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1

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In this issue

Rob Siebers, Editor

Acute promyelocytic leukaemia (APML) presentation is characterised by a distinct combination of morphological, immunophenotypic, molecular and coagulation features. The definitive diagnosis is made by demonstrating the presence of the PML-RARA (retinoic acid receptor-α) fusion gene and the classic t(15;17) (q24;q21) translocation. The molecular and cytogenetic tests are not available onsite at the SCL Dunedin laboratory. Without this onsite molecular service, the option for a follow-up flow cytometry assay tube specific for APML was investigated and reported by Terry Taylor in an article in this issue. A 2nd line flow cytometry tube consisting of CD9, CD18, CD45 and CD11c was trialled on 15 bone marrow aspirate samples to access performance in isolating APML over a range of different haematology malignancies. Incorporation of the 2nd line tube on cases with a suspect original APML immunophenotype raises awareness of the possibilities for either APML or NPM1 positive AML.

There is rapid rise in the prevalence of diabetes mellitus and pre-diabetes in Nigeria, however, there is a lack of data from south-south Nigeria. The aim of this study was to investigate the prevalence of pre-diabetes and undiagnosed diabetes mellitus in adults in the Warri Metropolis, Southern Nigeria. In this issue, researchers from Nigeria measured fasting plasma glucose levels in 420 adults over a wide age range. They found a pre-diabetes and diabetes mellitus prevalence of 10.7@ and 8.3% respectively. These rates are higher than previously reported in other areas of Nigeria.

Acute appendicitis (AP) is one of the most common causes of acute abdomen and requires emergency surgery. A number of studies have shown that serum bilirubin levels may be a complementary factor for the early diagnosis of perforated and/or non-perforated appendicitis. In this issue, researchers from Iran prospectively followed patients presenting to the ED with acute abdominal pain over a two year period and compared their total and direct bilirubin levels with a normal group. They found that total bilirubin levels were the highest in the perforated appendicitis group and were also raised in the non-perforated appendicitis group. Direct bilirubin levels were also significantly increased in the perforated appendicitis group. The authors conclude that total and direct bilirubin levels can be a valuable additional criterion for the early diagnosis of perforated and non-perforated appendicitis.

Very long-chain acyl-coenzyme A dehydrogenase deficiency (VLCADD) is a genetic disorder of fatty acid metabolism, with an autosomal recessive inheritance pattern. In this issue, Kayleigh Hancock and Karen McKinley present a case study of an infant with VLCADD repeatedly presenting with very high creatine kinase levels and comment on the dietary treatment of this disorder.

In this issue Terry Taylor tells us what it is like to be the President of the NZIMLS and points out what is involved with the governance and everyday responsibilities of the NZIMLS Council. He gives a valuable insight of what the NZIMLS does for its members.

With this issue there has been a change to the Journal's Editorial Board. First, Julie Creighton from Canterbury Health Laboratories has been appointed as joint Deputy Editor. Over a period of time she will learn all the intricacies (and problems) of putting together the Journal's issues under the guidance of myself as Editor and the other Deputy Editor, Mike Legge. In due course she will (hopefully) assume the role of Editor when I finally retire from this role. Cat Ronayne from Otago University is stepping down from the Editorial Board and her place will be taken by Craig Mabbett form LabCare Pathology, New Plymouth. We are sad to see Cat go, she has given valuable service to the Board over a number of years. We welcome Craig, and also Julie in her new role.

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Barrie Edwards Rod Kennedy

Successful applicants will be required to provide a full written report on return which will be published in the Journal. If not intended to publish elsewhere, successful applicants will be required to submit their study results for consideration by the New Zealand Journal of Medical Laboratory Science.

ORIGINAL ARTICLE

Using flow cytometry to assist in differentiating acute promyelocytic leukaemia cases from other acute myeloid leukaemia sub groups

Terry Taylor

Southern Community Laboratories, Dunedin

ABSTRACT

Acute promyelocytic leukaemia (APML) presentation is characterised by a distinct combination of morphological, immunophenotypic, molecular and coagulation features, and is found in 5- 8% of all adult acute myeloid leukaemia (AML) cases diagnosed in Western countries. Using data collected from our laboratory since 2001 the occurrence in Otago/Southland is 9%.

APML generally presents acutely and cases can deteriorate quickly. A quick and accurate diagnosis of APML therefore, ensures timely administration of all-trans-retinoic acid (ATRA) and the prioritised management of the resulting disseminated intravascular coagulation (DIC). APML presents with a myeloid immunophenotype and the early progenitor antigens CD34 and HLA-DR are generally negative. Definitive diagnosis is made by showing the presence of the PML-RARA (retinoic acid receptor-α) fusion gene and the classic t(15;17) (q24;q21) translocation (1,2).

A 2nd line flow cytometry tube consisting of CD9, CD18, CD45 and CD11c was trialled on 15 bone marrow aspirate samples to access performance in isolating APML over a range of different haematology malignancies. There were 12 myeloid neoplasms and 3 lymphoid neoplasms tested and two cases demonstrated the expected APML immunophenotype. The first case was confirmed with APML showing the PML-RARA fusion gene and the second case identified as an AML with the NPM1 mutation and absence of PML-RARA. This identified another cohort of AML patients that have a similar presenting immunophenotype to APML but have the NPM1 mutation.

Incorporation of the 2nd line tube on cases with a suspect original APML immunophenotype raises awareness of the possibilities for either APML or NPM1 positive AML in the Otago/Southland region.
Keywords: acute promyelocytic leukemia, acute myeloid leukemia, flow cytometry.

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INTRODUCTION

Acute promyelocytic leukaemia (APML) presentation is characterised by a distinct combination of morphological, immunophenotypic, molecular and coagulation features. Morphologically the APML blast cells can be either hypergranular or microgranular (2). The presentation is generally acute and cases can deteriorate quickly due to the effects of disseminated intravascular coagulation (DIC) and the resulting consumptive coagulopathy (2,4,10). APML is found in 5- 8% of all acute myeloid leukaemia (AML) cases diagnosed in Western countries (2,4). Treatment in New Zealand is based around ATRA therapy.

A quick and accurate diagnosis of APML ensures timely administration of ATRA and the prioritised management of the patient's DIC. The mortality without early intervention and treatment is higher than that of other subtypes of acute leukaemia (2,10). The definitive diagnosis is made by demonstrating the presence of the PML-RARA (retinoic acid receptor-α) fusion gene and the classic t(15;17) (q24;q21) translocation. The molecular and cytogenetic tests are not available onsite at the SCL Dunedin laboratory and results generally take up to 36 hours from the referral laboratory. Without this onsite molecular service the option for a follow-up flow cytometry assay tube specific for APML is to be assessed. It is also acknowledged that there is a small subset of APML cases that have molecular variations of the RARA fusion gene that will not be confirmed by the initial molecular screening investigations.

The other consideration for a quick assessment is that acceptance onto AML clinical trials for non-APML cases needs to be determined quickly. Being part of a clinical trial will give accepted patients access to new AML drugs and combinations that are generally not funded for use in NZ. Because confirmed APML already has an established proven treatment regime it is essential that patients are triaged into the appropriate group in a timely manner.

APML typically presents with a distinctive immunophenotype by flow cytometry (2,4,5,7,8). The early progenitor antigens CD34 and HLA-DR are generally negative and the myeloid antigens CD117, CD13, CD33 and cytoplasmic myeloperoxidaseare positive (2,4,5). The myelomonocytic antigen CD64 can be weakly positive and generally CD15 is negative.

The most common aberrant antigens expressed in APML are CD2 and CD56 (2,4). There has been a well described association between the presence of aberrant CD2 and the microgranular variant of APML (1, 4).

A search of the recent literature, as well as discussions with colleagues, was undertaken to establish what the best relevant 2nd line flow cytometry approach would be. The aim was to assess the possibility of setting up a 2nd line flow cytometry tube that would assist in providing a quick result if the initial morphology and/or immunophenotype raised the possibility of APML. Table 1 shows the combination that was determined would provide the most useful information.

The integrin's CD18 and CD11c are found on mature myeloid and monocytic cells and occasionally on myeloid blasts (6-8). Promyelocytes from APML patients are usually negative for both CD18 and CD11c (6-8). CD9 can be expressed on mature B and/or T-cells and can be expressed on B-ALL blasts and some myeloid leukaemic blast cells (2,10,11). Most APML blasts show moderate to strong expression of CD9 (5,10,11). The expected pattern in APML for the 2nd line monoclonal antibodies selected is CD9 positive and CD18 and CD11c negative. This is shown in Table 2 with the expression and the expected occurrence in APML and non-APML cases from the literature (6,7,11). It is noted that this data can vary due to the differing cut-offs used by laboratories to determine positive antibody expression and the different population cohorts used.

Table 1. Trial 2nd line APML tube.

Manufacturer	Beckman Coulter			
Antibody	CD9	CD18	CD45	CD11c
Clone	ALB6	7E4	J33	BU15
Fluorohrome	FITC	PE	PC5.5	APC
Volume	10µl	10µl	10µl	10µl

MATERIALS AND METHODS

The bone marrow aspirate samples for this trial all came from a selection of cases that were having initial flow cytometry investigations for malignant haemopoietic disease. These samples were prepared by lysing 1ml of bone marrow aspirate with 9ml of BD Pharm Lyse™ (diluted 1:10 in distilled water). This suspension was incubated for 10 minutes and then cetrifuged at 350g for five minutes and the supernatant discarded. The cell pellet was resuspended in 1ml cell wash. 10µl of each monoclonal antibody was added to a labelled 5ml opaque plastic tube and 100µl of the cell suspension was added. This was incubated for 20 minutes in the dark at room temperature. 1ml of BD FACS™ lysing fixative (diluted 1:10 in distilled water) was added and incubated for a further 5 minutes. The sample was washed twice for two minutes at 350g and resuspended in 500µl of cell wash for analysis. The samples were acquired and analysed on a Beckman Coulter Navios™EX flow cytometer.

A total of 15 bone marrow aspirate samples were analysed using the APML 2nd line tube to access performance over a range of different haematology malignancies. All of these samples had first line flow cytometry screening performed for the relevant malignancies being assessed using appropriate progenitor, myeloid, monocytic and lymphoid markers. There were 12 myeloid neoplasms and three lymphoid neoplasms tested to give an overall picture of how the expression varies between different malignant cell types. It is noted that without having access to a larger pool of HLA-DR negative AML cases that the literature findings have been used to anticipate the specificity of the 2nd line panel.

Table 2. Expected APML expression pattern and incidence in confirmed cases compared to non-APML cases of AML.

Antigen	CD9	CD11c	CD18	CD34	HLA-DR	CD117
Expression pattern	Mod/Strong Pos	Neg	Neg	Neg	Neg	Pos
APML incidence%	97%	100%	92%	83%	97%	78%
Non-APML Incidence%	40%	11%	45%	19%	15%	82%

Table 3. Results for 15 haemopoietic malignancies.

Sample	Blast count %	CD9	CD11c	CD18	HLA-DR	CD34	CD117	Diagnosis
1	90	Weak Pos	Pos	Neg	Pos	Neg	Pos	AML
2	40	Neg	Pos	Neg	Pos	Pos	Pos	AML
3	96	Strong Pos	Neg	Neg	Pos	Neg	Neg	B-ALL
4	80	Neg	Partial Pos	Pos	Pos	Pos	Pos	AML
5	97	Weak Pos	Neg	Neg	-	Neg	-	CLL
6	90	Neg	Pos	Pos	Pos	Neg	Pos	AMOL
7	25	Neg	Partial Pos	Pos	-	Neg	-	FL
8	57	Partial Pos	Partial Pos	Neg	Pos	Partial Pos	Pos	AML
9	36	Partial Pos	Neg	Neg	Pos	Pos	Pos	AML
10	80	Mod Pos	Neg	Neg	Neg	Neg	Pos	APML
11	85	Neg	Neg	Neg	Pos	Pos	Pos	AML
12	30	Neg	Neg	Neg	Pos	Pos	Pos	AML
13	30	Partial Pos	Partial Pos	Neg	Pos	Pos	Pos	AML
14	60	Neg	Neg	Neg	Pos	Pos	Pos	AML
15	91	Mod Pos	Neg	Neg	Neg	Neg	Pos	?APML*

APML: acute promyelocytic leukaemia; AML: acute myeloid leukaemia; B-ALL: B-cell acute lymphoblastic leukaemia); CLL: chronic lymphocytic leukaemia); AMOL: acute monoblastic leukaemia; FL: follicular lymphoma.

RESULTS

The results from these investigations are shown in Table 3. As the trial tube is a 2nd line test to assist in the diagnosis of APML it is noted that 13 cases in this trial that would not usually have this follow-up testing. Using the initial immunophenotyping and morphology to triage cases having suspicion for APML samples 10 and 15 from Table 3 would require 2nd line testing as these samples both show the expected APML phenotypic pattern.

The first case (number 10) presented with a classic APML immunophenotype and morphology with a consumptive coagulopathy and had positive molecular results for the PML-RARA fusion and had the t(15;17) translocation confirmed. The second case (number 15) presented with a high WBC and blast count and had a consumptive coagulopathy. The morphology was not classical for APML but the patient was given ATRA treatment while waiting for the result of the FISH (Fluorescence in situ Hybridization) analysis for the PML-RARA fusion gene. This patient had a negative result for the PML-RARA fusion gene and subsequent molecular analysis identified the presence of the NPM1 (Nucleophosmin-1) mutation.

DISCUSSION

Between January 2001 and October 2018 the Dunedin flow cytometry laboratory has performed immunophenotyping on 239 adult acute leukaemia cases from the Otago/Southland region. There have been 32 acute lymphoblastic leukaemia (ALL) cases (13%), 202 AML (85%) and 5 others (2%). From the AML group there have been 19 confirmed APML cases (9%) which gives a comparable rate to other studies (5-8%). From those figures it would be expected to see an average of 1-2 APML cases per year. The low numbers of expected cases within this data set is noted and future testing will give an overall indication of the relevance of this approach. At this stage the 2nd line test is a 4-colour tube with the potential to incorporate into a multicolour tube in the future.

The case of the NPM1 positive patient from Table 3 (sample 15) does highlight an issue in that this relatively common AML molecular finding (found in around 30% of all AML cases) can have blast cell expression that mirrors the APML immunophenotype (2,3,8). Recent publications have shown the incidence of patients with the NPM1 mutation showing an APML immunophenotype occur in 10% of all AML cases (3). Recent research indicates that patients with the APML immunophenotype have a longer relapse-free and overall survival than NPM1 patients with a conventional AML immunophenotype (9). There is data from an elderly cohort that shows that AML patients with the NPM1 mutation treated with ATRA combined with arsenic trioxide (ATO) prolongs time to relapse and overall survival although this is based on observation on patients not eligible for conventional AML therapy (9). It is recommended to begin ATRA treatment quickly if there is a strong suspicion of APML (8) in all AML cases. There is no evidence of initial ATRA treatment causing worse patient outcomes in NPM1 cases showing the APML immunophenotype which is reassuring for clinical providers (8,9).

CONCLUSION

The 2nd line CD9/CD11c/CD45/CD18 tube in combination with the frontline screening AML tubes will provide valuable initial diagnostic information as to the likelihood of either an APML or an AML with the NMP1 mutation. The 2nd line tube will be added on AML cases showing absence of HLA-DR and/or CD34 expression plus any morphologically or clinically suspect cases. It would be expected that the suspect APML immunophenotype would be found in 2-4 patients per year in the Otago/Southland region. This trial has helped to raise awareness of the possibilities for either APML or NPM1 positive AML in a cohort of patients and will assist in giving a quick and accurate assessment that will allow a swift clinical decision with regards to both treatment approach and trial eligibility moving forward.

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ORIGINAL ARTICLE

Prevalence of pre-diabetes and undiagnosed diabetes mellitus among adults in the Warri Metropolis, Nigeria

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ABSTRACT

Objectives: Diabetes mellitus, a disorder of multiple etiologies is characterised by chronic hyperglycemia and is usually preceded by pre diabetes a condition of impaired fasting glucose (IFG) which places individuals at high risk of developing diabetes and its complications. These two non-communicable diseases are not detected or diagnosed early when the symptoms have not yet manifested. Therefore, the aim of this study was to investigate the prevalence of pre-diabetes and undiagnosed diabetes mellitus of apparently healthy adults in Warri, Nigeria.
Methods: Glucose oxidase para-aminophenol spectrophotometric method was used to evaluate plasma fasting blood glucose concentrations in 420 adults within age limit of 21 to 85 years.
Results: Prevalence of pre-diabetes and diabetes mellitus were 10.7% and 8.3% respectively. Men had a higher prevalence of both pre-diabetes and diabetes mellitus of 12.4% and 9.5% respectively while prevalence of diabetes mellitus in females increased with age.
Conclusions: Prevalence of pre-diabetes and diabetes mellitus is increasing, and there is an urgent need for intervention relating to life style changes and frequent fasting blood glucose evaluation.

Key words: pre-diabetes, diabetes mellitus, fasting blood glucose, Nigeria.

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INTRODUCTION

Globally, diabetes is a health challenge and an issue of public health concern most markedly in the world's middle-income countries (1- 7). Diabetes mellitus is a disorder of multiple etiologies characterised by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both (8). Typical symptoms are hyperglycemia including polydipsia, polyphagia, polyuria, blurred vision, weight loss, and generalised pruritis. (9). Prior to these symptoms, diabetes is preceded by impaired fasting glucose (IFG) resulting in a pre-diabetic state that can exist undetected for many years (2,10).

Pre-diabetes is a practical term referring to impaired fasting glucose (IFG) and an impaired glucose tolerance which places individuals at high risk of developing diabetes and its complications (3,5,9,11). The World Health Organization's criteria for diagnosing pre-diabetes are a fasting plasma glucose of ≥6.1-6.9mmol.L^{-1} for pre -diabetes, while a fasting plasma glucose of ≥7.0mmol.L^{-1} meets criteria for diabetes mellitus (3). The longer a person lives with undiagnosed and untreated diabetes, the worse the health and social outcomes are likely to be, therefore early detection and diagnosis is the starting point for living well (1,7).

Globally, there are a total of 422 million adults (18+years) with diabetes of which 25 million are in the African region with a prevalence of 7.1% (1). In 2012 there were 1.5 million deaths worldwide directly caused by diabetes (1) and Nigeria is the most affected country with diabetes in the sub-Saharan region of Africa (12). The prevalence varied from 0.65% in rural Mangu village in northern Nigeria to 11.0% in Urban Lagos in southern Nigeria (7). In the south East, prevalence of diabetes was 1.1% (13). Prevalence of pre-diabetes and undiagnosed diabetes mellitus was 9% and 7% respectively in the south-south (14). Recent studies in Agbor, Delta State, Nigeria reported a prevalence of 59% of Type 2 diabetes mellitus from suspected subjects with the risk of developing diabetes mellitus found to be increasing with age (15). Due to the reported rapid rise in prevalence of diabetes mellitus and pre-diabetes in Nigeria (1), there is a lack of data in south-south Nigeria. The aim of this study was to investigate the prevalence of pre-diabetes and undiagnosed diabetes mellitus in adults in the Warri Metropolis, Southern Nigeria.

MATERIALS AND METHODS

Study population

A total of 420 apparently healthy adults (210 male, 210 female) were recruited within the age limit of 21yrs to 85yrs from the Warri metropolis. Inclusion criteria were that all subjects were ambulant, while exclusion criteria were adults in wheel chairs, hospitalized, with stroke, ascites, catheterised, pregnant and nursing mothers, and diagnosed diabetic and hyperglycemic individuals. Informed consent was obtained from participants as well as ethical consent from the Ethics Committee of Central Hospital, Warri, Delta State, Nigeria. A structured questionnaire was designed to obtain information on age, gender and freedom from overt illness. Participants were required to have fasted for at least 12h (overnight) prior to blood glucose sample collection. The WHO criteria for diabetes were used in which

the fasting plasma glucose of participants was classified as normal: ≤ 6.0 mmol.L^{-1}), pre-diabetes: 6.1-6.9mmol.L^{-1}, or diabetes: (≥7.0 mmol.L^{-1} (16).

Sample collection and analysis

Venous blood was collected by standard venipuncture into fluoride-oxalate bottles and well mixed. The blood was centrifuged at 3000rpm for 10 minutes. The plasma was aliquoted into a plain tube, frozen, and analysed within 24hrs. Plasma blood glucose was analysed on a spectrophotometer using the GOD-PAP method by Barham and Trinder (17). All test kits used were a product of Randox Laboratories, UK, and used according to the manufacturer's instructions.

Statistical analysis

The group mean ±SD was calculated for glucose and significant difference between means and correlations were evaluated using GraphPad Prism 6 for software (La Jolla, California USA) windows with $P<0.05$ considered as statistically significant.

RESULTS

Out of the 420 samples from apparently healthy adults tested for fasting blood glucose, 45 (10.7%) had pre-diabetes (12.4% males, 9.0% females) while 35 (8.3%) had diabetes mellitus (males 9.5%,females 7.1%) respectively (Tables1 and 2). Table 2 also shows that males had a higher incidence of both pre-diabetes and diabetes mellitus (12.4% and 9.5% respectively) than women (9.0% and 7.1% respectively). The incidence of pre-diabetes was highest in the age group of 71-85 years (21.4%) and lowest in the age group of 41-50 years (2.0%) while incidence of diabetes mellitus was highest in two age groups of 61-70years and 71-85 years (12.9%) and lowest in age group of 31-40 years (2.9%), (Table 3 and Figure1). Table 3 demonstrates a statistically significant increase in the incidence of diabetes mellitus ($p<0.05$) as age group increased which is represented in Figure 1. Figures 2 and 3, and Table 4 demonstrates that frequency of pre-diabetic males was significantly higher in age group of 71- 85 years compared to females of the same age group and highest compared to other age groups in both females and males in the study population. However, the incidence of diabetes mellitus in females also increased with age (Table 3) with a significant increase ($p=0.005$) in mean fasting blood glucose between age groups in the study population.

DISCUSSION

Our study covered apparently healthy adults in the 21 to 85 age group unlike some previous studies which were limited to 65 years (1,16,18). The incidence of pre-diabetes in our study of 10.7% and diabetes mellitus of 8.3% were higher than 6.0% and 4.6% for pre-diabetes and diabetes mellitus reported in the Oke-ogun region of Oyo State of Nigeria (9), and higher than 1.1 % and 3.0% for pre-diabetes and diabetes respectively reported in Umudike, Nigeria (13). The incidence of diabetes in our study was higher than 2.8% of undiagnosed diabetes mellitus cases reported in Port Harcourt, Nigeria (18) and was also higher than 0.8% reported in the Uyo metropolis, Nigeria (16). The incidence in our study is similar to pre-diabetes of 9% and undiagnosed diabetes mellitus of 7% reported in Calabar, Nigeria (14). This study agrees with previous studies where the incidence of these two non-communicable diseases are increasing in Nigeria and therefore there is need for intervention (7,15). Prevalence of pre-diabetes in our study was lower than 35% and the same with diabetes of 10.9% in a cross sectional study in China (19).

The statistically significant increasing prevalence of diabetes in age groups 31-40 and 71-85 age groups in our study agrees with reports from southern Nigeria (15) where it was observed that diabetes increases with age. The statistically significant increasing prevalence of diabetes with age in females agrees with studies that reported that females have a tendency to accumulate adipose as they increase in age (9,13), especially post-menopause and with relatively reduced physical activity (2). The higher prevalence of pre-diabetes and diabetes mellitus in men compared to women is similar to a study in Calabar (14), a Nigerian cosmopolitan city. The prevalence of diabetes in men, even though this did not increase in the 21-30 age group, showed a significant increase in the 31-40 to the 61-70 age groups which could be attributed to reduced physical activity as they advance in age. In the very advanced age group of 71-85 years, men in this study tended to have a leaner body mass because of their reduced food intake which could result in weight loss and consequent reduced blood glucose which may have contributed to the lower prevalence in this age group (2, 20).

The higher prevalence of pre-diabetes and diabetes in men compared women observed in our study agrees with another study (20) which could be associated with the extracurricular social life style of men because of urbanization.

CONCLUSIONS

Our study identified an increasing incidence of pre-diabetes and diabetes mellitus in the Warri metropolis compared to previous investigations undertaken in Nigeria. We therefore advocate appropriate intervention programs by government and non-governmental organisations for increased information and testing for pre-diabetes and for lifestyle changes, by appropriate health professionals to identify pre-diabetes and diabetes aimed at the prevention and treatment of diabetes mellitus.

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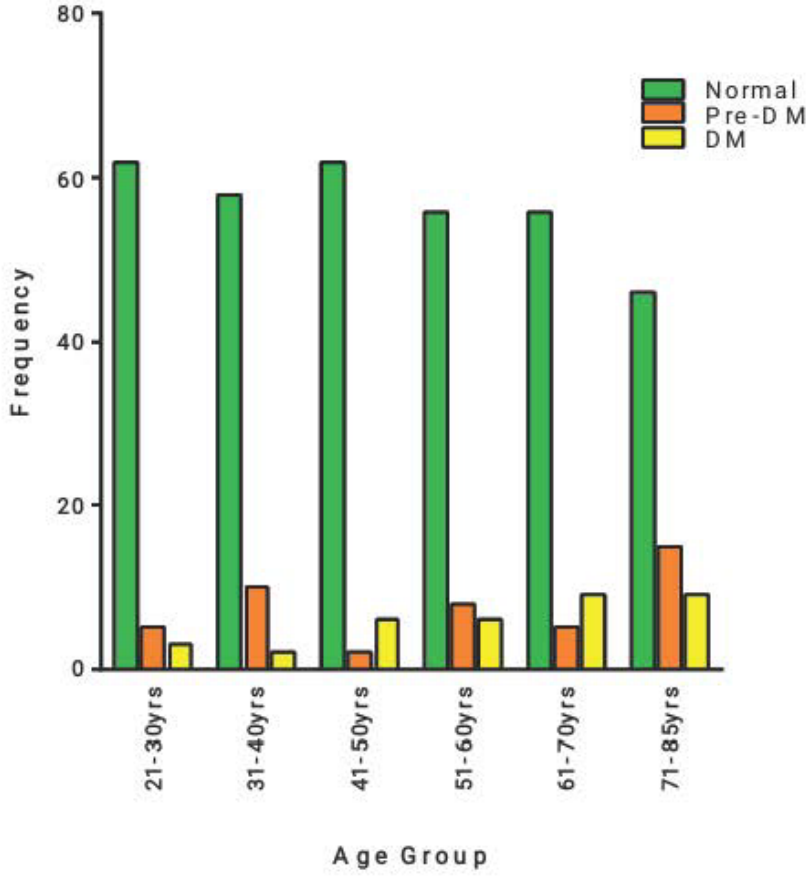

Figure 1: Shows frequency of Normal, pre-Diabetes and Diabetes mellitus according to age groups in the study population.

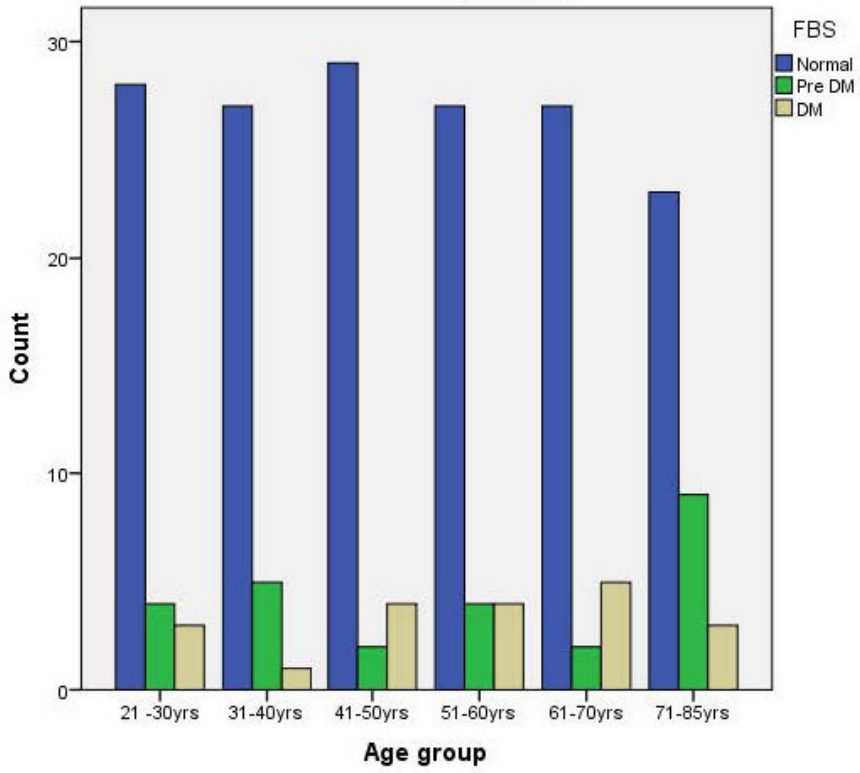

Figure 2: Frequency of Normal, Pre DM and DM in male age groups

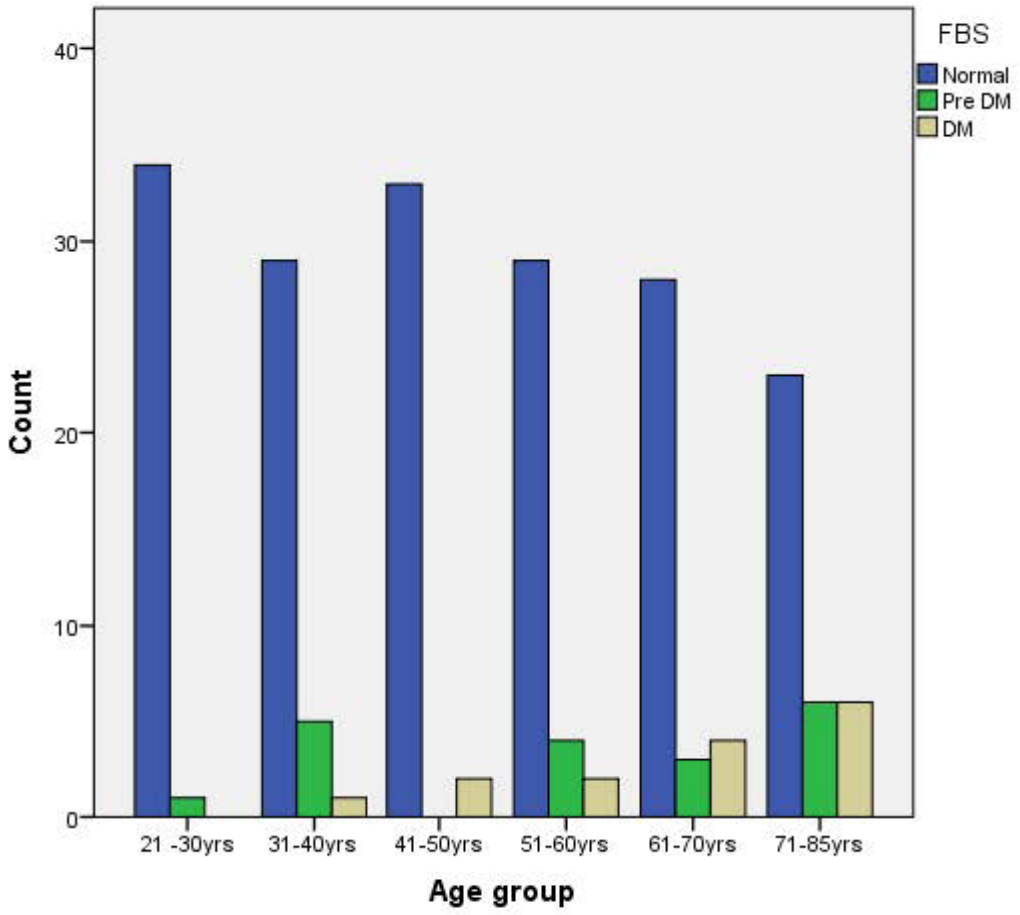

Figure 3: Frequency of Normal, Pre DM and DM in female age groups

Table 1. Incidence of pre-diabetes mellitus in the study population.

FBG Classification	No. of subjects	Prevalence (%)
Normal	340	81.0
Pre-Diabetes	45	10.7
Diabetes mellitus	35	8.3

Table 2. Incidence of pre-diabetes and diabetes mellitus according to gender in the study population.

FBG	Male	Female	X^2	P
Normal	164 (78.1)	176 (83.8)	2.227	0.328
Pre-Diabetes	26 (12.4)	19 (9.0)		
Diabetes	20 (9.5)	15 (7.1)		

Table 3. Fasting blood glucose (FBG) classification and incidence of pre-diabetes and diabetes mellitus according to age groups in the study population.

	21-30 yrs	31-40 yrs	41-50 yrs	51-60 yrs	61-70 yrs	71-85 yrs	P
FBG mmol/L ± sd	5.00 ± 0.14	5.01 ± 0.14	4.86 ± 0.14	5.11 ± 0.16	5.59 ± 0.27	5.61 ± 0.18	0.0005
Normal n (%)	62 (88.6)	58 (82.9)	62 (88.6)	56 (80.0)	56 (80.0)	46 (65.7)	0.006
Pre-diabetes n (%)	5 (7.1)	10 (14.3)	2 (2.9)	8 (11.4)	5 (7.1)	15 (21.4)	<0.05
Diabetes mellitus nu (%)	3 (4.3)	2 (2.9)	6 (8.6)	6 (8.6)	9 (12.9)	9 (12.9)	<0.05

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ORIGINAL ARTICLE

Comparison of serum direct and total bilirubin levels in patients with acute perforated and non-perforated appendicitis

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ABSTRACT

Objective: Acute appendicitis (AP) is one of the most common causes of acute abdomen requiring emergency surgery. The aim of this study was to compare serum total bilirubin (STB) and serum direct bilirubin (SDB) levels in patients with perforated appendicitis (PA) and non-perforated appendicitis (NPA).

Methods: Patients with acute abdominal pain referred to the emergency department (ED) of Golestan Hospital in Ahvaz from 2016 to 2017 were entered into the study based on the clinical criteria of abdominal pain in the lower right quadrant (LLQ), tendon right lower quadrant abdominal (RLQ), tenderness rebound of RLQ, anorexia, nausea, vomiting and fever, and were compared with a healthy group.

Results: Totally, 266 participants were studied. The results show that STB significantly changed with diagnosis of NPA ($P < 0.0001$), STB also significantly changed with diagnosis of PA ($P < 0.0001$). Although SDB did not significantly change with diagnosis of NPA ($P = 0.15$), it significantly changed with the diagnosis of PA ($P < 0.0001$).

Conclusion: Our findings showed that there is a correlation between both total and direct bilirubin levels and the detection of non-perforated appendicitis, and its measurement is beneficial. Total bilirubin levels were more consistent with the detection of perforated appendicitis than direct bilirubin levels.

Keywords: appendectomy, appendicitis, bilirubin.

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INTRODUCTION

Acute appendicitis (AP) is one of the most common causes of acute abdomen and requires emergency surgery (1,2). Symptoms of this disease are not always typical, and the differential diagnosis symptom is the right lower quadrant pain (3). Appendicitis occurs in 13% of men and 25% of women and the most common age of incidence of appendicitis is from the second to the fourth decade of life (4). If the appendix is perforated, severe abdominal pain occurs and the temperature rises to 39 to 40 degrees Celsius (5).

To date, different diagnostic criteria for acute appendicitis have been used such as the Alvarado score and diagnostic imaging techniques such as computed tomography (CT) scan, magnetic resonance imaging (MRI) and ultrasound. But these diagnostic criteria have some limitations (6). Alvarado score is based on clinical manifestations, C-reactive protein (CRP), white blood cell (WBC) count and leukocytosis. However, CRP, WBC count and increased leukocytosis is not specific for the diagnosis of acute appendicitis (7,8). In addition, although imaging techniques such as ultrasound, CT scan and MRI scans can be used for diagnosis, these methods are expensive and CT scan exposes patients to ionising radiation (9). The diagnosis of acute appendicitis is more likely for women, due to the wide range of differential diagnosis on genetic issues such as ectopic pregnancy, ovarian torsion, and mittal implant (10).

Despite the use of these diagnostic methods, the misdiagnosis in detecting AP has not decreased (9,11), and the results of several studies indicate that clinical and biochemical findings may be more valuable (11-18). In addition, these methods are not always available in some parts of low-income countries and the disease should be judged by clinical and laboratory evidence (14). The purpose of this study was to compare the serum total bilirubin (STB) and serum direct bilirubin (SDB) in patients with perforated appendicitis (PA) and non-perforated appendicitis (NPA).

MATERIALS AND METHODS

Design and study population

This prospective observational study was conducted according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) protocol (19) from 2016 to 2018. After obtaining approval from the Ethics Committee of the Ahvaz Jundishapur University as well as the written consent of participants, the patients referred to the emergency department (ED) of Golestan Hospital of Ahvaz, Iran were entered into the study.

Patients with acute abdominal pain who were referred to the ED were entered in the study based on the clinical criteria of abdominal pain in the lower right quadrant (LLQ), tendon right lower quadrant abdominal (RLQ), tenderness rebound of RLQ, anorexia, nausea, vomiting and fever, and compared to a healthy group. The exclusion criteria included age of less than 18 years, and medical conditions that may affect SDB and STB, such as hepatobiliary diseases associated with hyperbilirubinemia, hemolytic diseases, history of alcoholism, certain infectious diseases, inflammatory bowel disease, any malignancy, pregnancy, and recent abdominal surgery.

Data collection

Total bilirubin and direct serum levels were requested for patients and the healthy group. In addition, the clinical, medical imaging, and pathological features were analysed. At the same time, patients underwent treatment for acute appendicitis. Ultimately, patients with the diagnosis of appendicitis underwent surgery. The severity of appendicitis was classified as normal, PA or NPA based on the operative report (20).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software. Data are expressed as percentages and mean ± standard deviation. Continuous data was compared by independent t-test and categorical data was compared by the chi-square test or Fisher's exact test. A P value of < 0.05 was deemed statistically significant.

RESULTS

Demographic variables and STB and SDB levels in the healthy, PA, and NPA groups are shown in Table 1. These results show that STB levels in NPA and PA patients were significantly higher, compared to the healthy group ($P < 0.0001$). Although SDB levels did not significant change with a diagnosis of NPA ($P = 0.15$), SDB levels were significantly higher in the PA group ($P < 0.0001$).

The mean STB levels in the NPA and PA groups were higher than that of the healthy group ($P < 0.0001$). As well, the mean SDB levels in the NPA and PA groups were higher compared to the healthy group ($P < 0.0001$ and <0.003 respectively), and also in the PA group.

Table 1. Variables of the study group.

Variables	HG (N= 93)	PA (N= 35)	NPA (N= 138)	Total (N= 266)
Age years Mean ± SD	37.9 ± 8 (21-55)	39.4 ± 7.4 (27-51)	36.1 ± 9.7 (18-59)	37.0 ± 9.1 (18-59)
Gender, Female N (%)	20 (18.6)	16 (45.7)	81 (58.7)	117 (55.5)
STB (µmol/L)	8.2 ± 1.4	22.9 ± 9.6	14.4 ± 6.0	14.7 ± 7.5
SDB (µmol/L)	3.8 ± 1.2	8.9 ± 4.8	6.0 ± 3.6	6.0 ± 3.8
SDB: STB (%)	45.8%	38.8%	41.7%	40.7%

HG: healthy group. PA: perforated appendicitis. NPA: non-perforated appendicitis. STB: serum total bilirubin. SDB: serum direct bilirubin.

DISCUSSION

One of the ways to reduce costs and reduce ionising radiation for patients with appendicitis is the use of biomarkers to detect appendicitis. The liver is the location of the portal vein that receives food, bacteria and toxins from the digestive system. The reticuloendothelial system of the liver eliminates its toxins and bacteria with its detoxification and immunological function as the first line of defense (21). However, if the amount of the toxins becomes too much, the Kupffer cell function may lead to dysfunction and destruction of hepatocytes and an increase in serum bilirubin alone or in combination with other liver enzymes (22).

The results of our study indicate that the total and direct serum bilirubin can be a valuable criterion as a complementary factor for the early diagnosis of perforated and non-perforated appendicitis. Similarly, in a retrospective study by Emmanuel et al. it was found that the mean bilirubin level in acute appendicitis patients, especially those with perforated appendicitis, was higher than those who had non-inflammatory appendicitis; the specificity of hyperbilirubinemia was 88% as well as the sensitivity of 91% to detect acute appendicitis (23). A similar result was obtained in the study of Ran Hong et al. who showed that the total bilirubin level had a high diagnostic value for acute appendicitis (24). However, in a study by Panagiotopoulou et al., it was shown that high levels of simultaneously all three of the laboratory factors of WBC, CRP, and bilirubin can be effective in detecting appendicitis, but each of them alone was not a good diagnostic factor (9).

In our study, the mean serum total and direct bilirubin levels were significantly higher than in patients with non-perforated appendicitis. This is in agreement with studies by Vaziri et al., and Chaudhary et al. (2,15). As in our study, in a study by Parsa et al., the total bilirubin and direct bilirubin levels were significantly correlated with the detection of non-perforated appendicitis. In an analytic epidemiologic study in patients with high bilirubin and acute appendicitis symptoms, there was a higher and more complicated probability compared to those with a normal bilirubin level (25). Nevertheless, that study also showed that CRP was effective for the proper diagnosis of perforated appendicitis, but it does not have a diagnostic value of total bilirubin (6). Another study also stated that, despite severe and complicated forms of acute appendicitis and bilirubin levels, there was no direct relationship between these two factors. However, none of these factors had a diagnostic value for acute appendicitis (13). Nevertheless, other studies showed that high total bilirubin levels represent an impending condition that requires immediate surgical intervention to prevent peritonitis and septicemia (21,26) Other studies demonstrated a high level of sensitivity for the diagnosis of acute appendicitis, especially if perforated (10, 12,14,18,27,28).

Our study had several limitations. There was a lack of follow-up of patients after discharge from the ED. Secondly, the number of patients studied here was not large. Finally, we could not measure diagnostic accuracy for serum direct and total bilirubin.

In conclusion, our results showed that there was a correlation between both total and direct bilirubin levels and the detection of non-perforated appendicitis, and its measurement is beneficial. Also, total bilirubin levels were more consistent with the detection of perforated appendicitis than direct bilirubin levels.

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CASE STUDY

Very long chain acyl-coenzyme A dehydrogenase deficiency. A case study

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ABSTRACT

Very long-chain acyl-coenzyme A dehydrogenase deficiency (VLCADD) is a genetic disorder of fatty acid metabolism, with an autosomal recessive inheritance pattern and an incidence of 1:40,000 – 1:120,000. Deficiency of the enzyme can result in insufficient adenosine triphosphate (ATP) production. This can become life threatening particularly during times of fasting or increased exercise. This case study presents siblings patient A and patient B, who have been diagnosed with severe VLCADD. Patient B, the primary focus of this case study, repeatedly presents to the children's ward with extremely elevated creatine kinase (CK) levels. Treatment of this disorder can be complicated, particularly in infants and young children, as it involves avoidance of prolonged fasting and a very carefully monitored diet. Monitoring of the condition is made more difficult as there is currently no suitable point of care (POC) test available for CK.

Keywords: very long chain acyl-coenzyme A dehydrogenase deficiency, inborn error of metabolism.

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INTRODUCTION

VLCADD is an inborn error of metabolism inherited in an autosomal recessive pattern and first described in 1992 (2). Mutations in the ACADVL gene is found on chromosome 17p13.1 leading to disruption of β-oxidation of long-chain fatty acids (3). The autosomal recessive inheritance pattern means, that for a child to be affected with VLCADD, both parents must be carriers of an abnormal gene.

There have been over 80 mutations in the ACADVL gene identified, presenting as three clinical phenotypes, each characterised by severity and age of onset (4,5). The first presentation is severe infantile onset, typically within the first 3-12 months of life (5). Patients often develop cardiomyopathy, arrhythmia, hypoglycaemia, pericardial effusion, hepatomegaly and hypotonia (5). If left untreated this form of condition is often fatal (6). The second presentation is less severe and is characterised by onset during early childhood. Patients present with hepatomegaly and hypoketotic hypoglycaemia, but show no signs of cardiomyopathy (5). The third, and most frequent presentation of VLCADD, is late onset, typically presenting in older children and young adults (7). These patients often experience rhabdomyolysis, pain or cramping of the muscles and an intolerance to exercise. They do not typically experience hypoglycaemia (5). Other symptoms of VLCADD include lethargy and potentially renal failure (8). The gold standard of diagnostic testing for VLCADD is acylcarnitine analysis and genetic testing (5).

Treatment is diet dependent and requires patients to avoid prolonged periods of fasting. As a result the patient relies on metabolism of glucose and smaller chain fatty acids to provide ATP to their cells. Foods that are high in very long-chain fatty acids are avoided and the patient's diet is supplemented with food sources, such as medium-chain triglyceride (MCT) oil. During periods of metabolic stress, e.g. increased activity or prolonged fasting, it may be necessary to increase the patient's intake of medium-chain fatty acids, and glucose, especially as the patient grows and becomes increasingly active. In these situations, point of care (POC) testing could be useful for monitoring the patient's condition.

CASE REPORT

Patient A

Patient A was born at 37 weeks after induction of labour following premature rupture of membranes. Labour was uncomplicated and the patient was born apparently healthy with no concerning family history. While in hospital it was difficult to initiate feeding but the patient was later discharged able to feed every three to four hours. Patient A was found deceased in the family home at 48 hours old. Post-mortem laboratory tests showed undetectable glucose (0.0mmol/L) in both the cerebrospinal fluid and vitreous fluid. It was also noted that the patient had hepatic microvesicular steatosis and cardiomyopathy. Samples were sent for genetic profiling at Sheffield Diagnostic Genetics Service, UK which revealed the patient had undiagnosed VLCADD.

Patient B

Patient B was born at 36 weeks gestation. Investigations into patient A's cause of death indicated that there was a 25% chance of patient B having a severe form of VLCADD. Patient B was born at the local hospital and within an hour transferred to Neonatal Intensive Care. Guthrie cards were collected at birth, and at 12, 24 and 48 hours of age and sent for metabolic testing. Because of this presumptive diagnosis patient B was immediately started on intravenous (IV) 10% dextrose and regular feeds of Monogen, a nutritionally complete formula low in long-chain fatty acids and high in MCTs (9). Following regular spills during and after feeding, a nasogastric tube was inserted to ensure feeding was successful. The patient was transferred to Starship Children's Hospital in Auckland three days later to be monitored and received treatment under Metabolic Services.

Results from patient B's Guthrie cards showed elevated tetradecenoylcarnitine (C14:1). Fasting tests to monitor changes in C14:1 concentration over time were carried out at one, two and six months of age. C14:1 concentrations were measured for up to six hours post feeding. The patient also had elevated CK, possibly due to the trauma of birth, which returned to normal at one month of age (10) (Figure 1).

One incident that highlights the severity of VLCADD occurred when the patient was approximately 18 months old. The patient presented to the children's ward with vomiting, lethargy and poor oral intake. Blood tests performed on admission were normal except for an elevated CK and mildly decreased potassium (Table 1). The following day patient B's aspartate aminotransferase (AST), alanine transaminase (ALT) and CK continued to deteriorate, urine myoglobin testing was positive, while renal functions remained stable. Patient B was again transferred to Starship Children's Hospital for further treatment where the patient's CK peaked at greater than 100,000 U/L.

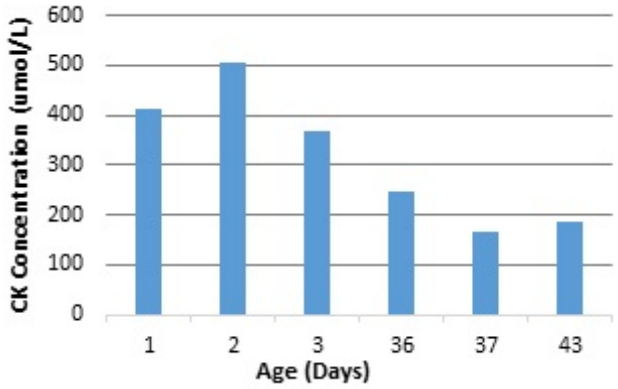

Figure1. Patient B's CK Concentration (Reference range 60-200 U/L)

DISCUSSION

Patient A's genetic investigation revealed mutations in the ACADVL gene; p.(Glu115fs), c.343del located on exon 6 and p.(Arg316_Val317del), c.942_947del located on exon 10. The exon 6 mutation, previously described in a patient in 1995 (11), carried by the patient's father is a single point deletion of glycine, at position 115. This mutation is predicted to alter the subsequent sequence resulting in formation of a premature stop codon and nonsense mediated decay (M Nesbitt – personal communication). The previously unreported exon 10 mutation carried by the mother is a deletion of 6 nucleotides which causes a frameshift in the amino acid sequence leading to the production of a whole but functionally abnormal protein (M Nesbitt – personal communication).

Combining these findings with the results obtained post-mortem, the patient was diagnosed with VLCADD. Unfortunately, the glucose provided by normal feeding was insufficient to prevent profound hypoglycaemia and the sequelae associated with that. The fatty liver that was also noted on examination may have been the result of the very long-chain fatty acids that the body was unable to metabolise. In order for this patient to survive, successful treatment would have needed to commence immediately and the patient's condition monitored from birth.

Diagnosis

Genetic testing was performed on the family several months after patient A's death. However, by this time patient B had already been conceived meaning pre-natal testing for VLCADD could not be achieved. Therefore the only way to ensure patient B's survival was to treat on the assumption that the patient had VLCADD until confirmation through laboratory testing was received.

Guthrie card samples were collected to confirm the diagnosis of VLCADD through acylcarnitine profiling, performed using liquid chromatography tandem mass spectrometry (LCMSMS). To analyse Guthrie card samples, which are routinely used for profiling in New Zealand, the dried blood spots are punched out and placed into the well of a microtitre plate, with an internal standard and methanol. The plate is inserted directly into the LCMSMS and analysis is performed (M de Hora - personal communication), with results appearing as spectrums like those shown in Figure 2.

Patient B's Guthrie card collected at birth revealed elevated C14:1 (Figure 3). In New Zealand the diagnostic cut-off for VLCADD requires C14:1 to exceed 2.5umol/L but patient B's initial elevated C14:1 did not. However, testing on the second Guthrie card demonstrated increased C14:1 that met the diagnostic criteria (12). Despite C14:1 being the most specific marker for VLCADD, it has been found that healthy neonates can show mild elevations at birth, which highlights the importance of testing multiple cards (12,13).

Table 1. Patient B's ALT, AST, CK and K+ results.

Date	6 April			7 April			
Time of collect (hr)	**14.35**	**18.30**	**23.30**	**04.30**	**07.00**	**10.55**	**14.00**
ALT Reference: 0-40 U/L	26				212	316	370
AST Reference: 20-80 U/L	68				1064	1515	1693
CK Reference: 60-200 U/L	1096	922	3654	34298	49460	79570	73190
K^+ Reference: 3.5-5.2 mmol/L	3.3	4.4	4.1	3.9	3.9	3.4	3.3

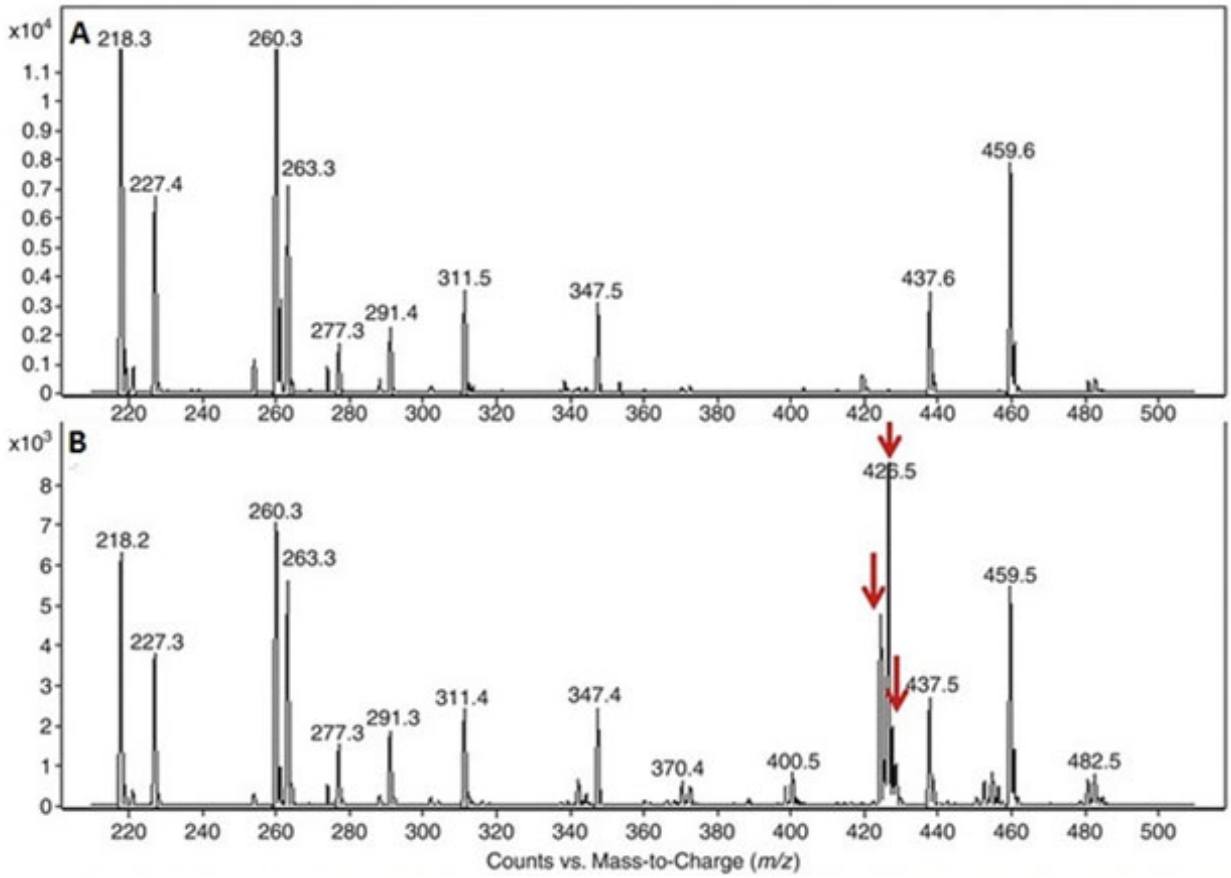

Figure 2. Examples of acylcarnitine profiles from a normal patient (A), compared to a patient with VLCADD (B). The profile for the patient with VLCADD shows elevated levels of C14:0, C14:1, and C14:2 acylcarnitines as well as other long chains (indicated by arrows). Image modified from Ye C et al (O). Reprinted by permission from Springer Customer Service Centre GmbH: Springer Nature. Biochemical Genetics and Inborn Errors of Metabolism: Yu, C, Wasserstein. M, Diax, G. 2013

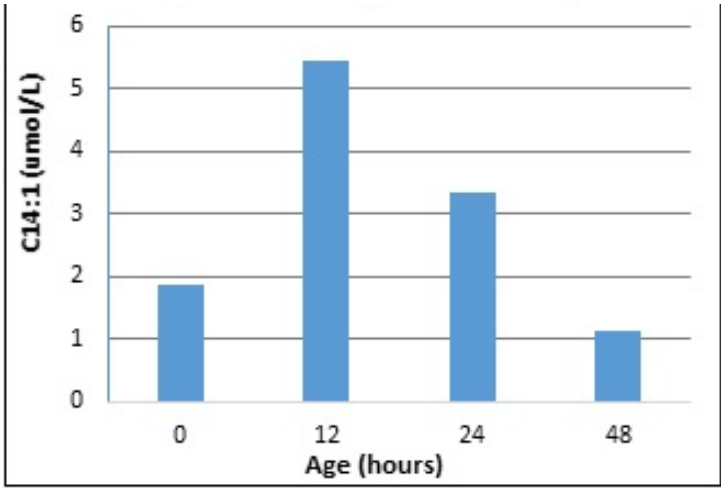

Figure 3. Patient B's C14:1 after birth (Reference range =<0.13umol/L)

PATHOPHYSIOLOGY

Similar to a normal patient, patient B still has the ability to metabolise glucose, the body's primary energy source, to produce ATP. However, during periods of glucose depletion, e.g. after exercise or prolonged fasting (i.e. overnight) ATP synthesis occurs through beta-oxidation of fatty acids (14). Beta-oxidation requires different acyl-CoA dehydrogenases specific for the differing lengths of fatty acids; i.e. short-chain, medium-chain, long-chain and very long-chain (5). Due to patient B's condition, they are unable to breakdown very long-chain fatty acids, relying more heavily on metabolism of smaller fatty acids. Skeletal muscle comprises approximately 40% of an average adult's body mass and is one example of cells that utilise ATP, and is of particular importance for patients with VLCADD (14). When ATP becomes depleted the integrity of cell membrane is compromised and breaks down, a process called rhabdomyolysis. Myocyte contents - including potassium, myoglobin, lactate dehydrogenase (LDH) and CK are released (8). CK is the analyte routinely measured on Patient B.

Rhabdomyolysis increases the risk of renal failure, having an overall mortality rate of 7-8% in children and adults (16). The cause of death is frequently related to renal and/or multi-organ failure (15). Renal failure is believed to be because myoglobin impairs kidney cells via three different mechanisms (8). The first is vasoconstriction. Damaged kidney cells accumulate extracellular fluid and swell, reducing the blood flow to the kidneys (8). Secondly, as myoglobin enters the lumen of the tubules, it interacts with the Tamm-Horsfall protein and precipitates, blocking the tubules (16). Precipitation in the urine is exacerbated due to the low pH environment, causing the

bonds between myoglobin and Tamm-Horsfall proteins to form more rapidly and strongly (8). The final mechanism is the formation of reactive oxygen species, which oxidises ferrous oxide into ferric oxide (8). This produces hydroxyl radicals that go on to cause oxidative damage to the kidney cells (8,16).

Diet

To prevent hypoglycaemia and subsequently rhabdomyolysis, patient B must be fed at regular intervals following a modified diet of approximately 1870kcal per day, compared to the normal recommended calorie intake for their age group of 1400kcal per day (Table 5) (17). This diet is low in long-chain fatty acids and is supplemented with Monogen, MCT oil, and Liquigen, a product made with 50% MCT oil and 50% water (18). Increasing activity has resulted in complaints of muscle pain and intermittent elevations of CK.

The frequency of patient B's feeding times has been determined by performing fasting tests. Unlike other fasting tests, e.g. glucose tolerance testing, the patient is not fasted as the risk of adverse reactions would make this extremely unsafe. Instead patient B is fed following their normal regime, blood samples are collected on to separate Guthrie cards at time zero through to five hours, at 30 minute intervals, which allows changes in C14:1 to be monitored (Table 2). This provides clinicians with a guideline as to the length of time that is safe and acceptable. Most recent testing showed that patient B is able to fast for approximately six hours with no negative impact. However, the patient is on a continuous pump feed overnight via percutaneous endoscopic gastrostomy tube and no longer needs to be regularly roused for feeding so will not be fasting for over 6 hours. If it is known that the patient will be more active than usual, extra feeds or MCT oil are given. These extra calories, combined with the patient's low level of exercise, has led to extra growth with the patient above the 98th percentile for both weight and height for their age group.

Emergency treatment

Patient B is regularly in the children's ward for CK monitoring. The patient has been admitted 22 times and has had approximately 600 laboratory test requests. Due to dependence on regular feeding, episodes of vomiting, diarrhoea or other severe illness can have serious consequences and may even cause the patient to experience a metabolic crisis. If the patient is unable to tolerate or absorb food, they are at an increased risk of rhabdomyolysis. When the patient does present to the children's ward under these conditions an emergency treatment plan is commenced.

The first step of emergency treatment is to determine the severity of the patient's condition. If the patient is severely unwell they are presenting with a high fever and concerns regarding the patient's ability to absorb or tolerate feeding. In this situation CK, renal and liver function tests are requested to evaluate the patient. Meanwhile patient B is started on IV 10% dextrose combined with 0.45% saline, infused at a rate of 5ml/kg/hour. The infusion may also contain extra potassium, but this is dependent on the patient's CK result. An attempt can be made to continue Monogen feeding if the medical staff are confident the patient will tolerate it. Liver functions, CK and glucose levels continue to be monitored every four to six hours. Should two glucose concentrations exceed 8mmol/L, an insulin infusion is commenced to prevent severe hyperglycaemia. Once the patient has recovered and tolerated feeds for two hours, infusion can be stopped. However, if the patient deteriorates, further despite treatment, Metabolic Services in Auckland are contacted. Though a significant symptom, for patient B's hypoglycaemia is a late sign of decompensation and is not used as an indication for admission.

Table 2. Example of patient B's daily diet.

Time	Food/dietary products consumed
07:30	1x toast, MCT butter and marmite ¾ cup Rice Bubbles with Calci-Trim milk or 1x Weetbix with milk and sugar
09:00	16.8g Monogen + 90ml water + 20ml Liquigen + 2 tablespoons of cornflour.
10:30	½ sandwich with MCT butter and marmite, and 1 yoghurt pottle
12:00	½ sandwich with MCT butter and marmite, and 1 banana
13:30	28.0g Monogen + 150ml water + 20ml Liquigen + 2 tablespoons of cornflour.
15:30	½ sandwich with MCT butter and marmite, and 1 yoghurt pottle
18:00	Meat meal (for example: chicken, venison, white fish) with MCT oil
19:30	28.0g Monogen + 150ml water + 1ml of walnut oil
21:00	Pump feed – 112g Monogen + 600ml water at 55ml/hr until 07:00 next day

Comparatively, when the patient is deemed to be less unwell, i.e. tolerating feeds and CK is between 10,000-20,000U/L, they are started on continuous MCT and CK is monitored six hourly. If CK exceeds 20,000U/L, feeding is continued with added volume. This added volume is achieved by adding 0.9% saline by IV, or by adding extra water to the feed. If the patient's CK continues to rise after 12 hours, despite therapy, this may indicate rhabdomyolysis and the patient may be given 10% dextrose and 0.45% saline in combination with the MCT formula. At the same time CK, liver and renal function is monitored six hourly until CK decreases below 10,000U/L and the patient becomes clinically stable. Once stable and recovered, normal feeding should be recommenced as soon as possible.

POC testing

VLCADD has also meant that the family is unable to travel far from home, as in the event of a medical emergency, clinicians need to be able to start treatment as quickly as possible. Something that could positively impact patient B and their family would be a POC CK meter, similar to glucometers used by diabetics. One option is the Roche Diagnostics POC system capable of measuring CK in whole blood, plasma and serum (19). The Reflotron Plus System uses test strips that are inserted into a measuring chamber (19). This system could be beneficial in a situation like patient B's as it does not require preparation of samples or reagents, does not require calibration, and would give the family convenience and peace of mind, particularly when they are out of town (19). Unfortunately, this system appears to be targeted towards laboratories (both hospital and private) and pharmacies, rather than for private use in a patient's home. It also has a large footprint, making it inconvenient to travel with.

Another option would be the Abbott i-STAT analyser. i-STAT is a handheld POC analyser that uses cartridges, to which 2-3 drops of blood (venous, arterial or skin puncture) are added (20,21). The cartridge is inserted into the device and analysed before results are displayed onscreen (20). Results may also be printed using an i-STAT printer, or can be transmitted wirelessly to a Data Management System which could prove useful for getting the results to Patient B's clinical team (21). This system would be useful as its size and portability mean it would allow the family to monitor the patient away from home. i-STAT has a variety of cartridges available that could allow the patient's renal function to be assessed outside of the hospital. While Abbott offers a cartridge for the measurement of CK-MB, a cardiac marker, it does not offer a cartridge for skeletal muscle CK (22).

As VLCADD is such a rare condition there may not be enough individuals that need to monitor their CK from home to justify Abbott developing a cartridge specific for CK testing.

CONCLUSION

VLCADD is a rare and potentially deadly metabolic disorder that, if suspected, must be presumptively treated from birth to ensure survival of the patient. Acylcarnitine profiling via LCMSMS, with mutation analysis of the ACADVL gene, is the gold standard for diagnosing VLCADD. In a positive case, C14 acylcarnitines will be elevated, though this can be seen in neonates that do not have VLCADD. Once the diagnosis has been confirmed it is crucial that the patient is started on a strict high carbohydrate, low long-chain fatty acid diet, and an avoidance of exercise to prevent development of potentially life-threatening complications, such as rhabdomyolysis and subsequently renal failure. Fortunately for the patient presented in this case, they have a very supportive family and clinical team, who have multiple emergency treatment plans in place, should the patient present acutely. The patient's diagnosis has also impacted the family, and they are rarely able to leave home for prolonged periods of time, as in the event that the patient has an acute episode, they must be able to get the patient to hospital as quickly as possible. A POC device that measures CK would help to relieve some of the pressure on the family but the available options are not suitable for use outside of a clinical setting.

ACKNOWLEDGEMENTS

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Submission of abstracts and registration will be available mid-April
The NZIMLS will notify members when the above is available

Invitation to Attend
The Australian Institute of Medical Scientists and the New Zealand Institute of Medical Laboratory Scientists is pleased to present their combined meeting, the South Pacific Congress, to be held at GCEC, Gold Coast, Queensland from 17-19 September 2019. It is our great pleasure to invite you to join us all at this exciting event.

The conference, exhibition and associated social events provide a range of opportunities for continuing education and professional development, catching up with colleagues and friends, networking, and of course enjoying the beautiful sights of the Gold Coast. We expect over 400+ delegates to attend and look forward to your participation.

The theme for the congress is "New Wave Science". It is a three day conference which will attract delegates from Australia, New Zealand and other international countries. We have a comprehensive programme which will appeal to all lab staff, ranging from phlebotomists, lab assistants, core lab scientists to specialised senior scientists and lab managers. The program has invited such high profile speakers such as the forensic anthropologist, Dr Donna MacGregor, international speakers from Ireland, Great Britain, Canada and NZ, cutting edge scientists such as Dr Ken Dutton-Register, Dr Maher Ghandi (named as one of the most influential researchers in Australia), and Dr Danielle Stanisic, along with many local and interstate experts. All the major disciplines will be covered, with a comprehensive pre-analytical two day programme also offered.

Other highlights of the meeting include the Industry Exhibition, submitted oral papers and posters, networking functions, industry symposia, meet the experts breakfast sessions and of course the gala dinner.

A couple of speaker profiles:
Professor Donna MacGregor, Forensic Anthropologist, Lecturer at QUT, QPS Forensic (part-time), Australian Army Reserve. Donna is currently a lecturer in Anatomy and her research interests within forensic anthropology include developing Australian standards in age and stature determinations via 3D bone reconstructions from CT data; taphonomic processes including times since death estimates based on local micro environments; and research interests in 3D crime scene enhancement techniques.
Other service includes:
Captain (Forensic Anthropologist), Australian Army where she unrecovered war casualties in a Reserve capacity and performed a specialist role of Forensic Anthropologist in army field teams.
Scientific Police Officer (Major Crime Scene Investigator), Queensland Police Service. This was where Donna was involved with crime scene examination and evidence collection from major crime scenes related to serious offences against persons and property. Crime scenes include fire, suspicious deaths, sexual assault, counter-terrorism and specialing in skeletal recovery and human identification. Expertise held in impression evidence (shoe soles), BPA, physical evidence recording and collection including DNA, and cannabis certification. Donna continues to be involved in this role on a part-time basis.

Professor Michael Reade is the Australian Defence Force (ADF) Chair of Military Medicine and Surgery and a member of the Burns, Trauma and Critical Care Research Centre at UQ. A specialist intensive care physician, anaesthetist and clinician-scientist, he leads a programme of research relevant to military trauma medicine and surgery, and guides the implementation of modern trauma care into ADF practice.

PRELIMINARY PROGRAMME Subject to change TUESDAY 17 SEPTEMBER	
0730-1800	Registration
0900-0930	**Opening Ceremony** Presentation of AIMS Fellowship Awards Presentation of AACB Membership/Fellowship Awards Welcome by COC Chair
0930-1030	**Opening Plenary** **Saal-Foley lecture**

1030-1100	***Morning Tea & Opening of Industry Exhibition***				
	Pre-analytical	**Micro**	**Transfusion**	**Biochem**	**Management**
1100-1130	Pre-Analytical Errors as part of the Medical Laboratory Science teaching program **Ian Cassady**	What's new in multi-resistance Gonorrhoea **A/Prof David Whiley**	Five focus points for the ARCBS **James Daly**	Post analytical issues Critical values **Robert Flatman**	Measuring competency **Alan Wainwright** *IBMS*
1130-1200	Antigen vs Antibodies. What do doctors really want? **Alana Jenkins**	Tuberculosis **Dr Sushil Pandey**	Platelet reference laboratory testing **Gail Pahn**	Informatics EQA **Derek Holzhauser**	Competency guideline development in Australia **TBA**
1200-1230	Problem with babies: Common sources of pre-analytical error in paediatric sampling **Donna Rudd**	Enteric bacteria **Dr Patrick Harris**	Innovations in ADF transfusion practice: frozen platelets, freeze-dried plasma and whole blood. **Michael Reade**	Identification of cryoprotectant aldehydes and their removal by thiol scavengers **Mike Legge**	NZ CPD and the regulatory system **Jillian Broadbent**
1230-1330	***Lunch, Posters & Industry Exhibition***				
	Concurrent sessions				
1330-1500	**Pre-analytical**	**Molecular/ Genetics**	**Haem/coag**	**Immunology**	**Education/ Training**
1330-1400	Putting your best team forward. **Angela Coriat**	Molecular testing in your lab **Fleur Francis**	POCT devices **Andrew Sargeant**	Allergies and the gut TBA	Simulation training in Canada **Christine Nielson**
1400-1430	Electronic ordering **Ajesh Joseph**	What is Genomic testing and what does it tell us? **Ben Lundie**	The efficacy of fibrinogen concentrates **John Roy**	The real story of gluten and coeliac disease TBA	Education biomedical scientists for the future **Marie Culliton**
1430-1500	Case Studies from Specimen Services (CSR) **David Kendall**	**TBA**	The downside of plasma components TBA	Auto-immune disease – is it on the rise and why? TBA	Regulation of Medical Laboratory Science Practitioners in New Zealand, Current experience and future directions **Don Mikkelsen**
1500-1530	***Afternoon Tea & Industry Exhibition***				
1530-1615	New ovarian cancer test **Lucy Shewell**				
1615-1700	The malaria vaccine project **Dr Danielle Stanisic**				
1700-1900	**Industry Gala Function**				

WEDNESDAY 18 SEPTEMBER					
0730-1700	Registration				
0730-0845	**Meet the Experts Breakfast sessions** Certification NZ and Australian style - Don Mikkelsen & Lee Riddout Measuring competency - Alan Wainwright Literature reviews – Catherine Pickering Blood cell morphology – Lyndall Dial **And more to come!**				
0900-1000	Why we need iron? **Prof Nathan Subramaniam**				
1000-1030	***Morning Tea & Industry Exhibition***				
	Concurrent sessions				
		Coagulation	**Transfusion**	**Biochemistry**	**Serology**
1030-1100	Cutting Edge Technology for Phlebotomy **Annette Bissett**	QC TBA	First trimester screening **Marie Culliton**	Emergency Chemistry Troponin **Gus Koerbin**	Transplant screening TBA
1100-1130	Flock swabs and the collection of NPA samples **Fleur Francis**	Coag Troubleshooting TBA	Foetal DNA testing **Helen O'Brien**	Glucose **Greg Ward**	
1130-1200	CX Bladder (NZ) PCR for the early detection of Bladder Cancer. **Jane Kendall**	Case studies TBA	Case studies **Deborah Longmore**	Keeping Safe – Perspectives on laboratory and patient safety over the last half century **Don Mikkelsen**	
1200-1330	***Lunch, Posters & Industry Exhibition***				
1300-1330	**AIMS AGM**				
	Concurrent sessions				
	Pre-analytical	**Education Workshop**	**Molecular**	**Haematology**	**Virology**
1330-1400	Sample collection at an outreach clinic **Katie Edmondson**	AIMS Research engagement scheme **Anne-Marie Christensen & Catherine Pickering**	POC molecular style **Michelle Williamson**	The good, bad and the ugly – lymphoma in the blood **Lyndall Dial**	Respiratory viruses **Prof Kirsten Spann**
1400-1430	Managing the errors and issues of specimens coming from remote areas. **Sam Hornsby**	Literature reviews **Catherine Pickering**	Our Illumigene LAMP experience **TBA**	Lymphomas **Kate Hill**	Title TBA **A/Prof Ian Mackay**
1430-1500	Testing sexual health samples and case studies **Fleur Francis**			HD immunotherapy and markers **Maher Ghandi**	
1500-1530	***Afternoon Tea & Industry Exhibition***				

1530-1615	Certification project update **Lee Riddout**
1615-1700	Talking about my generation **Christine Nielson**
1900-2330	**Conference Dinner**

THURSDAY 19 SEPTEMBER					
0830-1600	Registration				
0930-1030	Melanoma genetics **Ken Dutton-Register**				
1030-1100	***Morning Tea & Industry Exhibition***				
	Concurrent sessions				
1100-1230	**Profferred Papers**	**Proffered papers**	**Proffered papers**	**Proffered papers**	**Management**
1100-1130					How to manage underperforming and difficult staff **Wendy Branthwaite**
1130-1200					
1200-1230					
1230-1315	***Lunch, Posters & Industry Exhibition***				
1315-1400	**Bloodisloe Cup** Is wine good or bad for you?				
	Concurrent Sessions				
	Histo/general	**Biochem Data**	**Interesting Micro**	**Haem/ Coagulation**	**Transfusion**
1400-1430	Recent advances in 3-dimensional imaging and analysis **TBA**	Cybersecurity **Derek Holzhauser**	Leptospirosis **A/Prof Scott Craig**	Update on TTP **Jo Perel**	Transfusion challenges for regional labs **Deborah Longmore**
1430-1500	**ctd**	Data mining principles **Tony Badrick**	The gut microbiome **Donna Rudd**	ADAMTS13 testing **Joanne Beggs**	Case studies **Tim Stanton**
1500-1530	**ctd**	Data mining examples **Brett Lidbury**	Infectious diseases following the floods in Townsville? TBA	ECMO TBA	
1530-1600	***Afternoon Tea & Closing of Industry Exhibition***				
1600-1630	Forensic cases **Ewen Taylor**, *Senior Sergeant, Forensic Services Group, Qld Police Service*				
1630-1700	Forensic Anthropology **Donna MacGregor**				
1700-1715	**Conference close**				

So, what is it really like as President of the NZIMLS?

Terry Taylor

Southern Community Laboratories

Firstly, a bit about me. My name is Terry Taylor and I have worked in medical laboratory science since 1993. I am currently 2IC of the immunology laboratory at SCL in Dunedin where my main areas of expertise are flow cytometry and autoimmunity. I was voted onto Council as the Otago/Southland NZIMLS representative in 2009. I stood for Vice-President in 2014 and took over as President in 2017.

Most members probably don't really know what is involved with the governance and everyday responsibilities that are involved with being part of the NZIMLS Council Executive. There is a lot of time and effort that goes into ensuring that the NZIMLS runs smoothly and efficiently while striving to provide an organization that is both financially and professionally functional.

Part of our mission statement is *'the NZIMLS has an ongoing commitment to promote professional excellence through communication and education'* and with that comes a responsibility as an elected representative to ensure that is fulfilled.

The voting members of the NZIMLS Council consists of the five regional representatives, the Treasurer, the Vice-President and the President. Our Executive Officer is also part of the Council but has no voting rights. We also have the option of inviting others to attend our Council meetings such as the CPD Coordinator, Journal Editor or other advisors at any time. None of these invited people have any voting rights but certainly give valuable input on relevant items. The NZIMLS Executive consists of the President, Vice-President, Treasurer and the Executive Officer and this is where the important day to day decisions are generally decided.

Almost all my NZIMLS Council work is performed outside of the workplace as like most medical laboratory scientists I have a very busy and full day job. In saying that I get great support from my employer and, in particular, the department I work within. Being on Council can mean being away for up to two weeks a year at various meetings to do with all aspects of NZIMLS business.

Within an average week I will generally spend an hour or so most nights going over NZIMLS emails. With this comes the additional tasks of coordinating letters, reports and communications with both individuals and organisations we deal with. There are always ongoing reviews of other core functions such as the QMLT qualification and resource material, CPD, legislative reviews and qualification discussions with the Medical Sciences Council (MSC), NZIMLS meetings, sponsorship and many other administrative roles which includes answering any general queries.

There are usually four NZIMLS Council meetings held in a calendar year. Over the past year we have tried to hold these meetings over a Friday/Saturday to lower the impact on our workplaces by only being away for one working day. As President my responsibility is to chair these meetings and ensure that we get through what is typically a long and thorough agenda. From these meetings all Council members will get a number of tasks to follow up and these need to be completed within the timeframes agreed to. Some tasks can take many hours to complete but I have to say the NZIMLS is very fortunate to have such a hardworking and diligent council.

With being on Council comes the expectation of being available to give presentations on NZIMLS and/or professional issues at SIG meetings and North Island and South Island Seminars plus other tasks such as chairing sessions, judging presentations and being available to deal with any issues that may pop up. There is also the expectation to 'volunteer' to organize NZIMLS educational meetings in your home region.

Being part of the NZIMLS Council does also have many benefits. To see and meet some of the most amazing talented and passionate scientists and technicians around New Zealand is a very humbling experience. There is always a special feeling being welcomed into laboratories from all corners of New Zealand. Every laboratory has their own group of talented and passionate individuals that ensure that our professional, educational and workplace standards are well maintained. Plus, we are all human and there is nothing better than meeting socially and sharing ideas and passions about all facets of medical laboratory science and life itself. As I write this, I have one eye on my coming weekend away with some very diverse friends fishing on the glacial lakes plus the lure of scaling some of those central South Island peaks … but yes, I will still have my laptop and phone to tidy up anything that comes up!

Terry Taylor
President, NZIMLS
terry.taylor@scl.co.nz

BOOK REVIEWS

A Lab of One's Own. Science and Suffrage in the First World War

Author: Patricia Fara

Publisher: Oxford University Press, UK, 2018

Patricia Fara lectures on the history of science at Cambridge University, UK and has written a number of books on the history of science as well as contributions as a science journalist. Her most recent book: Science: A Four Thousand Year History was an excellent concise writing of the development and impact of science over four millennia. In the present book the author considers the untold lives and stories of women scientists up to and including after the First World War. The first three chapters trace the women's suffrage movement in the UK, touching on both the personalities and the politics of the day with the focus of women at Cambridge University. Despite successfully completing degree courses (often well ahead of the men) women were not allowed to graduate and were sent a certificate in the mail. This did not change until 1948! By 1914 women had been studying sciences at Cambridge and Oxford universities for almost 50 years and as men left for war female scientists gradually emerged to make valuable scientific contributions to both science and the war effort. Medical schools temporarily allowed female students but was reversed after the war. During this early period the author draws sharp contrasts on social classes in the UK. Progressively women worked in engineering, munitions, factories, hospitals and laboratories and at the work place class distinction was secondary to production. Woven in to the book is the women's suffrage movement with memorable personalities. One memorable incident was the formation of women's soccer teams that had previously been severely frowned upon with the British Medical Journal earlier severely cautioning on the potential damage to female reproductive organs. As the horrors of the war progressed women scientists were being exposed to many toxic agents especially in the munitions industry.

In the final section of the book the role of 'unknown' women scientists (such as scientist wives of scientist husbands) is laid bare, discussing their unacknowledged contribution across the science and engineering spectrum and the prejudice of both male scientists and institutions. Progressively women (usually, but not always, from wealthily families) became significant contributors both to science, medicine, engineering and the war effort. However, recalcitrant males still considered a women scientist's role was to produce 'baby scientists'! Progressively during the war women organized their own scientific societies but were paid less for any equivalent role.

The final chapters focus on women's role in medicine with remarkable accounts of work on the battlefields of Europe. With the exception of Marie Stopes, all these heroic women have been largely forgotten but their medical and scientific contribution in war torn Europe was significant. Emslie Hutton's contribution in Serbia is still honoured today in Serbia including a stamp with her image in 2014. With the end of the war women scientists were pressured to return to domestic life with fewer scientific positions being made available in industry and the professions. At Cambridge and Oxford universities that positions for women were kept under 'tight control' and women were banned from senior positions.

The book successfully merges the issue of the women's UK suffrage movement with those of inequality in science. While men were at war, women scientists not only made significant contributions to both science and the war effort, they also looked after children and families.

NOTE: New Zealand had voting rights for women in 1893 and the UK only gave those women over the age of 21 voting rights in 1928.

Nine Pints: A Journey Through the Mysterious, Miraculous World of Blood

Author: Rose George

Publisher: Portobello Books, London, 2018

Rose George is an established author, an investigative journalist and a public speaker. Her most recent book, "Nine Pints: A journey through the mysterious, Miraculous World of Blood" uses the blood volume (i.e. nine-pints) to introduce nine different and intriguing stories about blood. The book opens with the author donating a unit of blood and sketches a history of both the mythology, use of blood and social impacts of blood. A chapter on a visit to the UKs only medical leech farm in Wales provides a fascinating account, which moves in to the historic use of leeches in medicine as well as the procedure of 'blood-letting' which was the panacea for all ills in days gone by. A tour through the leech facility reveals that leeches are sensitive creatures; culture conditions are critical for the optimal leech. Surprisingly it takes 2 to3 years to get a leech "hospital ready" and they are 'starved' before dispatch. The facility dispatches leeches around the Northern Hemisphere (approximately 10 UK pounds per leech) and have been widely used for disaster victims.

Moving on from leeches the author trace the development of the voluntary blood donation system in the UK, established by two very different people working in different ways. Janet Vaughan was a medical graduate from a privileged background with a 'colourful family'. While undertaking obstetrics prior to the NHS in the East End of London she relates how she saw "deadly poverty", which converted her becoming a life-long socialist. Although she made significant discoveries treating anaemia, male doctors would only communicate with notes and she was not allowed to see patients. Having studied the Spanish Civil War, she knew that if, and when, war broke out in 1939 there would be a need for an efficient supply of blood. Here the author diverges in to the fascinating account of the history of blood transfusion and the impact during the First World War. The second significant person was Percy Oliver, a civil servant, and his wife. The First World War established the concept of voluntary donation (soldier to soldier). However, peacetime surgeons demanded fresh blood which necessitated paying donors (10 UK pounds) including walking the streets asking people to be paid for blood. At the time women were excluded due to the "disability of nervousness". The USA routinely paid donors in the 1920s ($US25) plus in Massachusetts and a pint of whisky. The Oliver's wanted a different system so they set up a register of reliable blood donors who would not require payment. Using a card index system of donor contacts, blood group and syphilis testing and the London Blood Transfusion Service was established. By 1930 he coordinated 68 London hospitals from home and the British Blood Transfusion Service was formed. With the advent of another war Janet Vaughn knew that mass collection of blood and safe transport was essential. By now sodium citrate/glucose was acknowledged as a safe additive but was fiercely debated by the medical profession. Although Percy Oliver was a pioneer of donor services, the medical profession progressively ignored him. Vaughn progressively worked on the collection (modified milk bottles), distribution, and transport using converted ice cream vans.

By now regional blood transfusion services were emerging and there are remarkable vignettes of its successes. The army set up it's own mobile service, which recorded 1657 pints collected in one day. After the war Vaughn went back to University life to continue her research employing women scientists.

Percy Oliver died in 1944 and was never acknowledged for his pioneering work on donor services and Janet Vaughn died aged 92 asking to be remembered as a scientist. She saw the advent of the NHS Blood Transfusion and Transplant Service.

The book quickly moves on to the issues of blood and HIV in South Africa and the complex issues of poverty, sex and blood. Issues relating to young women being bribed for sex by older men with gifts (termed 'blessers') who were often HIV carriers. This chapter has a number of personal accounts, especially those of young women who become HIV positive, but also on the work of Medecins Sans Frontieres (MSF) International in attempting to overcome significant issues from the government downwards relating to HIV and the problems of taking medication.

The following chapter considers the use of plasma, in particular the treatment of haemophilia. Interviews with haemophiliacs and their families highlight the contrasts between the differing geographical worlds of treatments. This includes the disastrous issues relating to HIV in blood products. The author visits the Canadian Plasma Resource Centre where she is shown the whole process of preparing plasma products and the commercial side of blood. The chapter closes with the ineffective efforts of various governments to resolve the HIV plasma contamination issues from commercial sources.

The following two chapters consider the social issues of menstruation taboos in mainly Nepal and India. In the villages visited the author discusses the social taboos and isolation of young women during menstruation that is driven by men and older women. Historic western accounts of "unclean" are discussed including the perceptions of other cultures. Although social isolation is technically banned in Nepal, it is widely practised. Both in Nepal and India menstruation is surrounded by mythology, superstition and ignorance, including as a disease. Western civilisation does not escape with similar taboos including the early days of NASA.

Following on, the next chapter provide an enlightening account of an Indian man ("Menstral Man") who decided to provide cheap pads for women. With no engineering background he has produced a kit-set machine that can be assembled and produce sanitary pads cheaply. Linked with this is the historic development of products such as Tampax, which nearly did not make it to the market. More disturbingly are comments of young women in Kenya and Ghana selling sex to be able to buy pads. The penultimate chapter moves in to emergency medicine and the fast response air ambulance A&E/Intensive Care relationship. By chance the author witnesses a young woman involved in an accident admitted with an open chest and quickly moves in to the world of trauma response and blood products. Despite best efforts the young woman died.

The final chapter looks back on the mythology and perception of blood including vampire theories, drinking blood (Romans bled out and drank gladiator blood), Jehovah Witness objections and the use of animal blood. Finally, the use of stem cells is considered.

This is fascinating account of the history, prejudices and use of that vital tissue – blood.

Reviewed by Michael Legge, Deputy Editor

Publications by NZIMLS members

This column is to highlight recent publications by NZIMLS members. If you have had a recent publication please provide full details to the Editor at rob.siebers@otago.ac.nz.

Kuo YC, Wu FF, Lee YC, Lin TR, Crane J, **Siebers R.** Effect of betel (acacia) nut chewing on fractional exhaled nitric oxide: a pilot study. *International Journal of Occupational and Environmental Medicine* 2018; 9: 205-208.

Kristono GA, Shorter C, Pierse N, Crane J, **Siebers R.** Endotoxin, cat, and house dust mite allergens in electrostatic cloths and bedroom dust. *Journal of Occupational and Environmental Hygiene* 2019; Jan 28: 1-8.

Townsley H, Crane J, **Siebers R**. Effect of haemolysis on the determination of CCL17/thymus and activation-regulated chemokine (TARC) and CCL22/macrophage-derived chemokine (MDC). *Clinical Chemistry and Laboratory Medicine* 2018; 56: 92-93.

Siebers R. Allergies in animals and humans. *Veterinary Sciences* 2018; 5: E5.

Goodman L, Cree L, Jones DDG, **Legge M**, Shelling A, Farquhar C. The futility of fertility research? Barriers to embryo research in New Zealand. *New Zealand Medical Journal* 2018; 131: 63-70.

Jones LM, **Legge M.** Plasma fatty acids as markers for desaturase and elongase activities in spinal cord injured males. *Journal of Spinal Cord Medicine* 2018; Jan 10: 1-14.

Rodger EJ, Porteous CM, Jones GT, **Legge M**, Kleffmann T, McCormick SPA. Proteomic analysis of liver from human lipoprotein(a) transgenic mice shows an oxidative stress and lipid export response. *BioMed Research International* 2018; 2018: 4963942.

Howard JC, Anderson T, **Creighton J**, Freeman JT. Geographical and temporal clustering of OXA-48-producing Escherichia coli ST410 causing community-onset urinary tract infection in Christchurch, New Zealand. *Journal of Antimicrobial Chemotherapy* 2018; 73: 2900-2901.

Ryzhov IM, Tuzikov AB, **Perry H**, Korchagina EY, Bovin NV. Blood group O→A transformation by chemical ligation of erythrocytes. *ChemBioChem* 2019; 20: 131-133.

Basu I, Bower JE, Roberts SA, Henderson G, Aung HL, Cook G, Lowe O, Newton S. Utility of whole genome sequencing for multidrug resistant Mycobacterium tuberculosis isolates in a reference TB laboratory in New Zealand. *New Zealand Medical Journal* 2018; 131: 15-22.

Shahid K, Alamri Y, Scowcro H, Dixon L, **Creighton J**, Isenman H, Metcalf S, Chambers S. Urinalysis orders and yield among General Medicine patients: a single-centre's experience in New Zealand. *New Zealand Medical Journal*. 2019 Jan 18;132 (1488): 21-27.

Blood transfusion science course at the PPTC 5 – 30 November 2018.

This course included units of study covering the theoretical and practical aspects of the following topics; routine blood grouping, blood group antigens, crossmatch techniques, antibody detection, transfusion reactions, haemolytic disease of the newborn, screening blood for infectious agents, blood donor selection, organisation of a blood bank and the appropriate use of blood components in transfusion medicine.

Three students attended this course: Maango Tara from TCH Hospital Lab, Tarawa, Kiribati; Fa'autu Ainuu Taulia from MT2 Hospital, Savai'i, Samoa; and Sokopeti Faka'osifola Vaiola Hospital, Tonga.

Blood transfusion science course. Students, PPTC staff and visitors 2018.

Centre Based Training Courses for 2019

- Biochemistry: 20 May – 14 June, 2019
- Laboratory health & safety; and quality management systems: 1 – 26 July 2019
- Haematology and blood cell morphology: 5 August – 13 September 2019
- Microbiology: 23 September – 18 October 2019
- Blood Transfusion Science: 4 – 29 November 2019

For further information contact:
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3rd WHO Collaborating Meeting, Ho Chi Minh City, Vietnam: 22-23 November, 2018

Phil Wakem, the PPTC'S CEO, attended this international forum in Vietnam, the main focus of which was described as follows:

- To strengthen communication and share innovative work and expertise of WHO Collaborating Centres in countries for best practice and resource mobilization.
- To share good practices and reflect on progress since the second forum in 2016.
- To strengthen and promote innovative collaboration and networking mechanisms.
- To identify opportunities to maximize contribution of WHO CC's towards WHO support at the country level.

WHOs' future vision:
Healthier populations: 1 billion more people enjoying better health and well being.
Health emergencies: 1 billion more people better protected from health emergencies.
Universal health coverage: 1 billion more people benefiting from **universal health coverage.**

Tonga

Russell Cole the PPTC's Laboratory Quality Manager made the first visit to Tonga's Vaiola Hospital for 2019 to carry out Pacific Laboratory Accreditation development.

Samoa

Filipo Faiga the PPTC's specialist Biochemistry Consultant made his first visit to Samoa for 2019 under the Pacific Laboratory Accreditation Development programme.

Can you help?

If any New Zealand medical laboratories have items of diagnostic instrumentation that have been recently upgraded or continue to be stored in the laboratory but are actually surplus to requirements, the PPTC would be most grateful if such items could be donated through its Centre to the Pacific Island laboratories where there is an exceptional need. Pacific laboratories have very restricted budgets and often cannot afford to replace troublesome instrumentation that continues to breakdown and which is often discontinued because it is so outdated.

The generosity shown to the Pacific Islands by New Zealand laboratories is displayed in terms of the following donations given over the last couple of years:

- Antibiotic stampers – SCL Laboratories
- Coagulation Sysmex CA 550 analyser – WSCL Kenepuru
- XS1000 Sysmex FBC analyser – TLab, Gisborne Hospital
- Various pipettes – WSCL Hutt Hospital
- Water bath – New Zealand Veterinary Pathology
- Tissue processor - Whangarei Hospital,
- Microtome – Medlab South
- Blood culture machines – SCL Wellington and Hutt Hospital
- Text books – SCL Dunedin, University of Otago,

The PPTC would also welcome teaching resources in terms of wall charts, haematology case studies (stained blood films), projector slides, textbooks and journals (within 10 years of publication), etc, for teaching purposes in the Pacific, if you no longer have a use for them. Any contribution is so valuable to us.

Please contact:
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Science Digest

Contributed by Michael Legge

Has the mechanism of thalidomide abnormalities been found?

Thalidomide was a non-addictive, non-barbiturate sedative with antiemetic properties that was widely prescribed during pregnancies in the 1950s and early 1960s. The use of this drug during pregnancy became linked to thousands of severe birth defects and increased miscarriage rates (estimated to be between 10,000 to 20,000 worldwide, including New Zealand). Despite confirmation that thalidomide and two close derivatives (lenalidomide and pomalidomide) were the causative agents for the birth defects the mechanism for causing the defects was unknown.

In a recent publication, researchers in the USA have identified the most likely cause of the thalidomide induced birth defects (1). They identified that two conditions, Duane Radial Ray syndrome and Holt-Oran syndrome both resulted in birth defects similar to those identified with thalidomide. The two syndromes are due to mutations in a protein SALL4, which is a transcription factor and an important regulatory factor in early embryonic stem cell development. When stem cells expressing SALL4 were exposed to thalidomide or derivatives of thalidomide degradation of the protein was induced; concluding that this was highly likely to be the mechanism for the thalidomide induced human defects. Additionally, the researchers identified that SALL4 mutations induced birth defects in humans, primates and rabbits but not in mice or fish. This has been identified as an inability of a protein cereblon in mice and fish to bind thalidomide and does not therefore get degraded. In humans cereblon binds thalidomide and presents the complex to SALL4 which then degrades. This important finding goes some way to answering a long-standing question as to why certain animal models were not affected by thalidomide during drug tests, although the drug manufacturers did not test on pregnant animals at the time. Thalidomide is still used for the treatment of multiple myeloma and certain cancers.

Plastics at sea: are they vectors for the spread of antibiotic resistance?

Plastic pollution at sea is becoming a major issue both form the release of pollutants and the interaction with marine wildlife. Once in the ocean plastics undergo significant transformation, which ultimately results in the production of smaller plastic debris including microscopic plastic particles. These can be physically deadly to marine life and in particular marine birds. In a recent research publication from Italy, another source of plastic interaction with the environment was identified. In this research, investigations were made as to whether plastic particles could serve as habitats for bacterial species expressing antibiotic resistance from an area around King George Island in Antarctica (2). The research identified the type of plastic particles and bacteria associated with the particles using molecular identification for the bacteria. A total of 27 bacterial strains were identified and all active in biofilm production on the plastic particles. When the assayed bacterial strains were tested for antibiotic resistance, they were resistant against ampicillin, amoxicillin + clavulanic acid, carbenicillin, mezlocillin, cefuroxime, cefazolin and cinoxacin. The authors concluded that bacteria can survive in extreme conditions by colonising plastic particles and the ability to produce biofilms. This ability to survive may be a significant factor in the identification of antibiotic resistant bacteria reported in the faeces of penguins.

Schistosomiasis in Europe: an emerging risk

Changes in climate over recent years has led to increasing temperatures and milder winters overall. The increasing temperatures is leading to sub-tropical disease vectors increasing their range and impact. In southern Europe locally acquired diseases such as malaria and Dengue are emerging aided in particular by the trading of car tyres facilitating the spread of mosquitoes. Although attention is paid to the distribution of mosquitoes, ticks and sandflies little attention has been paid to freshwater ecosystems. Four years ago, clusters of urogenital schistosomiasis were reported in France and Germany in patients who had not visited endemic countries but all of them had holidayed in Corsica and visited the same river famous for its clear water warm pools. Further cases were reported the following year and the year after, however no *Balinus trunccatus* snails (the intermediate host) were found. Analysis of the parasite *Schistosoma. haematobium* indicated that it was related to a population in Senegal, a popular holiday destination in France. Additional research indicated that there was hybridization between *S. haematobium* x *S. bovis* which it is believed to allow a shift in the use of an alternative intermediate snail host. Support for this has come from work in Europe demonstrating that the snail *Ferrissia tenuis* could provide an alternative intermediate host (3). Historic research data from the early 1900s added further information of the ability to host switch. The authors of the present research concluded that more detailed research is required on *Schistosoma* hybridization, intermediate hosts and freshwater ecology, including the impacts of climate change on the spread of this disease.

Can platelets be lethal in pre-term neonates with thrombocytopaenia?

Prophylactic platelet transfusions may be given to pre-term infants as a preventative measure to reduce the risk of bleeding. Previous clinical trials have demonstrated no benefit of platelet transfusions to neonates to maintain a platelet count of 150,000/cu mm. However, the previous trial excluded pre-term infants with severe thrombocytopaenia (platelet counts<50,000/cu mm). In the present study (4), research from the USA performed a randomised multi-centre trial on pre-term infants (birth age <34 weeks) and thrombocytopaenia (platelets <50,000/cu mm). Infants received randomly assigned platelet transfusions at 15ml/kg body weight when the platelet count was either <25,000 or <50,000/cu mm. Over a six-year period a total of 3731 infants was assessed. The researchers found that there was a higher morbidity and mortality when the 50,0000/cu mm threshold was used than the 25,000/cu mm threshold for platelet transfusion. In their conclusion they indicated that the use of adult platelets for transfusion may have widespread consequences beyond haemostasis relating to inflammatory response, haemodynamic shifts and the fragility of pre-term body organs.

Metabolomics in pre-natal diagnosis.

The pre-natal diagnosis of chromosomal disorders has a long history with major advances over the years. Historically amniocentesis and chorionic villus sampling have been the mainstay of these diagnostic procedures However, even with ultrasound guidance there are issues associated with the risk of fetal loss. With the advent of non-invasive maternal biochemical screening testing there was the advantage of safer techniques for both the mother and the fetus.

Maternal serum biochemical screening, however, was not a diagnostic test and gave a strong indication of a fetal abnormality to be confirmed by amniocentesis, chorionic villus sampling or ultrasound. Besides the diagnosis of neural tube defects, maternal serum screening has proven useful for the detection the three most common chromosome disorders, trisomy 21, trisomy 18 and trisomy 13. More recently the introduction of cell free fetal DNA (cffDNA) testing from maternal serum has become the most accurate maternal serum marker for the three common trisomies to date. However, at present it is expensive and cannot be used when a previous pregnancy resulted in fetal chromosomal disorder.

Research from Italy (5) has indicated that a different approach may be possible by using metabolomics. Using blood samples from known pregnancies with fetal chromosome abnormalities (n=108) plus unaffected controls (n=220) they analysed the samples by gas chromatography-mass spectrometry (GC-MS). Then, using a combination of statistical and discriminant function analysis tools, and artificial neural network techniques, they developed an ensemble machine learning (EML) model to identify metabolic fingerprints of fetal chromosome abnormalities from second trimester maternal serum. The model showed an accuracy of 100%, sensitivity of 100% and specificity of 100% for trisomy 21 and 18 as well as other fetal chromosomal abnormalities such as XXY and XO. Network analysis of the metabolic data identified multiple metabolic abnormalities in the chromosome abnormalities group compared with controls indicating defects in a number of metabolic pathways. The authors concluded that overall the biochemical patterns identified in maternal serum from the fetal chromosome abnormalities was suggestive of a defective metabolic oxidative environment and a disturbance of fetal central nervous system development and that further validation of the data will be required.

Are neutrophils an issue in metastatic cancer?

Metastatic cancer is a process that is poorly understood but the consequences of the tumour cells ability to spread to other body tissues and organs severely affect the prognosis in cancer treatment. It is acknowledged that for metastatic cancer to be initiated it must travel through the body to distant sites and the circulatory system is a prime vehicle for tumour cells (circulating tumour cells, CTC) to travel. The mechanisms for CTC to survive in the blood are again poorly understood; however, recent research from Switzerland has provided a valuable insight to both the transport and survival of CTC (6).

The research investigated the likelihood of CTC clustering with neutrophils in the blood and that this association enhanced the metastatic potential of CTC. To prove this they conducted three investigations. In the first they identified that patients with advanced breast cancer with circulating CTC-neutrophil clusters had a shorter time for the disease advancing compared with those patients lacking the cluster. In the second part of their research they injected CTC that had been separated from the cluster in to mice and identified that these mice had significantly higher metastases than mice receiving CTC not associated with a cluster. In the third investigation mice with breast cancer were depleted of neutrophils leading to the depletion of CTC-neutrophil clusters had delayed formation of metastases. The researchers went on to characterize what association there was with the CTC-neutrophil association and identified that the cells within the cluster had higher levels of cell-cycle progression genes and a high level of Ki67 (cell proliferation marker) than CTC alone. Leading them to conclude that the CTC-neutrophil cluster are already primed for proliferation when they reach another site and propose that preventing or disrupting the formation of the clusters may offer a new opportunity for therapeutic intervention.

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News from the Universities

The most outstanding BMLS graduate in transfusion science:
Priyansha Kumar
The most outstanding BMLS graduate in haematology:
Melissa Smith
The most outstanding Certificate in Applied Science graduate:
Nadia Boulle
The most outstanding BMLS graduate in immunology:
Rebecca Jasmine Shepherd
The most outstanding BMLS graduate in medical microbiology:
Diego Leonardo Riofrio

NZIMLS prize for the student with the top marks/grades for the third year BMLSc

Tahlia Hopkins

I grew up in Hastings, and went to Raureka Primary, Hastings Intermediate and then to Karamu High School. I then moved to Massey University in Palmerston North to study BMLSc.

I have played a lot of sports, including soccer, volleyball, canoe polo, orienteering and cross country. I also enjoy outdoor activities such as running, cycling and tramping. Other activities I like to do include reading, painting and listening to music.

I chose to do a BMLSc because I really enjoyed science in high school, especially biology, so wanted to continue with science at University and I was also interested in learning about the human body and what can go wrong with the body. BMLSc seemed like the perfect career choice for me since it involved both science and medical health and it would allow me to still help people by finding out what is wrong with them.

Inter-professional education

An inter-professional education activity was launched in July, involving students from the University's Schools of Oral Health and Dentistry and from the Medical Laboratory Science programme. Guided by staff, students collaborated to present patient cases involving all three disciplines. They discussed their roles and the opportunities and importance of interaction to improve patient care.

Roche User Group meeting

At the Roche User Group meeting in November, Cat gave two talks about teaching and learning in haematology, and the challenges of diagnosing vitamin B12 deficiency. It was great to see so many of our graduates presenting too!

Student numbers

This year we welcomed 37 students into second year and 30 into third year, with pizza and a scavenger hunt. We also have 23 students completing their fourth-year clinical placements around NZ and we have our first student on placement in Denmark. We thank all of our partner laboratories for their on-going support.

Farewell to Cat Ronayne and Lisa Gallagher

Lisa and Cat are leaving the University of Otago at Easter. They have been exceptional and dedicated teachers in the Medical Laboratory Science programme, always prepared to go the extra mile for students. They will be missed very much by both staff and students. Thanks Lisa and Cat for all your hard work and years of service.

Course administrator

The Support Services Review at the University of Otago resulted in major changes among the general staff during 2018. We are delighted to announce that Kirsten Wisneski, who joined us in Semester 2, 2018, will continue as the administrator for the BMLSc programme this year. Kirsten is from the USA where she gained wide experience in administration working for not-for-profit organisations.

The prize winners for the graduating class of 2018 are listed below. Congratulations to those students for their excellent achievements.

Sandy Smith Microbiology Prize
Top overall student in 3rd and 4th year Microbiology
Iva Anjani

Roche Haematology Prize
Top overall student in 3rd and 4th year Haematology
Iva Anjani

NZ Branch of the AACB
Deserving BMLSc student who has completed Biochemistry as a major in their final year
David Peart

Hugh Montgomery Trust Leadership Award
Deserving 3rd year BMLSc student selected for leadership and academic achievement
Kahla Tyson

NZIMLS 2nd Year Top Student Prize
Top overall student in 2nd year
Olivia Liu

NZIMLS 3rd Year Top Student Prize
Top overall student in 3rd year
Annabella Yee

NZIMLS 4th Year Top Student Prize
Top overall student in 4th year
Iva Anjani

Colin Watts Prize
Top overall graduating student
Hanlin Chen

Journal Questionnaire

Below are ten questions based on articles and the Science Digest column from the April 2019 issue. Read the articles carefully as most questions require more than one answer. Answers are to be submitted through the NZIMLS website. Make sure you supply your correct email address and membership number. It is recommended that you write your answers in a word document and then cut and paste your answers on the web site.

The site has been developed for use with Microsoft's Internet Explorer web browser. If you are having problems submitting your questionnaire and you are using the Firefox web browser, try re-submitting using Microsoft's Internet Explorer.

You are reminded that to claim valid CPD points for successfully completing the journal questionnaire you must submit an individual entry. It must not be part of a consultative or group process. In addition, members who have successfully completed the journal questionnaire cannot then claim additional CPD points for reading the articles from which the questions were derived.

The site will remain open until Friday 28th June 2019. You must get a minimum of eight questions right to obtain five CPD points. The Editor sets the questions but the CPD Co-ordinator, Jillian Broadbent, marks the answers. Direct any queries to her at cpd@nzimls.org.nz.

APRIL 2019 JOURNAL QUESTIONNAIRE

1. Acute promyelocytic leukemia presentation is characterised by which features?
2. How is the differential diagnosis of acute promyelocytic leukemia made?
3. Which are the most common aberrant antigens expressed in acute promyelocytic leukemia?
4. What is the expected pattern in acute promyelocytic leukemia for the selected 2nd line monoclonal antibodies?
5. What are the typical clinical symptoms of diabetes mellitus?
6. What are the World Health Organisation's criteria for diagnosing pre-diabetes and diabetes mellitus?
7. The Alvarado score for the diagnostic criteria for acute appendicitis is based on what?
8. Patients with the severe infantile onset phenotype of very long chain acyl-coenzyme A dehydrogenase deficiency often develop which conditions?
9. What is the gold standard for diagnosing very long chain acyl-coenzyme A dehydrogenase deficiency?
10. What has become the most accurate maternal serum marker for the three most common trisomies? Name these three trisomies.

NOVEMBER 2018 JOURNAL QUESTIONNAIRE AND ANSWERS

1. Resistance to carbapenems can be caused by which mechanisms?
   Acquired, extended -spectrum beta-lactamase(ESBL) or AmpCbeta-lactamase production, combined with porin loss (commonly seen in Enterobacter spp) or efflux mechanisms.
2. What are some of the epidemiological risk factors(s) for the acquisition of CPE?
   Overseas travel or hospitalisation, previous known CPE colonisation, or a household member with CPE.
3. What is the recommended screening carbapenem for the detection of CPE and what breakpoints should be used?
   Meropenem – Breakpoints : Mereponem MIC >0.12 mg/L or Meropenem disc zone diameter <25mm or Meropenem disc diameter 25-27mm, if also resistant to piperacillin-tazobactram (and/or temocillin) or Automated AST system indicates decreased susceptibility to meropenem or that a carbapenemase may be present.
4. Name two phenotypic methods which would be suitable for confirmation of CPE.
   Any two of : Colorimetric tests, carbapenem inactivation method, combination disc testing, immunoassays for detection of carbapenemases.
5. When should the presence of CPE be notified to the clinical microbiologist and infection prevention services?
   If in a health care facility notification ASAP and on the same day for both clinical microbiologist AND infection prevention services. For community patients notification ASAP and on the same day to clinical microbiologist and by the next working day to the infection prevention services.
6. Name the range of histological features of pulmonary adenocarcinoma.
   Histologically heterogeneous, presenting with a wide range of histologic features including solid growth with mucin production, acinar, papillary, lepidic, enteric within the current WHO adenocarcinoma classification.
7. What are considered standard diagnostic criteria for papillary thyroid carcinoma?
   Combination of classic nuclear features includes nuclear pseudo-inclusions, nuclear grooves, ground glass nuclei along with true papillary architecture.
8. Intranuclear pseudo inclusions are present in what other malignancies than papillary thyroid carcinoma?
   Pulmonary papillary adenocarcinoma, hepatocellular carcinoma, melanoma, meningioma and variants of parenchymal renal cell carcinoma.
9. Recent research has implicated ABO blood type as a risk factor for which diseases?
   Cancer, myocardial infarction and venous thromboembolism.
10. During tumour progression stiffness or elasticity of the tumour increases. What are these changes due to?
    Modification of the extracellular matrix associated with cancer cells.

Correction

The answer for question 8 from the April 2018 questionnaire published in the August 2018 issue was incorrect. The correct answer is **"Hydrolysing ESCs and aztreonams. Inhibited by clavulanic acid, tazobactam and salbactam."**

NZIMLS

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Learn something new!

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Contact Jane Kendall:

janek@medlabcentral.co.nz

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Index to Volume 72, 2018

AUTHOR INDEX

2019 NZIMLS CALENDAR

Dates may be subject to change

DATE	COUNCIL	CONTACT
22-23 March	Council Meeting, Rangiora	fran@nzimls.org.nz
May	Council Meeting, TBA	fran@nzimls.org.nz
15-16 August	Council Meeting, Auckland	fran@nzimls.org.nz
DATE	**SEMINARS**	**CONTACT**
23 March	South Island Seminar, Commodore Hotel, Christchurch	mealine.eason@nzblood.co.nz
17 - 19 May	NICE Weekend, Wairakei Resort, Taupo	raewyn.cameron@pathlab.co.nz
29 June	Pre-Analytical SIG Seminar, Waipuna Hotel & Conference Centre	janek@medlabcentral.co.nz
17 August	North Island Seminar, Waipuna Hotel & Conference Centre	linda.keat@middlemore.co.nz
18-19 October	Microbiology SIG Seminar, LabPlus, Auckland City Hospital	tbathgate@adhb.govt.nz

NZIMLS ANNUAL GENERAL MEETING

The Annual General Meeting of the NZIMLS for 2019 will be held in conjunction with the North Island Seminar Waipuna Hotel & Conference Centre. Time to be confirmed.

DATE	CONFERENCE	CONTACT
17-19 September	South Pacific Congress, Gold Coast Convention Centre, Gold Coast, Australia	fran@nzimls.org.nz
DATE	**MEMBERSHIP INFORMATION**	**CONTACT**
January	Membership and CPD enrolment due for renewal	sharon@nzimls.org.nz
31 January	CPD points for 2018 to be entered before 31 January	cpd@nzimls.org.nz
15 February	Material for the April issue of the Journal must be with the Editor	rob.siebers@otago.ac.nz
15 June	Material for the August Journal must be with the Editor	rob.siebers@otago.ac.nz
18 June	Nomination forms for election of Officers and Remits to be with the Membership (60 days prior to AGM)	fran@nzimls.org.nz
8 July	Nominations close for election of officers (40 days prior to AGM)	fran@nzimls.org.nz
26 July	Ballot papers to be with the membership (21 days prior to AGM)	fran@nzimls.org.nz
01 August	Annual Reports and Balance Sheet to be with the membership (14 days prior to AGM)	sharon@nzimls.org.nz
09 August	Ballot papers and proxies to be with the Executive Officer (7 days prior to AGM)	fran@nzimls.org.nz
15 September	Material for the November Journal must be with the Editor	rob.siebers@otago.ac.nz
DATE	**NZIMLS EXAMINATIONS**	**CONTACT**
02 November	QMLT Examinations	fran@nzimls.org.nz

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