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Endocrinological Aberrations in Survivors of the Severe Acute Respiratory Syndrome (SARS) in Singapore

Epidemiology of Recurrent Abdominal Pain among Singaporean Adolescents

Comparison Between Haematological Parameters in Severe Acute Respiratory Syndrome (SARS) and Dengue Fever (DF)

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Endocrinological Aberrations in Survivors of the Severe Acute Respiratory Syndrome (SARS) in Singapore

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Introduction

Ever since Singapore was stricken in March 2003 with severe acute respiratory syndrome (SARS), it became apparent that many survivors experienced chronic morbidities including a multitude of psychosomatic manifestations.

We hypothesise that these symptoms could have an endocrinological basis due to their resemblance to various hormonal and metabolic disorders that frequently feature non-specific symptomatology.[1] Studies have linked aberrations in the hypothalamic-pituitary-adrenal (HPA) axis to psychiatric conditions.[2] Moreover, correlations of thyroid dysfunction with certain psychosomatic syndromes have been described.[3]

The primary focus of this prospective study is to determine the existence of any chronic endocrine sequelae in SARS survivors, while characterisation of their prognostic outcomes constitutes its secondary objective. Given that the endocrinopathic properties of the SARS-associated coronavirus (SARS CoV) is currently an inadequately explored domain, any hormonal aberrations unravelled through this preliminary investigation will contribute new scientific insights to the medical database with the potential of translating into clinically relevant therapeutic strategies for SARS-associated endocrinopathies and paradigm shifts in treatment approaches to endocrine disorders as future spin-offs.

Materials and Methods

Subject Recruitment

This research was conducted in Tan Tock Seng Hospital with approval from its Institutional Review Board. All survivors of probable SARS in Singapore aged 21 years and above were eligible. Sixty-one provided written informed consent and were prospectively enrolled about 3 months post-discharge. Those with pre-existing endocrine disorders before SARS were excluded.

Sample Collection and Processing

Blood samples were collected at 0800 h by venepuncture into EDTA and plain tubes for: 1) full blood count, 2) electrolytes, 3) cortisol, 4) adrenocorticotropic hormone (ACTH), 5) free thyroxine (FT4), 6) free triiodothyronine (FT3), 7) thyroid stimulating hormone (TSH), and 8) dehydroepiandrosterone sulphate (DHEAS). 24-hour urinary cortisol was done to assess integrated cortisol secretion. Hormone measurement techniques including immunochemiluminometric assay (ICMA) and radioimmunoassay (RIA) were employed according to standardized protocols. Subjects with serum cortisol below 275 nmol/L as cutoff underwent dynamic HPA axis evaluation using low dose (1 mcg) short Synacthen test (SST). Subjects with 8 am serum cortisol below 138 nmol/L and/or post-stimulation serum cortisol under 550 nmol/L at 30 minutes were deemed hypocortisolic. SST assessment for HPA axis recovery was repeated at 3 to 6 monthly intervals. Although the study was terminated a year following diagnosis of HPA axis dysfunction, reviews were extended for those with persistent hypocortisolism as medically appropriate. Symptomatic patients with orthostatic hypotension were prescribed physiological doses of hydrocortisone replacement until their SST normalised.

Statistical Analysis

Descriptive statistical analysis was performed on raw data where applicable.

Results

Table 1 shows the demographic/clinical profile of the study population. Twenty-four (39.3%) patients had hypocortisolism, of which 20 (32.8%) had central hypocortisolism as evidenced by concomitant low or inappropriately normal ACTH levels and 4 (6.6%) had primary hypocortisolism with plasma ACTH above the upper reference limit. Of those with central hypocortisolism, 6 received systemic glucocorticoids during SARS while one was an asthmatic on inhaled corticosteroids. The remaining 13 (21.3%) had no prior steroid exposure. One had elevated serum cortisol, ACTH and urinary cortisol, though Cushing's disease was excluded by dexamethasone suppression testing. Among 25 (41%) with HPA axis dysfunction, 15 (24.6%) resolved within a year paralleled by improved well-being, 7 (11.5%) had residual hypocortisolism of which only 1 still required hydrocortisone replacement, whereas 3 defaulted follow-up. There was a definite temporal trend towards improvement in stimulated adrenal cortisol output (Fig. 1). Two of the hypocortisolic cohort had transient subclinical thyrotoxicosis. Four were biochemically hypothyroid, comprising 3 with central hypothyroidism and 1 with primary hypothyroidism. Two of the 3 with central hypothyroidism had concomitant central hypocortisolism.

Discussion

SARS is a new infection with significant morbidity and mortality posing a serious threat to mankind. Theoretically, this coronavirus can involve any organ during the viraemic phase. Because certain forms of hypophysitis, thyroiditis and adrenalitis have viral etiologies,[4] it is instructive to determine the endocrinopathic impact of SARS-CoV. Recently, researchers have examined the pulmonary and psychological aftermath of SARS survivors.[5] However, most studies were cross-sectional with limited longitudinal data, and endocrine derangements have not been reported.

Table 1. Clinical Characteristics of the Study Population (n = 61)

Variable	Value
Age	36.5 (25.5 – 47.5)
Gender (male : female)	14 : 47
Race	Chinese (39), Malay (13), Indian (7), Others (2)
Use of corticosteroids during SARS	10
Mechanical ventilation	7
Need for tracheostomy	3

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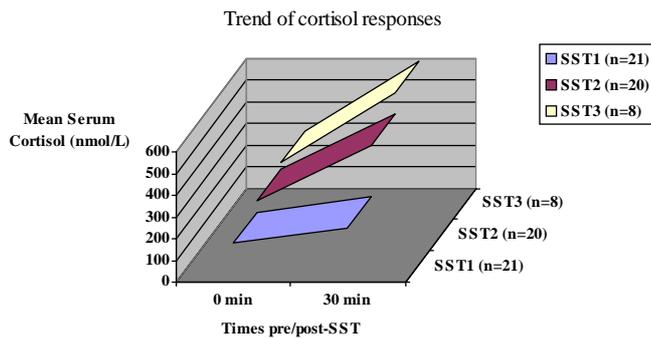
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Fig. 1. Results of Short Synacthen test (SST) showing mean serum cortisol responses over a year of follow-up of 21 survivors of SARS SST performed at the first, second and third clinic visit.

Our investigation was an unprecedented effort to chronicle the natural history of endocrinological aberrations in SARS survivors for up to a year. Serial longitudinal evaluation facilitated characterisation of trends and prognostication. A sizeable proportion surprisingly exhibited hormonal deficiencies rather than upregulated HPA axis or thyroid status typical in depression, post-traumatic stress disorder and panic disorder, any of which can occur in SARS survivors. These results provide compelling evidence that the HPA axis and thyroid are candidate targets of SARS-CoV. Central hypocortisolism consequent to a pathological effect of SARS rather than glucocorticoid-induced HPA axis suppression was also suggested by absence of steroid use in nearly two-thirds of this group. Of 5 cases with normal retrospective pre-steroid SST (unpublished ICU data) who received high-dose systemic corticosteroids, 3 with intact HPA axis post-steroids support this postulation. The negative thyroid autoantibodies in all but 1 patient implicate SARS-CoV induced-thyroiditis as a pathogenetic mechanism causing transient subclinical thyrotoxicosis or hypothyroidism. The onset of endocrinopathy in the post-SARS period rather than during acute SARS infection reflects delayed processes possibly mediated at the genomic level.

The prognosis appears favourable as complete resolution occurred in the majority at 1 year. Pending future SARS epidemics, adequately powered clinical studies to clarify this could prove daunting. In-vitro studies and animal models of SARS might define the endocrine lesions. Predictably, unravelling SARS-cellular interactions and post-receptor molecular cascades could boost drug development to prevent endocrine sequelae. Deciphering SARS-CoV (S1) spike-glycoprotein cross-talk with angiotensin-converting enzyme-2 may serendipitously identify critical pathways nature employs in maintaining endocrine gland integrity.[6] Translational research in this direction may fuel the design of novel therapeutics to cure endocrine disorders that currently rely on hormonal replacement or suppressive medications for disease control.

Conclusion

Endocrinological perturbations occur frequently in SARS survivors. Although speculative, these findings highlight a possible aetiologic role of SARS-CoV as an endocrinopathic factor deserving of future elucidation by in-vitro, animal and clinical studies.

Acknowledgement

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NHG Doctor Award Finalist

Epidemiology of Recurrent Abdominal Pain among Singaporean Adolescents

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Introduction

Recurrent abdominal pain (RAP) is a fairly commonly encountered clinical problem in children. This entity was described by Apley in 1958 when he conducted a field study of 1000 children in the British community. He defined RAP as "paroxysmal abdominal pain occurring in children between 4 and 16 years of age and persisting for more than 3 months and affecting the child's normal daily activity."[1]

The incidence of recurrent abdominal pain has been reported to be 10% to 15% in children between 4 to 16 years of age.[2] Over the years, we have been seeing an increase in referrals for children with RAP at our hospital. However, there have been no local data about RAP

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in children. The aim of this study was to determine the prevalence and epidemiology of RAP among school-going children in Singapore.

Methods

This study is a cross-sectional survey conducted from June 2003 to October 2003, in Singapore among primary and secondary school students. The study was approved both by the Ministry of Education and the various school administrators. Ten schools were randomly selected using random sampling numbers. Children within each school were randomly selected using cluster sampling.

In addition to information about the students' demographics, socio-economic status and family size, questions were asked about the occurrence and frequency of recurrent abdominal pain, dietary history (e.g., intake of soy milk, vegetables, fruits and milk), stool frequency and common life-event related stresses (e.g., change of school, illness in family and parental job loss). The questionnaires were self-administered by the secondary school students, whilst parents of primary school students were asked to respond to the questionnaires.

Data entry was done by 3 data entry clerks and checked by one of the authors for accuracy and consistency. Data held were password-protected. Statistical analysis was performed using SPSS 12.0. Multivariate logistic regression was performed on the outcome of RAP with the predictors of life, family and school events, dietary and bowel habits and demographics. A forward-stepwise logistic was also performed. Statistical significance was set at $P <0.05$.

Results

The questionnaire was distributed to 5000 students. Overall response rate was 72% with 3590 students returning complete questionnaires. The incidence of RAP was 23.4% (95% CI, 22%-24.8%). The mean age was 11.7 years (range, 6 to 17 years) of which 62.4% were female. Race distribution was similar to student population distribution with 83% Chinese, 10.3 % Malay, 4.8% Indian and 1.9% other races. Significant factors associated with RAP were female sex ($P <0.001$, OR = 1.7, 95% CI, 1.3-2.1), school work stress ($P = 0.007$, OR = 1.4, 95% CI, 1.1-1.9), changing school ($P = 0.008$, OR = 1.7, 95% CI, 1.2-2.6), parental job loss ($P = 0.007$, OR = 2.1, 95% CI, 1.2-3.5), constipation ($P = 0.002$, OR = 1.8, 95% CI, 1.2-2.5) and number of times admitted to hospital ($P = 0.03$, OR = 1.8, 95% CI, 1.1-3.0).

Discussion

One of the concerns in a self-reported questionnaire study was that patients with undiagnosed organic disease could have been "misclassified" as having functional pain. However, 30.6% of children with RAP in our study had consulted their general practitioners or specialist, and no organic cause had been found. In addition, after excluding all children with constipation from the analysis, there was still a similarly high prevalence of 22.1% children with RAP. We are thus fairly confident that this study is a good reflection of the prevalence of RAP in our local school-going children. This is the first such large-scale epidemiological study in South-East Asia. The only other reported study was performed in rural and urban school children in Malaysia, where Boey et al found a prevalence of 10.2%,[3] a much lower figure than what we have found. In another study published in 1995, Hyams described the occurrence of RAP to be approximately 20% of American middle school and high school students, consistent with our belief that there may be a temporal increase in the prevalence of this condition since Apley's study.[4] It is interesting that this was similar to our local figures suggesting that
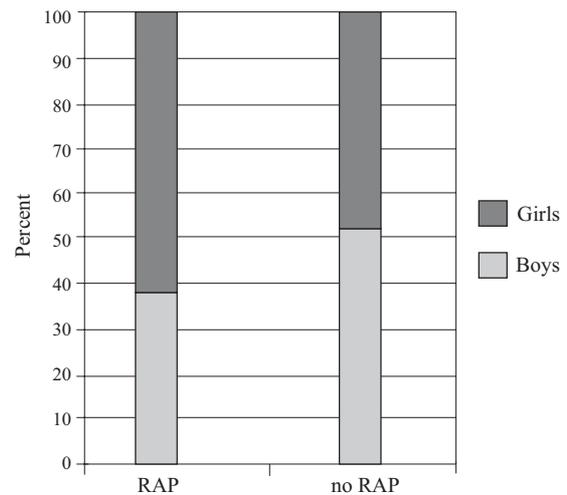

Fig. 1. Sex incidence (P < 0.001)

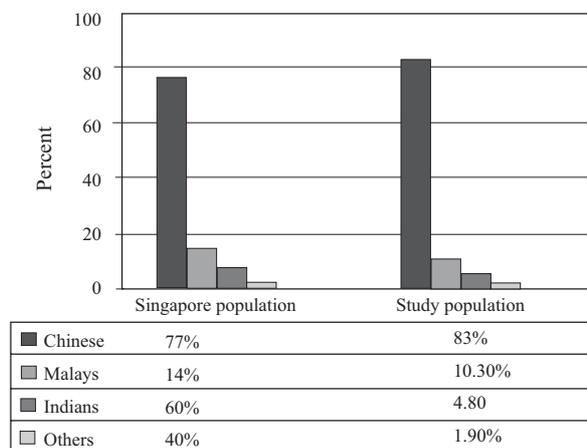|	Singapore population	Study population
■ Chinese	77%	83%
▦ Malays	14%	10.30%
▨ Indians	60%	4.80
▫ Others	40%	1.90%

Fig. 2. Racial Incidence

environmental and social factors may play a more important role compared to race and cultural factors in children with RAP.

Conclusion

Our population study determined that the prevalence of RAP in Singapore, an urban developed country in South-East Asia, was 23.4%. This is higher compared to previous reported figures of 10% to 15%. Multivariate analysis found significant associations of RAP with school work stress, changing school, parental job loss, constipation and the number of times the child was admitted to hospital.

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Comparison Between Haematological Parameters in Severe Acute Respiratory Syndrome (SARS) and Dengue Fever (DF)

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Introduction

One of the largest SARS outbreaks occurred in Singapore with most of the patients managed in the SARS-designated Tan Tock Seng Hospital. The cause of SARS has been identified as a novel coronavirus.[1]

The WHO clinical case definition of SARS is highly insensitive highlighting the non-specific nature of presenting symptoms.[2] Although sequencing of the coronavirus genome[3] has allowed the development of more specific diagnostic tests, none of these are very sensitive and may not be positive during the first few days of disease.

During the SARS outbreak, tremendous burden was placed on hospitals to provide isolation facilities due to the highly infectious nature of the coronavirus. It would be helpful if some routine laboratory tests could help differentiate SARS from other common infective causes of fever presenting with similar symptoms like DF. This would allow more efficient use of limited isolation facilities.

We studied the use of routine full blood count in discriminating SARS and DF, 2 common causes of febrile illness during the SARS outbreak.

Materials and Methods

SARS cases confirmed by serological testing or identification of viral RNA by reverse-transcriptase polymerase chain reaction (RT-PCR) from March 15 to May 12, 2003 were included. Patients not treated at the SARS-designated hospital, less than 9 years old, or whose history of symptom onset was unclear were excluded. Patients with DF confirmed serologically or by PCR during the same period were included for comparison.

Sequential results of haematological indices including haemoglobin (Hb), white cell (WCC), platelet (PLT), absolute neutrophil (ANC) and absolute lymphocyte counts (ALC) were obtained for each patient and tabulated according to day of illness. The day of symptom onset was designated day 1 of illness.

Longitudinal data analysis technique was applied to detect the difference between SARS and DF patients in terms of the sequential trend of ALC, ANC, Hb, PLT and WBC levels. The measurements of ALC, ANC, Hb, PLT and WBC in the first 6 days were used for the analysis. In addition, the medians of ALC, ANC, Hb, PLT and WBC levels were also compared for each day by Mann-Whitney U test. Parameters that were significantly different were selected for receiver operator characteristics (ROC) analysis to obtain discriminatory values for the 2 conditions.

Results

Overall, there were 185 and 82 confirmed SARS and DF cases respectively. Of these, the haematological information of 78 SARS patients and 82 DF patients for the first 6 days of illness was available.

SARS patients had significantly lower ALC and Hb and higher ANC and PLT. For some of these parameters, the differences were also significant for the effect of time and interaction between time and groups of patients by longitudinal data analysis (Table 1). The difference in PLT between SARS and DF patients was most marked with a mean difference of 102×10^9/L (95% CI, 87×10^9/L-117×10^9/L). SARS patients also have significantly higher nadir PLT than DF patients (median PLT 151×10^9/L versus 34.5×10^9/L, $P < 0.0001$, Mann-Whitney U test).

Multiple comparisons adjusted by Bonferroni technique and using Mann-Whitney U test showed that ALC was significantly different between SARS and DF from day 3 to day 6, ANC from day 1 to day 5, Hb from day 1 to day 4 and day 6, PLT from day 1 to day 6 and WBC from day 2 to day 3 (Table 1 and Fig. 1).

As PLT and ANC appear to be the most significantly different between the 2 conditions and the difference is most marked in the first 5 days, we decided to subject these 2 parameters during the first 5 days to ROC analysis to find the best discriminatory value between the 2 conditions. The results showed that PLT is a better discriminator than ANC and day 2 and day 3 values are most useful. Using the mean

Table 1. Comparison of Sequential and Daily Haematological Parameters between SARS and DF

Parameters	SARS vs DF(Sequential)	Mean difference	Effect of time	Interaction between time and patient group	SARS vs DF(Daily)
ALC	SARS Lower($P < 0.0001$)	0.79×10^9/L(95% CI, 0.62-0.92×10^9/L)	$P < 0.0001$	$P < 0.0001$	D1 ($P = 0.622$)D2 ($P = 0.01$) D3 to 6 ($P < 0.0001$)
ANC	SARS Higher($P < 0.0001$)	1.62×10^9/L(95% CI, 1.18-2.06×10^9/L)	$P = 0.24$	$P < 0.0001$	D1 to 5 ($P < 0.0001$) D6 ($P = 0.012$)
Hb	SARS Lower($P < 0.0001$)	1.08 g/dL(95% CI, 0.62-1.53 g/dL)	$P < 0.0001$	$P = 0.0025$	D1 to 3 ($P = 0.002$)D4 ($P = 0.005$) D5 ($P = 0.132$)D6 ($P = 0.004$)
PLT	SARS Higher($P < 0.0001$)	101.9×10^9/L(95% CI, 86.9-117.0×10^9/L)	$P < 0.0001$	$P < 0.0001$	D1 to 6 ($P < 0.0001$)
WBC	No Significant Difference($P = 0.089$)	-	$P = 0.142$	$P < 0.0001$	D1 ($P = 0.012$)D2 ($P < 0.0001$) D3 ($P = 0.002$)D4 ($P = 0.919$) D5 ($P = 0.154$)D6 ($P = 0.014$)

ALC: absolute lymphocyte counts; ANC: absolute neutrophil count; DF: dengue fever; Hb: haemoglobin; PLT: platelet; SARS: severe acute respiratory syndrome; WBC: white blood count

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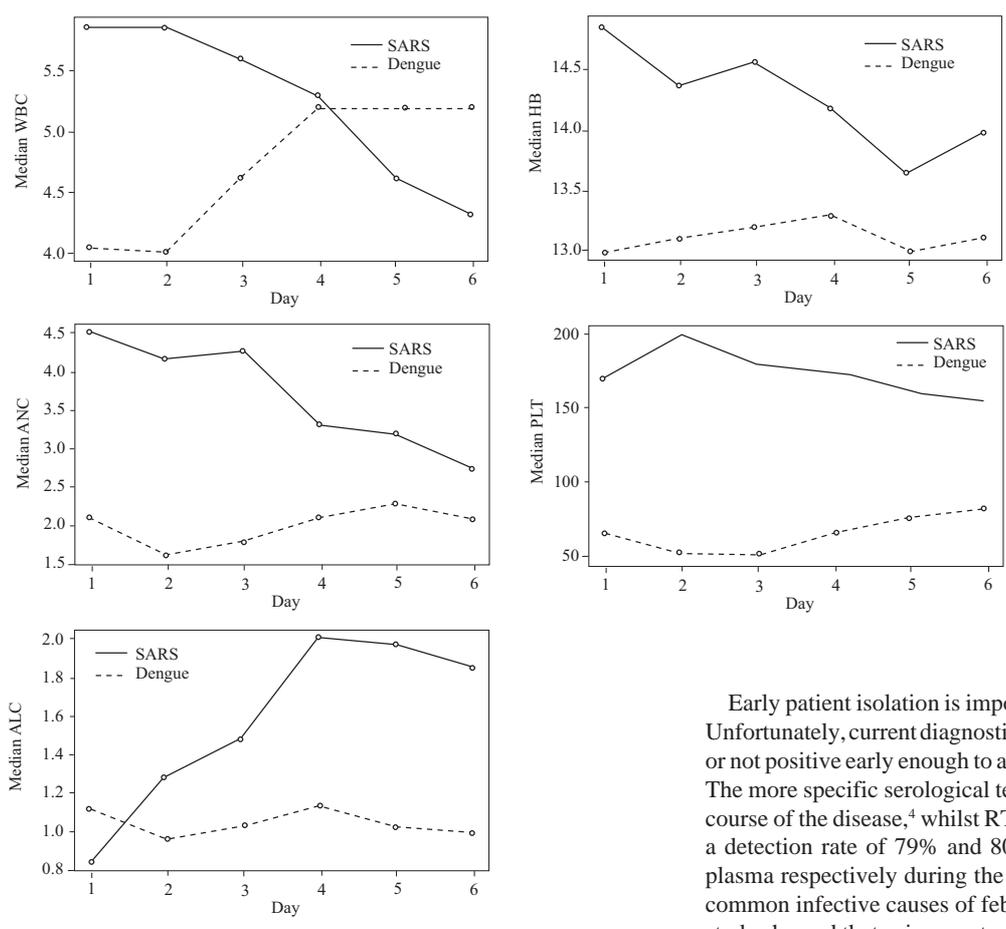
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Fig. 1. Trends in different haematological parameters during the first 6 days of illness for SARS and dengue patients.

of day 2 and day 3 PLT as the predictor, the area under ROC curve is 0.976 (95% CI, 0.95-1). The best cut-off PLT value is 123.5 x 10^9/L and this will differentiate SARS from DF with a sensitivity of 95.9% and specificity of 92%. Using logistic regression with the mean of day 2 and day 3 PLT and the mean of day 2 and day 3 ANC as the predictors, a predicted probability of SARS is calculated for each patient, and the predicted probability is used for ROC analysis. The area under ROC curve is only improved to 0.978 (95% CI, 0.952-1) but the interpretation will be difficult because the cut-off point will be using predicted probability calculated from the model and this cut-off point is not easy to use in practice. So the mean of day 2 and day 3 platelet count alone is probably good enough as a discriminator between these 2 common causes of febrile illness during a SARS outbreak.

Discussion

During a SARS outbreak, most patients with fever presented themselves to the emergency department at Tan Tock Seng Hospital. This gave us the opportunity not only to study the sequential changes in haematological parameters in SARS but also other common infections like DF.

Early patient isolation is important for the containment of SARS. Unfortunately, current diagnostic tests are either not sensitive enough or not positive early enough to allow identification of SARS patient. The more specific serological test only becomes positive late in the course of the disease,[4] whilst RT-PCR for the coronavirus RNA has a detection rate of 79% and 80% in nasopharyngeal aspirate and plasma respectively during the first 3 days of illness.[5,6] One of the common infective causes of febrile illness in Singapore is DF. Our study showed that using a cut-off platelet count of 123.5 x 10^9/L on day 2 and day 3 of febrile illness, SARS could be differentiated from dengue with a sensitivity and specificity of greater than 90%.

Conclusion

Platelet count early on in the disease allows for differentiation between 2 common infective causes of febrile illness during a SARS outbreak and may facilitate more effective utilisation of isolation facilities.

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EXTENDED ABSTRACTS

Prevalence of Dementia in Singapore – Results of the National Mental Health Survey of the Elderly 2003

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Background/Aims

Singapore's rate of population ageing (3% annually) is 2 to 3 times greater than those in developed countries. The population comprises of 7.6% elderly people ≥65 years old. The three main ethnic groups are the Chinese (77%), Malay (14%) and Indians (8%).

Two major surveys were previously done in Singapore to determine the prevalence of dementia in Singapore. The first survey done in 1985 involved 612 Chinese living in the community, using the Geriatric Mental State Examination (GMS),[1,2] found the prevalence of dementia to be 1.8%.[3] Another survey done in 1990 involving 349 elderly subjects,) using the Elderly Cognitive Questionnaire (ECAQ) to screen, followed by the GMS, found the prevalence of dementia to be 4.0% in Malay elderly and 2.5% in Chinese elderly.[4] A study on 234 elderly Chinese living in the Queenstown district in 2002 found the prevalence of cognitive impairment to be 7.7% using the ECAQ and 13.2% by the Informant Questionnaire on the Cognitive Decline of the Elderly (IQCODE).[5]

This study aims to provide nationally representative estimates of the prevalence of dementia in the elderly population of Singapore.

Method

A cross-sectional community survey of a national ethnically stratified random sample of older adults 60 years and above (n = 1092) was conducted. Selection of households is culled from MOH's census of addresses in Singapore. As close to an equal number of clients per district as possible was recruited. The criteria for inclusion into the study were: 60 years or above; citizens or permanent residents of Singapore; Chinese, Malay and Indian ethnicity; must not be incapacitated or mentally unfit to answer the interview questions. Domestic workers and sub-tenants were not qualified for the interview. The subjects were interviewed in their homes by Chinese, Malay or Indian psychiatric nurses who have been trained to administer the GMS. Chinese and Malay translated versions of the GMS were used for interviewees who could not understand English. A pilot study involving 100 elderly was done before the actual survey. Socio-demographic data was collected and the GMS[3,4] was administered. The Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) was used to diagnose dementia.

Results

The response rate was 72.4%. The non-response rate was 27.6%. The number of cases who could not be contacted was 345 (22.9%). The number who was rejected was 71 (4.7%). The final number in the sample was 1092. The overall prevalence of dementia for older adults ≥60 years, ≥65 years and ≥75 years were 5.2%, 6.0% and 13.9% respectively. The prevalence of dementia in the age groups 60-64 years, 65-74 years, 75-84 years and ≥85 years were 0.8%,

Table 1. Population-weighted Prevalence Point Estimates (95% Confidence Intervals) of Dementia in Older Adults Aged 60 and Above in Singapore, 2003

	N	%	(95% CI)
≥60 years (overall)	77	5.2	(3.6-6.7)
≥65 years	73	6.0	(4.0-8.0)
≥75 years	40	13.9	(7.9-19.9)
Age			
60-64 years	4	0.8	(0.0 -1.8)
65-74 years	33	4.0	(2.0-5.9)
75-84	28	9.2	(4.5-13.9)
≥85 years	12	32.2	(11.7-52.7)
Gender			
Male	16	2.2	(0.7-3.6)
Female	61	7.8	(5.1-10.4)
Ethnicity			
Chinese	22	4.2	(2.5-6.0)
Malay	34	9.4	(6.2-12.6)
Indian	21	8.8	(5.0-12.5)

There were statistically significant differences in dementia prevalence by gender ($P < 0.001$), age ($P < 0.001$), and ethnicity ($P < 0.001$).
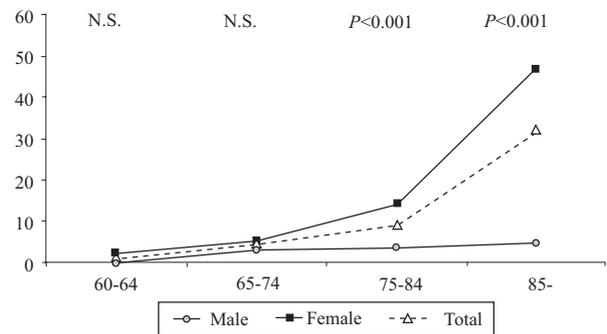

Fig. 1. Prevalence of dementia by gender and age.

4.0%, 9.2% and 32.2% respectively. Among elderly ≥ 65 years old, the prevalence of dementia in male and female subjects was 3.2% and 8.3% respectively ($P < 0.001$); in Chinese, Malay and Indian ethnic groups it was 5.2%, 11.1% and 7.2% respectively ($P < 0.001$).

Conclusion

These are the first estimates of dementia prevalence based on a nationally representative sample of elderly subjects in Singapore. They are twice as high as those determined from limited sample data from selected districts a decade ago, and point to a need for current review and future planning of resources to provide for adequate and effective care and management of the cognitively impaired/demented elderly in a rapidly ageing community.

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NHG Doctor Award Finalist

Preoperative Microalbuminuria, Haptoglobin Phenotype 2-2, and Age Are Independent Predictors for Acute Renal Failure Following Coronary Artery Bypass Graft

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Introduction

Acute renal failure (ARF) after coronary artery bypass graft (CABG) is associated with high morbidity and mortality. Microalbuminuria (MAU) and haptoglobin phenotype were recently reported to be associated with mortality in patients with ischaemic heart disease. We hypothesised that the presence of pre-op MAU and an Hp2-2 phenotype may also be independent risk factors for post-CABG ARF.

Materials and Methods

Over 2 years, 148 patients referred for elective isolated CABG by their cardiologists were recruited for this prospective study at National University Hospital (Singapore). ARF was defined as a rise in serum creatinine (cr) level of ≥ 0.5 mg/dL when baseline cr was <2.0 mg/dL or ≥ 1.5 mg/dL when baseline was ≥ 2.0 mg/dL. MAU was defined as a 24-hour urine albumin excretion of 30 mg to 300 mg. Hp was determined by non-denatured polyacrylamide gel electrophoresis (PAGE) and peroxidase staining.

Results

Out of 148 patients (male gender 80%; age: 59.7 ± 8.7 yrs; Chinese: 70.3%, Malay: 12.8%, Indian: 16.9%; type 2 DM: 60%), 27 patients developd postoperative ARF (18.2%). Three patients (2%) required dialysis (1 Hp2-1 and 2 Hp2-2) and 3 patients (2%) (3 Hp2-2) died. On univariate analysis, ARF was significantly associated with age (65.6 ± 6.5 years versus 58.4 ± 8.6 years, $P = 0.0001$), lower preoperative eject fraction (EF) ($36 \pm 15\%$ versus $45 \pm 13\%$, $P = 0.007$), Hb (12 ± 2 versus 14 ± 1 mg/dL, $P = 0.006$) and 24 h urine creatinine clearance rate (59 ± 23 versus 73 ± 24, $P = 0.01$), higher preoperative creatine level (12 ± 36 versus 102 ± 36 umol/L, $P = 0.01$) and polymorphic WBC percentage ($63 \pm 7\%$ versus $59 \pm 9\%$, $P = 0.009$), preoperative left ventricular (LV) enlargement (30% versus 12%, $P = 0.008$) and Digoxin use (67% versus 15%, $P = 0.001$). Hp2-2 (25% Hp2-2 versus 11% Hp1-1 and Hp2-1 combined,

$P = 0.03$) and MAU were also significantly associated with ARF (55% MAU versus 8% non-MAU, $P = 0.0002$). On multivariate analysis preoperative MAU (OR = 56, 95% CI, 7-445, $P = 0.0003$), Hp2-2 (OR = 5.4, 95% CI, 1.2-24, $P = 0.03$) and age ≥ 60 years (OR = 18, 95% CI, 3-126, $P = 0.003$) remained as independent predictors for ARF after adjusting for gender, race, diabetes, preoperative LV enlargement, digoxin use, Hb level, EF and creatinine level (Table 1).

Table 1. Multivariate Analysis of Factors Associated with Acute Renal Failure Following Elective Isolated Coronary Artery Bypass Graft

Covariate	OR	95% CI for OR	P value*
Race [Malay vs (Chinese + Indian)]	6.3	0.8-42	0.08
Gender (Female)	1.4	0.2-9.9	0.73
Preoperative Hb (<12g/dL)	1.3	0.2-7.2	0.75
Preoperative LV enlargement (Yes vs No)	3.6	0.8-17	0.1
Preoperative EF (<45%)	1.04	0.2-5.2	0.96
Diabetes (Yes vs No)	0.2	0.04-1.2	0.08
Preoperative digoxin usage (Yes vs No)	2.0	0.2-1.2	0.06
Preoperative serum creatinine ($\geq 120\,\mu$mol/L)	3.3	0.6-19	0.19
Age (≥ 60 y)	18	3-126	0.003
Hp phenotype [Hp2-2 vs (Hp1-1+Hp2-1)]	5.4	1.2-24	0.03
Preoperative microalbuminuria (Yes vs No)	56	7-445	0.0003

P values from Wald test.

Discussion

Proteinuria has been accepted as a reliable indicator of the severity of end-stage renal disease. Microalbuminuria (MAU) is defined as the presence of urinary albumin excretion of 30 to 300 mg/24 h. MAU is a clinical marker for early kidney dysfunction. The presence of MAU defines the clinical onset of diabetic nephropathy. MAU has also been previously reported to be a powerful predictor of cardiovascular disease in both diabetic and nondiabetic subjects.[1,2] Our finding of MAU as the strongest predictor of ARF following CABG, independent of such known variables such as diabetes,

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EXTENDED ABSTRACTS

hypertension and pre-existing renal dysfunction, is novel and unexpected. The underlying basis for this association remains unclear. We hypothesise that MAU may be a clinical marker for small vessel disease in the kidney, which is likely to be common in high-risk patients with large vessel atherosclerotic disease (e.g., coronary artery disease) requiring CABG surgery. It is likely that patients with small vessel disease of the kidney are more vulnerable to the decrease and maldistribution of renal blood flow, the increase in renal vascular resistance, and the decrease in glomerular filtration rate that occur during CABG surgery.

Haptoglobin (Hp), an α_2-sialoglycoprotein with haemoglobin (Hb)-binding capacity, has 3 phenotypes: Hp1-1, Hp2-1 and Hp2-2. The Hb-binding function of Hp prevents iron loss and has until recently been generally accepted as the major mechanism underlying prevention of kidney injury ("pigment nephropathy") during haemolysis. However, recent studies show that Hp appears to play an important physiological role as an antioxidant rather as an Hb-binding protein which prevents renal deposition of Hb during haemolysis. The known ability of Hp to inhibit the synthesis of vasoconstricting prostaglandins may underlie the renal vasoconstriction leading to ARF in this mouse model of chemically-induced haemolysis.[3,4] Hp 2-2 has been reported to be associated with the prevalence of autoimmune and inflammatory disorders, as well as cardiovascular conditions such as essential hypertension, CAD mortality, and restenosis after PTCA.[3,5] During CABG surgery, the requirement for intraoperative cardiac pulmonary bypass is associated with haemolysis. We now report the novel identification of Hp 2-2 as an independent risk factor for the development of ARF following CABG.

A steady decline in renal function is a normal event associated with ageing. The ageing process results in anatomic and functional changes in the kidney. Histological examination confirms the disappearance of functional nephrons with age; as many as half of the glomeruli present in young adults may be gone or rendered nonfunctional by 80 years of age.[6] The common functional change is a diminution in renal reserves, along with constraints on the kidney's ability to respond appropriately to acute illness. Consistent with previous studies of ARF following CABG,[7,8] we found that age ≥60 years is an independent risk factor for ARF in our study.

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