to discriminate between known groups defined by chronic medical conditions as well as by responses to EQ-MOB and EQ-AD. However, results of the confirmatory factor analysis suggest that model fit does not meet the threshold. Hu and Bentler[23] suggested that a two-index presentation strategy is more effective than a single-index presentation strategy in rejecting reasonable proportions of various types of true-population and mis-specified models. On the basis of this two-index presentation strategy, the factor structure of the WHOQOL-BREF is not supported even though the threshold for good model fit is met with SRMR but not TLI. Seeing as the outcomes from SRMR and TLI did not agree with each other, it is probably due to the nature of model mis-specification. It has been suggested that SRMR is better at detecting model mis-specification related to factor covariance whereas TLI is better at detecting model mis-specification related to factor loadings.[23]

The findings of this study should be interpreted in light of its limitations. First, given that the true QoL may have changed during the 2-week interval, we may have underestimated the true test-retest reliability in this study, the extent to which is not known. Second, the WHOQOL-BREF is designed to be self-administered. We have, however, administered the questionnaire through face-to-face interviews. While we know that different modes of

Table 4. Internal Consistency and Test-Retest Reliability of the English-, Chinese- and Malay-Language Versions of the WHOQOL-BREF

	Cronbach's α	Intraclass Correlation Coefficient* (95% CI)
English-Language	n = 454	n = 60
Physical Health	0.83	0.62 (0.37 to 0.77)
Psychological	0.85	0.58 (-0.13 to 0.82)
Social Relationships	0.82	0.68 (0.46 to 0.81)
Environment	0.86	0.83 (0.72 to 0.90)
Chinese-Language	n = 443	n = 49
Physical Health	0.82	0.88 (0.79 to 0.93)
Psychological	0.85	0.67 (0.14 to 0.85)
Social Relationships	0.73	0.64 (0.37 to 0.80)
Environment	0.83	0.81 (0.66 to 0.89)
Malay-Language	n = 419	n = 45
Physical Health	0.89	0.68 (0.46 to 0.81)
Psychological	0.82	0.58 (0.06 to 0.79)
Social Relationships	0.83	0.66 (0.38 to 0.81)
Environment	0.82	0.69 (0.44 to 0.83)

CI: Confidence interval; WHOQOL-BREF: World Health Organization Quality of Life

*<0.40: poor; 0.40 to 0.59: fair; 0.60 to 0.74: good; and 0.75 and above: excellent.

All values are expressed to 2 significant figures.

administration may elicit different degrees of true responses (e.g. respondents tend to report socially desirable behaviours in face-to-face interviews),[27] the bias is consistent across all the questionnaires and does not affect the accuracy of the psychometric analyses which are largely comparative in nature. In addition, we have yet to examine measurement invariance of the WHOQOL-BREF. For example, the Taiwanese-Chinese version of the WHOQOL-BREF was reported to be equivalent between men and women and across various educational levels.[28] This should be undertaken as part of future work. Alternative analysis such as Rasch analysis may also be explored in future work.[29]

Conclusion

Based on our findings, the WHOQOL-BREF could be a useful tool for assessing HRQoL in Singapore, showing good known-group validity, high internal consistency and test-retest reliability.

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In the informed consent form, patients were informed that data collected are the property of the National University Hospital and National Heart Centre Singapore. In the event of any publication regarding this study, their identity will remain confidential.

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Unusual Clinical Presentation of Nutcracker Phenomenon

Dear Editor,

A 34-year-old female presented with progressively worsening left flank pain. The pain was initially relieved by analgesics but subsequently increased in severity and frequency. There were no complaints of haematuria, dysmenorrhoea or dyspareunia. Physical examination was essentially unremarkable with no palpable abdominal mass or pelvic varicose veins. Urinalysis suggested mild urinary tract infection.

Ultrasonography revealed mild left-sided hydronephrosis. This was further evaluated with computed tomography (CT) which demonstrated a vascular aneurysm compressing upon the left pelvi-ureteric junction (PUJ) (Fig. 1A). The initial impression was that of a large left renal artery aneurysm.

Catheter angiogram was performed with a view to treat the vascular lesion via endovascular approach. Diagnostic angiogram demonstrated no arterial abnormality. A renal venogram was acquired. It showed a venous aneurysm arising from the left renal vein (LRV), causing compression upon the left PUJ (Fig. 1B). The pressure gradient between the LRV and inferior vena cava measured approximately 5 mmHg, clinching the diagnosis of nutcracker syndrome (NCS). LRV hypertension is defined as a gradient equal or greater than 3.0 mm Hg.[1,2] However, in advanced cases where collateral circulation has formed, the pressure gradient may be normal. The increase in venous pressure within the LRV is believed to be the cause of the large venous aneurysm.

The decision was made to proceed with endovascular treatment of the venous aneurysm. "Jailing" technique was used with stent-assisted coil embolisation of the venous aneurysm. At the same time, overlapping stents were deployed into the LRV. Longer stents were not available locally and hence 2 overlapping stents were used. Post-treatment venogram showed complete occlusion of the venous aneurysm (Fig. 1C).

The patient was discharged well 2 days later and remained asymtomatic after 6 months of follow-up.

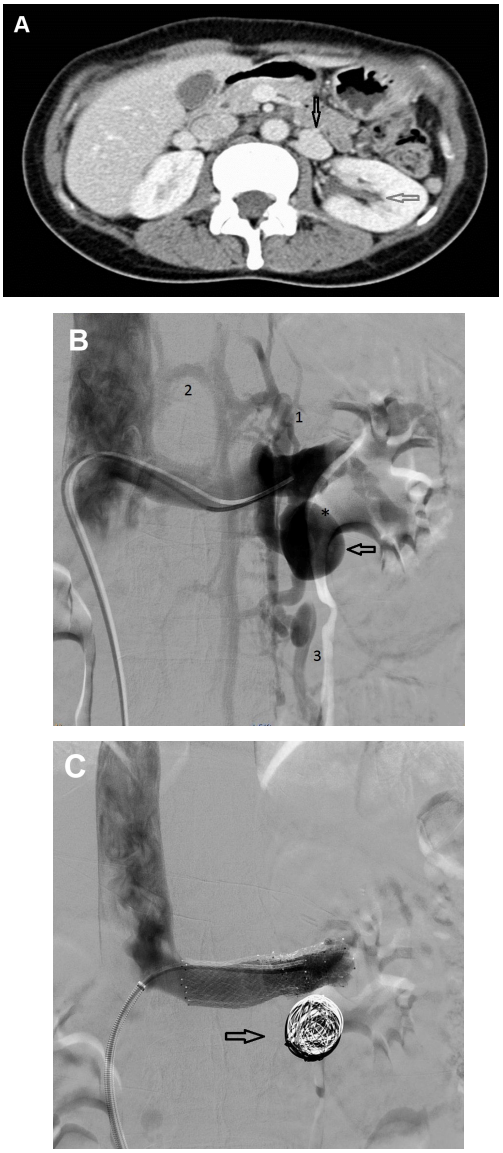

Fig 1. In A, contrast-enhanced computed tomography (CT) of the abdomen reveals a vascular aneurysm (black arrow), which compresses on the left pelvi-ureteric junction (PUJ), causing mild left hydronephrosis (grey arrow). In B, renal venogram shows a venous aneurysm (black arrow) arising from the distal left renal vein (LRV), causing compression on the left PUJ. Backflow into the hemiazygous system (1), left paravertebral venous plexus (2) and left gonadal vein (3) are noted, objective evidence of increased venous pressure (IVC). The pressure gradient between the LRV and IVC measured approximately 5 mmHg. In C, post-treatment venogram shows complete occlusion of the venous aneurysm (black arrow). In addition, satisfactory flow across the stented LRV is seen. Of note is also the absence of backflow into the LRV venous tributaries, indicative of reduced left renal venous pressure.

Discussion

Nutcracker phenomenon (NCP) is a result of LRV compression, leading to outflow impedance from the LRV into the inferior vena cava and left renal venous hypertension.[3] NCS is the clinical equivalent of NCP,

characterised by complex symptoms with substantial variations.[4] Compression of the LRV between the aorta and superior mesenteric artery (SMA), known as anterior NCP, is the most common subtype. Less commonly, a retroaortic or circumaortic renal vein may be compressed between the aorta and adjacent vertebral body, known as posterior NCP. Occasionally, the third part of the duodenum courses anterior to the LRV. Hence, anterior NCP may coexist with compression of the duodenum by SMA, known as SMA syndrome (Wilkie syndrome).

The main presenting symptom is that of haematuria, believed to be due to rupture of thin-walled varices into the collecting system, presumably induced by renal venous hypertension.[5] Patients may also present with left-sided flank pain, gonadal vein syndrome and varicocele.[5] Gonadal vein syndrome is characterised by abdominal and flank pain aggravated by sitting, standing or walking, due to pelvic venous congestion. Left flank pain may also be a consequent of left ureteric colic, from passage of blood clots into the left ureter.

Management options for NCS range from expectant management to nephrectomy, depending on the severity of symptoms. Those with severe symptoms may benefit from surgical or endovascular intervention, as in our patient. Most interventions aim to reduce venous pressure within the LRV. Intravascular stenting, as applied in our patient, is a relatively new technique, extrapolated from stenting experience in May-Thurner and superior vena cava syndromes.[6] Until stent endothelialisation occurs, anticoagulation therapy is hence recommended.

To our knowledge, although there has been previous report of PUJ obstruction associated with nutcracker syndrome, none was secondary to the presence of a venous aneurysm which was subsequently treated with coil embolisation.

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Letter to the Editor

Subpleural Lung Cysts in Children with Trisomy 21

Dear Editor,

Trisomy 21 is a common chromosomal disorder with an incidence of 1 in 750 live births. Many factors contribute to disorders of the respiratory system in children with trisomy 21, and these include structural abnormalities of the airways and lungs, recurrent lower respiratory tract infections and obstructive sleep apnoea.[1]

Cystic lung disease in children with trisomy 21 was first described in 1986 by Joshi et al from the autopsy findings of 2 infants with lung cysts and congenital heart disease.[2] A later study in 1991 on autopsies of children with trisomy 21 showed a 20% prevalence for subpleural cysts[3] and they were more frequent in children with congenital heart disease. They are difficult to pick out on chest radiographs.[4] Chest computed tomography (CT) is more sensitive in detecting these cysts. Biko et al found a prevalence of 36% for subpleural cysts amongst 25 children with trisomy 21 who underwent CT scanning.[5] The clinical impact of subpleural cysts in children with trisomy 21 is still uncertain. This study aimed to investigate the appearances of subpleural cysts on CT scans of children with trisomy 21, and any associated clinical morbidity.

Materials and Methods

We conducted a retrospective review of the medical notes and radiology results of all children with trisomy 21 (aged under 18 years) attending outpatient clinics and inpatient wards at a tertiary university hospital in Singapore over a 5-year period (from January 2011 to December 2015). Patient details obtained included age, gender, prematurity, coexisting congenital heart disease and any history of respiratory illness, other comorbidities, and prolonged ventilation or extracorporeal membrane oxygenation (ECMO) therapy. Prematurity was defined as <37 weeks of gestation and prolonged ventilation as >21 days of mechanical ventilatory support.[6]

Chest CT scans were performed with high resolution reconstruction. Scans were reported independently by a consultant radiologist and paediatric pulmonologist. Children with CT scans repeated at a later date had their scans analysed for changes in location and size of cysts. Scans were performed on a multidetector CT system with tube current adjusted for each child's age and size. Subpleural cysts were defined as small cystic dilatations along the lung surface. They were defined according to location. Coexisting abnormal CT findings were also described.

The study was approved by the hospital's research ethics committee.

Results

Forty-eight children with trisomy 21 were identified during the study period. Thirteen children underwent chest CT scans. Age range was 2 weeks to 8 years (median 18 months) at the time of CT scanning. Eight children underwent CT scanning following bilateral diffuse airspace changes on their chest X-rays. Two children underwent CT scans to investigate recurrent pneumonia. One child underwent CT scanning of the chest to investigate a persistent stridor from birth while another went for necrotising pneumonia. One child had CT scan to investigate an acute pulmonary hypertensive crisis.

Of the 13 children, 10 had subpleural cysts on CT scanning while cysts were absent in the other 3. For each child, there was complete agreement on the presence or absence of subpleural cysts by the 2 reporters.

Table 1 shows the demographic and clinical characteristics of the children with subpleural cysts. None required ECMO.

Table 2 describes the distribution of subpleural cysts. Eight of the 10 children with subpleural cysts (80%) had cysts along the bronchovascular bundles. Four children (40%) had fissural cysts, predominantly in the oblique fissure, and with significant sparing of the horizontal fissure. Four children (40%) had intraparenchymal cysts (Fig. 1).

Two children underwent repeat chest CT scans 2 years after the first scans. Both children had evidence of new cyst development in follow-up scans. The first scans in these children were done at 2 years 11 months and 8 years 3 months of age, respectively. These new cysts were located in the posterior and basal areas of the lung in both children. Increase in the sizes of the apical and anterior cysts were also noted in both children.

Interstitial lung disease was reported in the CT scans of 2 children with subpleural cysts (20%). One child had findings of ground glass opacities in both lungs, suggesting lung fibrosis. The child did not undergo any further investigations

Table 1. Clinical Characteristics and Demographic Details of Patients

Patient (Gender)	Age at CT Diagnosis	Gestation	Coexisting Congenital Heart Disease	History of Prolonged Ventilator Support (>21 Days)	History of Recurrent Respiratory Infections	Pulmonary Hypertension	Other Comorbid Conditions
Patient 1 (female)	2 weeks	Term	VSD, ASD, PDA, bicuspid aortic arch	Yes (from birth for 74 days)	No	Yes (post-VSD repair)	Stridor from innominate artery compression on trachea, GORD
Patient 2 (male)	4 months	36 weeks	AVSD	No	No	No	None
Patient 3 (female)	6 months	Term	ASD, PDA	No	Yes (mainly ventilator-associated pneumonia)	Yes (severe refractory pulmonary hypertension after viral URTI)	Intrahepatic vascular malformation (involving left portal vein with hepatomegaly), Grade 1 IVH, subclinical hypothyroidism, GORD
Patient 4 (male)	8 months	Term	PDA	No	No	No	Hypothyroidism, GORD
Patient 5 (male)	10 months	Term	TOF	No	No	No	Hypospadias, reactive airways disease, Grade 1 vesico-ureteric reflux bilaterally
Patient 6 (male)	1 year 5 months	Term	TOF	No	Yes (recurrent aspiration pneumonia)	No	Bilateral cleft lip and palate, hiatus hernia with GORD
Patient 7 (male)	1 year 7 months	Term	ASD, mild left pulmonary artery stenosis	Yes (necrotising pneumonia)	Yes (recurrent community-acquired pneumonia)	Yes (following necrotising pneumonia)	Imperforate anus, OSA
Patient 8 (male)	2 years 2 months	Term	AVSD	No	Yes (recurrent aspiration pneumonia)	Yes (post-AVSD repair)	Swallowing dysfunction, severe GORD
Patient 9 (female)	2 years 11 months	Term	None	No	No	No	GORD, OSA
Patient 10 (female)	8 years 3 months	Term	None	No	No	No	OSA

ASD: Atrial septal defect; AVSD: Atrioventricular septal defect; CT: Computed tomography; GORD: Gastroesophageal reflux disease; IVH: Intraventricular haemorrhage; OSA: Obstructive sleep apnoea; PDA: Patent ductus arteriosus; TOF: Tetralogy of Fallot; URTI: Upper respiratory tract infections; VSD: Ventricular septal defect

Table 2. Distribution of Subpleural Cysts on Chest CT Scans in Children with Trisomy 21 at the Time of Diagnosis of Subpleural Cysts

Patient (Gender)	Distribution of Subpleural Cysts
Patient 1 (female)	Right-sided, anteriorly located
Patient 2 (male)	Bilateral, posteriorly located
Patient 3 (female)	Bilateral, anterior and posteriorly located
Patient 4 (male)	Bilateral, anterior and posteriorly located
Patient 5 (male)	Left-sided, laterally located
Patient 6 (male)	Left-sided, posteriorly located
Patient 7 (male)	Bilateral, anterior and posteriorly located
Patient 8 (male)	Bilateral, posteriorly located
Patient 9 (female)	Bilateral, anterior and posteriorly located
Patient 10 (female)	Bilateral, anterior and posteriorly located

CT: Computed tomography

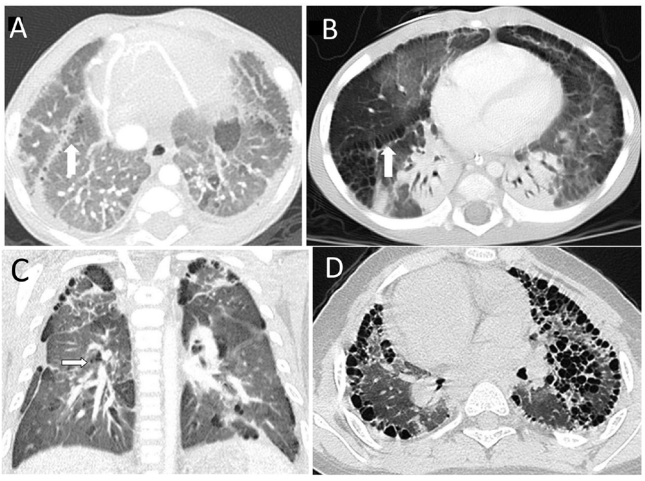

Fig. 1. Subpleural cysts in children with trisomy 21. A) Fissural cysts (white arrows) in a female aged 6 months and B) a male aged 1 year and 7 months. C) Bronchovascular cysts (white arrow) in a male aged 8 months. D) Parenchymal cysts within the left lung of a female aged 2 years and 11 months.

as he remained clinically well from a respiratory standpoint, but he remains under close follow-up for any respiratory symptoms of concern. The other child had findings of coarse reticular pattern in both lungs on the initial scan, suggesting lung fibrosis, but these appearances resolved on a subsequent scan (despite an increase in the sizes of subpleural cysts). None of the 10 children with subpleural cysts had signs of pulmonary hypertension, changes in the pulmonary vasculature, or pleural thickening. The child who was investigated for pulmonary hypertension had dilated pulmonary arteries consistent with pulmonary arterial hypertension but did not have subpleural cysts.

Discussion

Subpleural cysts exist in children with trisomy 21, but are rarely found in non-trisomy 21 children.[7] The origins of these cysts are not entirely clear, but may be related to alveolar hypoplasia in trisomy 21.[2,3,8] Reported histological examinations of the lungs of children with trisomy 21 demonstrated reduced alveolar numbers, increased alveolar size, and deficiency of elastic fibres in the entrance rings to the alveoli.[9] These processes may result in cyst development in the postnatal period during the time of continued alveolar growth, hence their subpleural location. Cysts were much more likely to be found beyond the first month.[3] We found that cysts can increase in size with time, and new cysts can continue developing even in children up to 10 years of age, suggesting that the appearance of cysts can change during childhood.

There were suggestions that subpleural cysts developed from ischaemic tissue damage and compression of bronchi and small airways, presumedly related to congenital heart disease, left-to-right shunting and subsequent compression of bronchi by enlarged arteries and small airways by interstitial fluid.[3,10] However, children with congenital heart disease in the absence of trisomy 21 do not normally manifest with subpleural cysts, so this cannot completely explain the pathogenesis of subpleural cysts. Nevertheless, we found that most of our children with subpleural cysts had coexisting congenital heart disease, although this could be a reflection of children with heart disease who were more likely to have undergone chest CT scans, and therefore, more likely to have subpleural cysts revealed.

Tyrrell et al suggested that subpleural cysts were associated with increased mortality and morbidity from congenital heart disease in children with trisomy 21.[7] This has been postulated due to the presumed earlier than expected death in their case, and a higher incidence of pulmonary hypertension in Gonzalez et al's postmortem series.[3] They also proposed an altered postoperative course in these children, with subpleural cysts reducing gas exchange surface area, and altering lung mechanics making ventilation less effective. In our study, only 2 of 5 children who underwent cardiac operations needed prolonged ventilation postoperatively. We could not demonstrate a clear association with pulmonary hypertension; only 3 children with subpleural cysts (30%) had evidence of pulmonary hypertension by echocardiography.

We demonstrated some consistent features with regard to subpleural cyst location. Although most of the children had cysts in the posterior and basal regions, the cysts can be present in any part of the lungs. New cysts tended to appear in the posterior and basal regions on subsequent CT scans. Fissural cysts were confined to the oblique fissure. The reasons for these patterns of distribution were not clear.

There are limitations to our study. Due to the small number of patients in our series, a definitive association between the presence of cysts and comorbid conditions such as prematurity, congenital heart disease and pulmonary hypertension could not be drawn. This is compounded by the fact that it is not possible to know whether children who did not undergo CT scans had subpleural cysts. However, our data does demonstrate that children with trisomy 21 and subpleural cyst do not necessarily have a poor cardiovascular or respiratory outcome.

Conclusion

Subpleural cysts may be a feature of children with trisomy 21. They may be present in any location in the lungs, but subsequent new cyst development tend to be in the posterior and basal regions. They are not necessarily associated with significant cardiac or respiratory morbidity. These cysts can increase in size over time, with the development of new cysts occurring at any stage of childhood.

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An Audit of Critical Value Parameters at Two Regional Hospitals in Singapore

Dear Editor,

Dr George Lundberg first defined 'critical value' as one that represents a pathophysiological state at such variance with normal (expected values) as to be life-threatening, unless something is done promptly, and for which some corrective action could be taken.[1] Since then, there have been several reports of individual institutional or regional experiences with critical values.[2,3] Accurate and timely transmission of such values to the appropriate caregiver is one of the criteria that regulatory bodies worldwide require laboratories to meet for licensing and accreditation purposes.[4,5]

In this study, we conducted an audit of critical values encountered at Alexandra Hospital (AH; 400 beds) from January 2015 to June 2015, and Ng Teng Fong General Hospital (NTFGH; 700 beds) from July 2015 to July 2016 (the purpose of a longer study period at NTFGH being to appreciate transition to steady state). Both are public hospitals that offer the services of major medical and surgical specialties, are run by the same management (JurongHealth) and have similar departments of clinical chemistry, haematology, blood transfusion services, microbiology and anatomic pathology. Also, both hospitals share the same critical result list, workflow and protocol. The aim of our study was to compare and contrast the critical results data and use the information gathered to identify areas for improvement.

Critical results data were obtained from reports generated from our Laboratory Information System (LIS) and then exported to Microsoft Excel spreadsheets for further analysis. Statistical analysis was performed using the z-test of proportions.

Audit of Critical Values at AH from January to June 2015

Out of 430,719 results, 2096 (0.49%) were critical. The top 5 critical results were positive blood culture (14.5%), platelets (14%), serum potassium (K+, 13.5%), plasma glucose (9.1%) and serum sodium (Na+, 6.9%). Clinical chemistry had the most number of critical results (60.2%), followed by haematology (20.6%) and microbiology (17.9%). Comparing locations, the inpatient department had the highest proportion of critical results (68.9%), followed by the emergency department (ED; 24.6%) and outpatient (6.5%) department. The top 3 critical results within each location were: ED–plasma glucose (26.4%), serum K+ (20.9%) and lactate (10.7%); inpatient–positive blood culture (20.6%), platelets (16.7%) and serum K+ (10.5%); and outpatient – serum free thyroxine (fT4, 37.6%), plasma glucose (24.1%) and serum K+ (15.8%). The specialty with the greatest proportion of critical results was Medicine (55.3%), followed by ED (24.6%) and Intensive Care Unit (ICU; 10.3%). The 4 pm to 12 am period had the highest proportion of critical results (46%), followed by the 8 am to 4 pm period (30.6%) and 12 am to 8 am period (23.4%).

Audit of Critical Values at NTFGH from July 2015 to July 2016

Out of 1,868,752 results, 10,968 (0.59%) were critical. The top 5 critical results were positive blood culture (21.0%), platelets (12.0%), serum K+ (9.82%), serum Na+ (9.33%) and plasma glucose (8.42%). Clinical chemistry had the most number of critical results (52.5%), followed by microbiology (26.3%) and haematology (21.2%). Comparing locations, inpatient accounted for 72.1%, ED 24.8%, and outpatient 3.1%. The top 3 critical results within each location were: ED–plasma glucose (27.6%), serum K+ (17.3%) and haemoglobin (10.1%), inpatient–positive blood culture (28.5%), platelets (13.7%) and plasma glucose (11.6%) and outpatient–plasma glucose (13.5%), serum K+ (12.6%) and serum fT4 (11.7%). The specialty that had the most number of critical results was Medicine (52.6%), followed by ED (24.8%), then ICU (10.4%). The 4 pm to 12 am period had the highest number of critical results (48.5%), followed by the 8 am to 4 pm period (26.9%) and 12 am to 8 am period (24.6%).

Table 1 shows a summary of the comparison of critical results between AH and NTFGH.

We adopted the critical reportable result health care messaging system (CRR-HMS), an automated notification system (Fig. 1) which has an electronic audit trail, to help in performance monitoring and evaluation.

At AH, the time taken for a response to be recorded by CRR-HMS, or turnaround time (TAT), was between 11 to 30 minutes (48%), within 10 minutes (42%), between 31 to 60 minutes (9.3%) and beyond 60 minutes (0.7%). At NTFGH, TAT was between 11 to 30 minutes (55.8%), within 10 minutes (30%), between 31 to 60 minutes (13.2%)

Table 1. Comparison of Critical Results between AH and NTFGH

Parameter	AH January 2015 to June 2015 (n = 2096)	NTFGH July 2015 to July 2016 (n = 10, 968)	95% CI for Proportion Difference	*P* Value
Top 5 critical results, n (%)				
Positive blood culture	303 (14.5)	2298 (21.0)	(-0.082, -0.048)	<0.0001
Platelets	293 (14.0)	1311 (12.0)	(0.004, 0.037)	0.01
Serum potassium	283 (13.5)	1077 (9.8)	(0.021, 0.053)	<0.0001
Plasma glucose	191 (9.1)	923 (8.4)	(-0.007, 0.021)	0.32
Serum sodium	144 (6.9)	1023 (9.3)	(-0.037, -0.012)	0.0004
Laboratory section, n (%)				
Clinical chemistry	1296 (60.2)	5753 (53.0)	(0.071, 0.117)	<0.0001
Haematology	432 (20.6)	2335 (21.0)	(-0.026, 0.012)	0.50
Microbiology	376 (17.9)	2880 (26.0)	(-0.102, -0.065)	<0.0001
Hospital location, n (%)				
Inpatient	1444 (68.9)	7911 (72.1)	(-0.054, -0.011)	0.003
ED	516 (24.6)	2724 (24.8)	(-0.023, 0.018)	0.85
Outpatient	136 (6.5)	333 (3.0)	(0.023, 0.046)	<0.0001
Physician specialty, n (%)				
Medicine	1159 (55.3)	5769 (52.6)	(0.003, 0.051)	0.03
ED	516 (24.6)	2720 (24.8)	(-0.022, 0.019)	0.88
ICU	215 (10.3)	1140 (10.4)	(-0.016, 0.013)	0.88
Time period, n (%)				
8 am to 4 pm	642 (30.6)	2952 (26.9)	(0.015, 0.059)	0.0005
4 pm to 12 am	965 (46)	5314 (48.5)	(-0.048, -0.001)	0.05
12 am to 8 am	489 (23.4)	2702 (24.6)	(-0.033, 0.007)	0.21

AH: Alexandra Hospital; CI: Confidence interval; ED: Emergency Department; ICU: Intensive Care Unit; NTFGH: Ng Teng Fong General Hospital

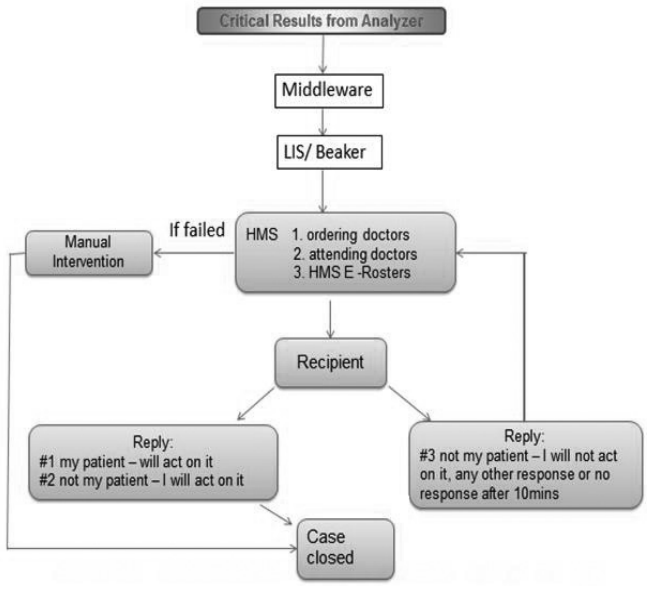

Fig. 1. Chart showing the critical result notification workflow.

and beyond 60 minutes (1%). The main reason for delayed notification (i.e. beyond 60 minutes) was delayed closure of the case by the call centre operator. Further investigations revealed no compromise in patient safety as appropriate management plans were already in place based on prior clinical suspicions.

Our audit shows that despite a larger patient population with an expected increase in workload at NTFGH, the proportion of critical results (0.59%) has remained comparable to that found by a College of American Pathologists (CAP) Q-Probes study of 121 institutions (less than 2%).[6]

Streamlining operational processes is crucial and one important component is the critical result list, which has considerable interlaboratory variation (Table 2). Making changes to this list can possibly reduce workload, and this should be done in discussion with the relevant clinicians and/or medical review board.[7] Doing a relevant literature review beforehand is beneficial as previously published lists from various studies[8,9] have advantages in terms of having undergone robust clinical evaluation. CAP has

Table 2. Comparison of Critical Result Limits at AH/NTFGH versus US* and UK†‡ Institutions

Test	AH/NTFGH	US	UK
Sodium (mmol/L)	<120 or >160	<120 or >158	<121 or >155
Potassium (mmol/L)	<2.5 or >6.0	<2.8 or >6.2	<2.7 or >6.2
Glucose (mmol/L)	<2.5 or >25.0	<2.6 or >26.9	<2.4 or >22.7
Platelet (x 10^9/L)	<50 or >1000	<37 or >910	<30 or >1000

AH: Alexandra Health; NTFGH: Ng Teng Fong General Hospital; UK: United Kingdom; US: United States

*Kost GJ. Critical limits for urgent clinician notification at US medical centers. JAMA 1990;263:704-7.

†Tillman J, Barth JH; ACB National Audit Group. A survey of 'laboratory critical (alert) limits' in the UK. Ann Clin Biochem 2003;40:181-4.

‡The Royal College of Pathologists (UK). Out-of-hours reporting of laboratory results requiring urgent clinical action to primary care: Advice to pathologists and those that work in laboratory medicine. Available at: https://www.rcpath.org/resourceLibrary/out-of-hours-reporting-of-laboratory-results-requiring-urgent-clinical-action-to-primary-care.html. Accessed on 29 April 2016.

also published a survey of critical result comparison of several clinical laboratories[10,11] which serves as a good reference. However, the selection of critical result values should be institution-specific and tailored to specific patient populations and their needs (e.g. a specialist haematology-oncology centre will have a very different white blood cell count critical result value compared to that in a polyclinic).

Another contributing factor is the notification process. There have been several studies[12,13] reporting the use of information technology to enhance the effectiveness of laboratory processes. To further improve on our TAT, we have sent out circulars to all stakeholders involved, such as call centre operators, reminding them of the need to close the case promptly. Automated alerts, such as red/green flags on-screen, can also serve as useful reminders. A repeat audit is planned in the near future to assess the impact of our improvement measures on TAT.

Personalising the notification process (e.g. building alerts that take into account not only the critical value, but also other information such as patient demographics, other related results and a change in current results from previous results) will possibly reduce the proportion of critical results and hence, laboratory workload. However, we have deliberated and found the risks of specialty/physician-specific lists to outweigh the benefits. For instance, the same patient may be admitted under different disciplines during different hospital admissions, and a specialty-specific list would only serve to complicate matters. Hence, we have decided not to adopt this personalised notification approach, mainly to safeguard patient safety.

In conclusion, this study has allowed us to understand our unique patient population characteristics better. Continued critical value audit and sharing of information with the relevant stakeholders are essential to maximising laboratory efficiency and maintaining patient welfare. Upholding such standards should be the joint effort of the laboratory, responsible healthcare professionals, information technology experts and all other relevant personnel involved.

The biggest challenge that remains is finding out how physicians actually deal with the critical results and the impact on patient management thereafter. We are planning to conduct an audit of such data in the near future, with hopes that the results will aid us further in tailoring laboratory processes to better meet the ever-changing needs of physicians and their patients.

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Auto-Amputations

An 88-year-old man presented with catheter-related urinary tract infection. Deformities of both hands and feet were seen, with amputations of the digits being prominent features (Figs. 1 and 2). Radiographs of the right foot are shown in Figure 3.

What is the cause of this patient's multiple fingers and toes amputation?

A. Diabetes with peripheral neuropathy
B. Scleroderma
C. Ainhum (dactylolysis spontanea)
D. Buerger's disease
E. Leprosy

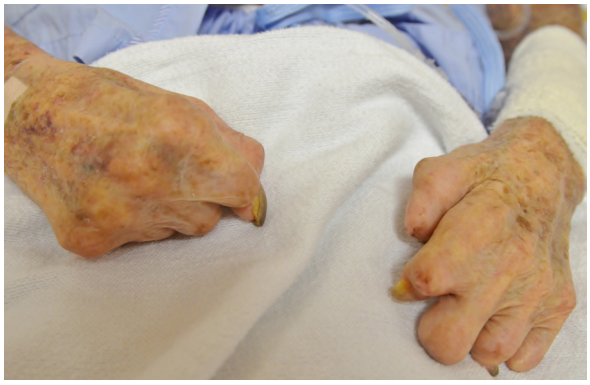

Fig. 1. Hands of the patient (dorsal view).

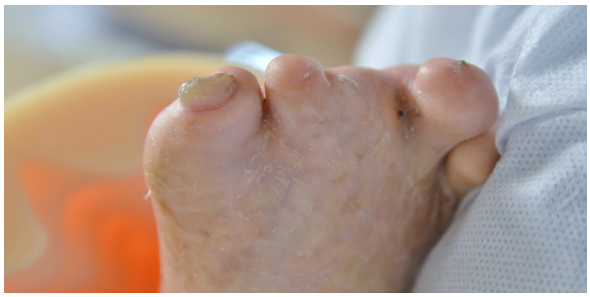

Fig. 2. Right forefoot and toes of the patient (dorsal view).

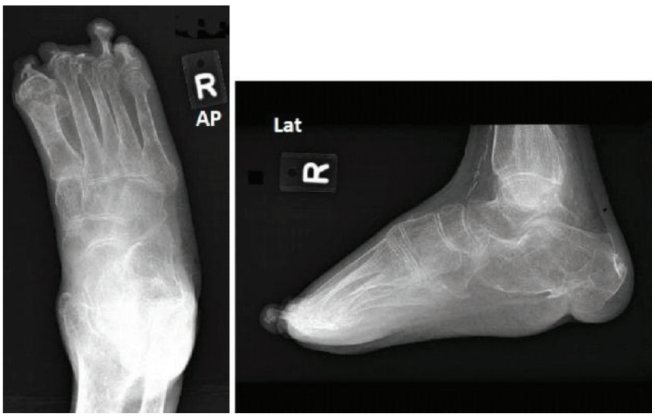

Fig. 3. Radiographs of right foot of the patient. There was diffuse resorption and acral osteolysis of the first to fourth phalanges. Charcot's deformity was also noted in the talus and possibly in the subtalar joint.

Findings and Diagnosis

Further history-taking revealed that our patient had been previously diagnosed with Hansen's disease, which was treated many years ago. He was unable to recall the details of the treatment. There had been no past history of diabetes mellitus. The patient was a non-smoker. He recalled no pain in the hands and feet prior to the progressive digital resorption.

A physical examination did not show any nodular lesion in the face to suggest leonine facies. No skin tightening, microstomia, calcinosis, nor telangiectasia were found. Greater auricular, ulnar, common peroneal and sural nerves were not palpable. Neurological examination showed normal deep tendon reflexes. There was loss of pain sensation, with anaesthesia involving gloves and stocking distribution bilaterally.

The patient's fasting sugar and glycated haemoglobin (HbA1c) levels were within normal limits, and hence these excluded the differential diagnosis of diabetes peripheral neuropathy. There were no clinical signs to suggest scleroderma such as Raynaud's phenomenon, gastro-oesophageal reflux or dysmotility or respiratory problems. Systemic sclerosis tends to affect women and the degree of auto-amputation in this patient was too extensive compared to what is usually seen in scleroderma.

Answer: E

The absence of a history of heavy smoking and limb pain from claudication make the differential diagnosis of Buerger's disease less likely (this typically causes ischaemic pain in the digits that progressively leads to skin ulcerations and gangrene). The patient did not have any gangrene at the digital tips preceding the shortening of the digits.

The patient, being an elderly Chinese man, did not fit the typical patient profile for ainhum which affects mainly African males aged between 30 and 50 years.[1] Moreover, there was no history of bulbous enlargement of the affected toes and no previous constricting bands prior to an amputation which is the main feature in ainhum.[1] Additionally, his auto-amputations involved multiple toes in comparison to ainhum which usually involves only the fifth toe.

Discussion

The incidence of leprosy in Singapore has greatly diminished over the past 5 decades—from 21.3 per 100,000 populations in 1960 to 0.1 per 100,000 populations in 2013.[2] The highest prevalence of the disease is observed in India, Africa and South America, and leprosy still occurs frequently in Southeast Asia.

Although the incidence of leprosy is lower than other causes of neuropathic arthropathy and auto-amputations, we would like to highlight this case as an important differential diagnosis not to be forgotten especially in the context of presentation in an elderly person living in Southeast Asia.

Transmission of *Mycobacterium leprae* (*M. leprae*) is through inhalation of the bacilli contained in nasal secretion and droplets.[3] Upon entering the body, the bacilli migrates and infects mainly Schwann cells and macrophages. Endothelial cells involvement has been described in leprosy, although specific endothelial cells and ligands mediating the uptake of the bacilli remains to be expounded.[4] Endothelial cells have also been identified to be a potential delivery system of viable bacilli to Schwann cells.[5] Proliferation of endothelial cells containing bacilli is found to be responsible in the pathogenesis of necrotising vasculitis.[6]

The manifestation of the disease is a spectrum determined by the ability of the host to mount cellular immunity response to *M. leprae*. When cell-mediated immunity (CMI) response is effective in eliminating the bacilli, skin lesions and peripheral nerves heal spontaneously, or the infection produces pauci-bacillary (PB) type of leprosy. If CMI is impaired, the disease spreads and produces multi-bacillary (MB) leprosy whereby in addition to skin and nerves, the eyes, testes, kidney, voluntary and smooth muscles, reticuloendothelial system and vascular endothelium can be infiltrated.

Infiltration with bacilli, inflammation from immune-modulatory cascades and granuloma within the epineurium sheath results in segmental demyelination, infarcts, oedema, and axonal damage.[7,8] This leads to impairment in sensation, autonomic and motor functions. Long-standing insult causes nerve destruction and replacement by fibrous tissue.

Acral osteolysis refers to resorption of the distal phalanx. The terminal tuft is most commonly affected and the shaft of the distal phalanx can also be affected. The mechanism of acral osteolysis of the digits is poorly understood; possibly from hypaesthesia from nerve involvement, compounded poor healing from vascular deficit and secondary infection from trophic ulcers.[9]

Firstline medications include dapsone and rifampin for tuberculoid leprosy, with addition of clofazimine for lepromatous leprosy. National Hansen's Disease Program (NHDP) advocated a treatment duration of 12 and 24 months for tuberculoid and lepromatous leprosy, respectively while the World Health Organisation (WHO) favours a shorter duration of treatment (6 and 12 months, respectively). Whilst the complex mechanism of acral osteolysis in leprosy is not completely understood, the implication of amputation is clearly understood—loss of function, leading to handicap and dependency. Early occupational therapy and podiatry care can help to delay the downhill progression of arthropathy.

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