College of Chemical Pathologists of Sri Lanka

CCPSL NEWSLETTER

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Issue 04

COVER STORY

6th Annual Academic Sessions (AAS)
College of Chemical Pathologists of Sri Lanka 2021
SUSTAINABLE LABORATORY SYSTEMS FOR QUALITY RESULTS

7th Annual Academic Sessions
College of Chemical Pathologists of Sri Lanka 2022
OVERCOMING CHALLENGES AND SUSTAINING CHEMICAL PATHOLOGY SERVICES AMIDST CRISIS

Editors

Dr Eresha Jasinge
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Message form the President (2020/2021)

Dr Rajitha Samarasinghe
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I am honoured and privileged to hold office as the 6th President of the College of Chemical Pathologists of Sri Lanka (CCPSL); the leading professional organization of laboratory professionals in Sri Lanka. In January 2022, I am completing my tenure as the President of the CCPSL successfully closing a challenging chapter, and this newsletter conveys the story of success gained towards maintaining high standards in the college activities amidst the COVID-19 pandemic.

The productivity of the College was enhanced by the successful completion of the 6th Annual Academic Sessions and the Medical Laboratory Workshop, as a hybrid event, conducting a webinar series as an academic activity for the benefit of the postgraduate trainees in chemical pathology, maintaining consistent rapport with administrative officials of Ministry of Health, regarding the policies related to chemical pathology field in Sri Lanka and collaborative work with international organizations pioneering in medical laboratory profession. The CCPSL was able to liaise with the Ministry of Health to establish a policy to conduct all activities related to chemical pathology services in Sri Lanka through proper channels. Continuous Professional Development (CPD) programme was commenced in view of augmenting the membership in maintaining the highest professional standards. Furthermore, the CCPSL office was shifted to a new location with improved facilities to conduct council meetings and other official activities of the college.

I would like to convey my sincere gratitude to the Council, the office bearers and all CCPSL members who were instrumental in securing success in all activities conducted by CCPSL at times of a pandemic.

I wish the CCPSL all success!

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CCPSL NEWS

Message form the President (2021/2022)

Dr Kisali Hirimutugoda

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District General Hospital, Negombo

I am honoured and privileged to hold office as the 7th President of the College of Chemical Pathologists of Sri Lanka (CCPSL). In January 2023, I am completing my tenure as the President of the CCPSL after facing both the COVID-19 pandemic and economic crisis, of the country. I feel that myself as the president and the Council faced these challenges successfully. We were able to carry out ten webinars with local and overseas resource persons, three case discussion sessions where chemical pathology trainees presented interesting cases guided by the consultant chemical pathologists by participating in the final discussion. We were also able to conduct four workshops and out of that, one workshop was for phlebotomists and one was for non-postgraduate medical officers working in medical laboratories.

The pinnacle of all these academic activities is the Annual Academic Sessions themed "Overcoming challenges and sustaining chemical pathology services amidst crisis" and this was successfully completed with two parallel academic programs. This time there were two new additions to the Annual Academic Sessions. The CCPSL oration was introduced to the inauguration ceremony. The first ever chemical pathologist in Sri Lanka, Dr Saroja Siriwardena delivered the CCPSL oration of 2022 on 'The journey of establishing chemical pathology services in Sri Lanka'. Furthermore, the industrial exhibition was transformed to "Clinical Lab Expo" this year which was open to the public. The interested parties including laboratory directors, managers and medical laboratory scientists had the opportunity to visit the Clinical Lab Expo and this was a unique educational experience and opportunity to interact and find solutions for laboratory related problems.

During my official period, CCPSL was able to liaise with the Ministry of Health to establish a policy to conduct all activities related to chemical pathology services in Sri Lanka and specially to work together towards the development of cost-effective laboratory plans during this economic crisis.

I would like to convey my sincere gratitude to the Council, the office bearers and all CCPSL members who gave me an amazing support in all activities conducted by the CCPSL

I wish the CCPSL all success!

Induction of the 6th President of CCPSL & Inauguration Ceremony of Annual Academic Sessions of CCPSL 2021

The induction of the 6th President of the College of Chemical Pathologists of Sri Lanka and the inauguration of the 6th Annual Academic Sessions, 2021 was held on 26th July, 2021 at the Grand Ballroom, Hotel Hilton, Colombo. It was conducted as a hybrid event due the prevailing restrictions related to the COVID-19 pandemic.

The chief guest for the occasion was Dr Asela Gunawardena, Director General of Health Services, Ministry of Health, Nutrition and Indigenous Medicine.

Dr Rajitha Samarasinghe was inducted as the 6th President of CCPSL by the immediate Past President, Dr Manjula Dissanayake. The presidential address was delivered by Dr Rajitha Samarasinghe, highlighting the importance of the chemical pathology services in managing patients with cancers.

Dr Eresha Jasinge was awarded the CCPSL fellowship in recognition of her service to uplift the services provided by the Department of Chemical Pathology, Lady Ridgway Hospital for Children Colombo, Sri Lanka. Mrs Sharmalie Nanayakkara was felicitated for her immense service to the medical laboratory profession.

Dr Saroja Siriwardene Memorial Gold Medal for the best performer at the MD chemical pathology, Part II examination (PGIM, University of Colombo), 2021 was awarded to Dr Thurairetnam Inthujah.
At the end of the inauguration the audience was entertained by a musical event.

The ceremony concluded with a grand reception.

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6th Annual Academic Sessions of CCPSL

The 6th Annual Academic Sessions of College of Chemical Pathologists of Sri Lanka was held on 26th and 27th July 2021 at Hotel Hilton, Colombo.

The academic programme was conducted as a hybrid event and the medical laboratory workshop was held as a virtual event. The programme was designed to cover a wide range of topics aligned with the theme "Sustainable Laboratory System for Quality Results". The sessions were attended by over 350 participants. Besides chemical pathologists and clinical scientists the lectures were held by excellent colleagues from clinical medical disciplines. There were 12 international and 32 local speakers who shared their expertise followed by extensive, fruitful discussions.

The poster presentations were also carried out on a virtual platform with 63 posters which included communication of research and case presentations.

The professional program was complemented by a virtual industrial exhibition of companies dealing with laboratory instruments and reagents which attracted a large audience.

The sessions were concluded on 27th July evening following the award ceremony for best poster presentations.

Winners of the awards - 6th Annual Academic Sessions of CCPSL

Poster presentations (research category)

First place

Screening of PCSK9 variant, rs11591147, with a novel method in a cohort of patients with familial hypercholesterolaemia

Hewa SP[1], Wetthasinghe KT[2], Dissanayake HW[2]

[1]Department of Chemical Pathology, Colombo South Teaching Hospital, Kalubowila, Sri Lanka

[2]Human Genetic Unit, Faculty of Medicine, University of Colombo, Sri Lanka

Second place

Evaluation of the immune response to Covishield vaccine in a cohort of participants in Colombo

Gunawardane SA[1], Jinasena TMRR[2], Katulanda GW[1], Hewa SP[2], Agampodi SB[3], Dissanayake DJGGN[1], Jayasinghe IN[2], Inthujah T[1], Samarakoon SMPP[1], Balasooriya BMCM[1], Sujeeva N[1], Thowfeek ZTM[1], Prashanthan S[1], Wijesuriya WAM[1], Thushyanthi P[2], Athpaththu AMTU[2], Samarasinghe M[2], Ediriweera TW[1]

[1]Department of Chemical Pathology, National Hospital of Sri Lanka

[2]Department of Chemical Pathology, Colombo South Teaching Hospital, Sri Lanka

[3]Department of Community Medicine, Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka

Third place

Determination of Postoperative Hypocalceamia in Patients Undergoing Total Thyroidectomy by Using Single Measurement of Pre-Closure Plasma Intact Parathyroid Hormone Level (PC-iPTH)

Pathirana VPATV[1], Samarasinghe R[2], Perera E[3], Wanigasooriya SS[3], Yapa YMAB[3]

[1]Department of Chemical Pathology, District General Hospital, Vavuniya, Sri Lanka

[2]Department of Chemical Pathology, National Cancer Institute, Maharagama, Sri Lanka

[3]Surgical Unit, Base Hospital, Avissawella, Sri Lanka

Poster Presentation (Case report category)

First place

Two children with late infantile manifestation of multiple sulfatase deficiency.

Abeysekera WLRM[1], Panapitiya M[2], Perera D[3], Jasinge E[1]

[1]Department of Chemical Pathology, Lady Ridgeway Hospital for Children, Sri Lanka

[2]Paediatric unit, Colombo North Teaching Hospital, Ragama, Sri Lanka

[3]Paediatric unit, Lady Ridgeway Hospital for Children, Sri Lanka

Second place

Influence of CYP3A5 polymorphism in tacrolimus bioavailability

Kiyamudeen F[1], Jayawardana RPD[1], Rajapaksha RDDM[1], Wazil AWM[2]

[1]Department of Chemical Pathology, National hospital, Kandy, Sri Lanka

[2]Department of Dialysis and Renal Transplantation, National Hospital, Kandy, Sri Lanka

Third place

Typical inferior petrosal sinus sampling results in a patient with severe Cushing disease

Balasooriya BMCM[1], Samarakoon SMPP[1], Sujeeva N[1], Dematapitiya BRCM[2], Pathmanathan S[2], Sumanatilleke M[2], Katulanda GW[1]

[1]Department of Chemical Pathology, National Hospital of Sri Lanka

[2]Diabetes and Endocrinology Unit, National Hospital of Sri Lanka

Induction of the 7th President of CCPSL & Inauguration Ceremony of Annual Academic Sessions of CCPSL 2022

The inauguration ceremony was a great success and the prestigious CCPSL oration for the 1st time titled “Journey of establishing chemical pathology services in Sri Lanka “ was delivered by Dr Saroja Siriwardene. This event was witnessed by a large number of participants. The Chief Guest was Dr Asela Gunawardena and in his speech, he highlighted the important role played by chemical pathologists in relation to the diagnosis, monitoring and management of patients. This year the CCPSL fellowship was awarded to Prof. Lal Chadrasena in recognition of his valuable contribution to chemical pathology and laboratory medicine while Mr Saman Samaranayake was felicitated for his tremendous support and commitment to the medical laboratory field throughout his over 30 years career as a medical laboratory technologist. The audience was entertained by a peaceful relaxing instrumental music at the end of the inauguration ceremony.

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7th Annual Academic Sessions of CCPSL

The 7th Annual Academic Sessions of the CCPSL was successfully concluded at the Grand Ballroom, Hotel Galadari, Colombo on 28th August 2022 after 2 days of new knowledge under the theme of "Facing challenges and sustaining Chemical Pathology services amidst crisis".

The scientific programme included two parallel programmes, academic and medical laboratory science (MLS), extending for 2 days. In the academic programme, there were ten plenaries and six symposia covering a wide range of timely and important topics of chemical pathology. The MLS programme was a hybrid event with virtual and physical participation giving the opportunity to more attendees. Forty-three resource persons contributed to the 7th Annual Academic Sessions and there were 17 overseas speakers who shared their knowledge and experience generously. The topics related to laboratory management, electrophoresis, nutrition, endocrinology, metabolic medicine and lipids were discussed in symposia.

This event was an excellent gateway for chemical pathology trainees and other researchers to present their research work. There were 63 abstracts and out of them 9 were chosen for oral presentation while the rest were displayed as e-posters.

The oral presentation competition was a new addition to the Annual Academic Sessions of the CCPSL. It was conducted as a hybrid event on a pre-scheduled date prior to the main programme and judged by imminent researchers in the field. The main objective was to develop research interest and presentation skills among chemical pathology and MLS trainees. The winners of the oral presentation and e-poster competition were announced at the closing ceremony.

The 2022 AAS – CCPSL clinical Lab Expo was open on both days for all attendees of the main programme and also for non-registered laboratory professionals who were interested to learn about latest diagnostic technologies and laboratory medicine developments. It gave them the opportunity to interact with the exhibitors in person and find solutions to laboratory related needs.

Activities in Brief (2021/2022)

		Title	Resource persons
Webinars	25.01.2022	Delivering an effective lecture	Professor Jankai Hewavisenthi Dean of the Faculty of Medicine University of Kelaniya
	11.02.2022	Patient safety in laboratory medicine	Dr. Dilinika Perera, Consultant Chemical Pathologist, SBSCH - Peradeniya
	25.02.2022	Gut-brain-axis and obesity	Dr. Royce Vincent, Consultant Chemical Pathologist, King's College Hospital NHS Foundation Trust, London, UK
	18.03.2022	Newborn screening	Dr. Mehdi Mirzazadeh, Consultant in Chemical Pathology and Metabolic Medicine, Epsom & St Helier University Hospital and Honorary Senior Lecturer, St George's University Hospital, London, UK
	24.03.2022	Bone markers	Dr. Nandani Rao, Consultant in Chemical Patthology and Metabolic Medicine, King's College Hospital NHS Foundation Trust, London, UK
	08.04.2022	Biochemistry case scenarios – An interactive case based discussion	Dr. Gayani Weerasinghe Consultant Chemical Pathologist, Buckinghmashire Healthcare NHS Trust and Honorary Consultant, Oxford University Hospital, UK
	22.04.2022	Assay interferences	Dr Gayan de Cota, Consultant in Chemical Pathology, University of Sussex NHS Foundation Trust, Roya Sussex County Hospital, Brighton, UK
	06.05.2022	Trace elements	Dr. Ruvini Ranasinghe, Specialty Registrar in Chemical Pathology, King's College Hospital NHS Foundation Trust, London, UK
	18.11.2022	Inherited metabolic diseases in adults	Dr. Subadra Wanninayake, Fellow in IMD, Queen Elizabeth Hospital and University Hospital Birmingham, Birmingham, UK

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	15.12.2022	Renal stones	Dr Lanka Liyanage Locum Consultant Chemical Pathologist Mid Yockshire Hospital NHS Trust
Case discussions	17.06.2022	Hyperamylasaemia, Hypernatraemia, ACTH stimulated adrenal venous sampling	Conducted by Dr Gaya Katulanda, Consultant Chemical Pathologist, National Hospital of Sri Lanka, Colombo Dr Madhu Wijayasuriya Dr T Inthuja Dr Menaka Balasooriya
	22.07.2022	Adrenal venous sampling, Hypercalcaemia	Conducted by Dr Dulani Jayawardena, Consultant Chemical Pathologist, National Hospital Kandy Dr Fasilaas Kiyamudeen Dr Madubashini Rajapaksha Dr Thilini Premadasa
	21.10.2022	Fasting hypoglycaemia in adults	Conducted by Dr Thamara Herath, Consultant Chemical Pathologist, Medical Research Institute, Colombo Dr S B Mohideen Dr R P M M R Pathirana Dr W A D S Sandaruwani Dr S S K Mudunkotuwa

Workshops

On 31st March, 2022 a workshop on sample collection was held successfully through an online platform. The target audience was the phlebotomists and the nursing staff. For each hospital one link was arranged to facilitate the webinar to be broadcast in the auditorium which enabled a wider participation. A majority of laboratory errors occur during the pre-analytical phase and the proper specimen collection plays an important role in reducing these errors. This workshop provided a detailed account on patient preparation, identification, sample collection and risk management. Furthermore, most frequently encountered issues by the laboratorians and clinicians due to improper sample collection were discussed illustrating clinical cases. There was a Q and A session which was found extremely helpful by the participants.

March 3rd and 4th, 2022 were reserved for a great workshop for medical officers in pathology which was conducted virtually. It was free for all participants in order to disseminate knowledge for a wider audience. During this workshop the concept of quality control, critical values and complaint handling were introduced. Furthermore, interpretation of common biochemistry tests such as liver functions, renal functions and thyroid functions were discussed. This workshop was found very useful by the participants.

The "Trainee Day" was aimed at members of the CCPSL who were preparing for MD Chemical Pathology examinations. The current economic crisis in the country made this workshop converted to an entirely virtual programme which was held for 2 days on 24th June and 8th July 2022. This programme covered topics that are traditionally not taught well in textbooks or for which practical experience is needed. Laboratory ethics, method verification of glucose meters, analytical performance specification, biological variation and biosafety in clinical laboratories were some of them. This workshop received excellent feedback from the trainees as well as the experts in the field of chemical pathology and the CCPSL hopes to conduct similar training days in an interactive way in the future.

An onsite workshop on procurements was conductedon 1st, 10th and 11th November 2022 at Hector Kobbekaduwa Agrarian Research and Training Center with the participation of about 40 participants including consultants and senior registrars in chemical pathology.

A workshop on research methods was conducted on 13th December, 2022 at Clinical Medicine Academic and Research Centre, National Hospital of Sri Lanka, with the physical participation of about 50 consultants and postgraduate trainees in chemical pathology.

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Winners of the awards - 7th Annual Academic Sessions of CCPSL

Oral presentations (Research and audits category)

First place

Practical utility of laboratory data including D-dimers in COVID-19: A multivariate regression model to predict the disease severity

Sujeeva N[1], Balasooriya BMCM[1], Manathunga SS[2], Samarakoon SMPP[1], Gunawardena SA[1], Inthujah T[1], Wijayasuriya WAM[1], Aroon T[1], Katulanda GW[1]

[1]Department of Chemical Pathology, National Hospital of Sri Lanka
[2]National Hospital of Sri Lanka

Second place

Evaluation of the association between severity of acute SARS-CoV-2 infection and vaccination: A cross-sectional study on a group of patients admitted to a tertiary care hospital in Sri Lanka

Balasooriya BMCM[1], Sujeeva N[1] Manathunga SS[2], Samarakoon SMPP[1], Gunawardena SA[1], Inthujah T[1], Dissanayake DGN , Katulanda GW[1]

[1]Department of Chemical Pathology, National Hospital of Sri Lanka
[2]National Hospital of Sri Lanka

Third place

An audit on the impact of age-adjusted thyroid stimulating hormone (TSH) reference interval (RI) for the elderly, on classifying thyroid status

Amarasekara M.H.K, Gunasekara R.A.S.R, Samarasinghe R

Department of Chemical Pathology, Apeksha Hospital, Maharagama

Oral presentation (Case report category)

First place

Elevated creatine kinase (CK) enzyme in an asymptomatic patient

Gunarathna KKSK, Gallage BMP, Sanjeewani JAP, Samarasinghe R

Department of Chemical Pathology, National Cancer Institute Maharagama, Sri Lanka

Second place

Misleadingly high Ca125 in a patient with tuberculosis

Amarasekara MHK, Gunasekara RASR, Samarasinghe R

Department of Chemical Pathology, Apeksha Hospital, Maharagama

Third place

A neonate with intractable seizures

Vithanage TK

Monash Pathology, Monash Medical Centre, Clayton, VIC, Australia

Winners of the awards - 7th Annual Academic Sessions of CCPSL

E-Poster presentations (Research and audits category)

First place

The association of high sensitivity C-reactive protein and albumin to creatinine ratio with HbA_{1c} level among type 2 diabetic patients in a tertiary care hospital in Sri Lanka

Warnakulasuriya BC[1], Nirmanika KKT[1], Marasinghe HMKSD[1], Vithanage AA[1], Karunarathna WAC[1], Jayasekara JKMB[1], Sumanatilleke M[2], Thilakarathna L[3], Katulanda GW[3]

[1]Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, General Sir John Kotelawala Defence University, Sri Lanka
[2]Diabetes and Endocrinology Unit, National Hospital, Sri Lanka
[3]Department of Pathology, National Hospital, Sri Lanka

Second place

Bilirubin interference on creatinine assay by Jaffe and enzymatic methods and its elimination by photolysis

Wickramarathne WRS[1], Jayasinghe S[3], Dharmapala A[2], Dissanayaka DM[3]

[1]Department of Medical Laboratory Science, Faculty of Allied Health Sciences, University of Peradeniya, Sri Lanka
[2]Department of Surgery, Faculty of Medicine, University of Peradeniya, Sri Lanka
[3]Department of Pathology, Faculty of Medicine, University of Peradeniya, Sri Lanka

Third place

Evaluation of accuracy of blood glucose meters in all medical wards in a tertiary care hospital in Sri Lanka

Gunawardena SA, Inthujah T, Dissanayake DJGGN, Samarakoon P, Katulanda GW

Department of Biochemistry, National Hospital of Sri Lanka

E-Poster presentations (case report category)

First place

A case report of two children with hyperphenylalaninaemia: Importance of measuring tetrahydrobiopterin levels in hyperphenylalaninaemia

Puliyadda TMNK[1], Senanayaka UE[1], Jayawardena A[2], Weerasekara K[2], Dayanath BKTP[1], Blau N[3], Jasinge E[4]

[1]Department of Chemical Pathology, Colombo North Teaching Hospital
[2]Department of Paediatrics, Lady Ridgeway Hospital for Children
[3]Dietmar-Hopp Metabolic Center, University Children's Hospital, Heidelberg, Germany
[4]Department of Chemical Pathology, Lady Ridgeway Hospital for Children

Second place

A girl with early Fanconi syndrome harboring a novel variant of Wilson disease

Kularathne MSS[1], Jasinge E[2]

[1]Department of Chemical Pathology, Medical Research Institute, Colombo
[2]Department of Chemical Pathology, Lady Ridgeway Hospital for Children, Colombo

Third place

Turner syndrome-mosaic (46, XY/45, X) presenting with primary amenorrhea and altered thyroid functions

Kulasinghe MSN[1], De Silva P[2], Dayanath BKTP[1]

[1]Department of Chemical Pathology, Colombo North Teaching Hospital, Ragama, Sri Lanka
[2]Obstetric unit, Colombo North Teaching Hospital, Ragama, Sri Lanka

Evolution of clinical chemistry-from tasting of urine to modern biochemical diagnostics

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Department of Chemical Pathology,
Teaching Hospital, Anuradhapura

"I have found a reagent which is precipitated by haemoglobin and by nothing else" - A Study in Scarlet - The Adventures of Sherlock Holmes 1887.

Sherlock Holmes became the first and only fictional fellow honored by the Royal Society of Chemistry when an extraordinary honorary fellowship endowed for the concept of chemistry implemented to identify blood to crack crime.[1]
The idea that the results of a chemical reaction applied in medical diagnosis sprouted into clinical chemistry.

Clinical chemistry during ancient era

Ancient Egyptians (1550 BC) described urine in cystitis as contaminated by mucus, pus and blood.[2] Indian ayurvedic physicians diagnosed a patient based on Ashtavidha Pariksha which means eight types of examination including urine and stools inspection. Urine examination included colour, appearance, consistency and Tailabindu Pariksha. The latter was carried out by dropping Tila Taila (sesame oil) slowly over the surface of urine. The patterns and the distribution of the oil drop on urine were then considered to determine the diagnosis and prognosis.[3]

Around the 5th century BC, the famous Indian surgeon Sushruta, in his work "Samhita" described sweet taste of urine in patients with diabetes mellitus which is one of the earliest concepts of "detection of unusual chemicals" in diagnosis of diseases.[4]

Hippocrates (300 BC) advised examination of urine and related froth in urine to kidney disease and chronic illness. The first description of haematuria by Rufus of Ephesus surfaced at around AD 50 and was attributed to the failure of kidneys to filter blood.

Clinical chemistry during the medieval period

Inspection of excreta and sometimes semen was practiced during the medieval period. Isaac Judaea (832-932), a Jewish physician laid guidelines for the use of urine as a diagnostic aid. A book envisaging colour, density, quality, and sediment in urine was written around the same period.[5] By around AD 1300 urine macroscopy became a near universality in European medicine.

Clinical chemistry during early modern era

In 1964, Frederik Dekkers of Netherlands, observed that protein in urine makes a precipitate when heated with acetic acid. Anthanasius Kircher (1602-1680) of Germany was probably the first to use the microscope to investigate the causes of disease. Though his work primarily confined to microbiology it paved the pathway to microscopic examination of patient samples.[5]

Clinical chemistry in the modern era

Matthew Dobson proved that the sweetness of the urine in diabetes is caused by sugar (1776) and Francis Home developed the yeast test for sugar in diabetic urine (1780) which is one of the earliest concepts of specificity in clinical chemistry.[5]

Sir William Osler 1892-1898 in his Textbook of Medicine described urinalysis and examination of cerebrospinal fluid. Otto Folin at Harvard (1907) pioneered quantitative assays. He developed analytical methods to quantify urine analytes including urea, ammonia, creatinine, uric acid, total nitrogen, phosphorus, chloride, total sulfate, and acidity. He also attempted to measure blood ammonia and introduced Jaffe alkaline picrate method for creatinine.[5] Folin introduced the colorimetric method for measuring epinephrine and published the first normal values for uric acid, nonprotein nitrogen and protein in blood and made a reagent for protein assay. In 1914 P N Patton described spectroscopic examination, visual detection of bilirubinaemia and Garrod technique for uric acid, urinalysis, fecal examinations for fat and stercobilin.[5]

German mathematician, August Beer, in 1852 postulated Beer law which astride its roots in many clinical chemistry assays today. Arnold O Beckman in 1940 designed the spectrophotometer based on Beer's principle which now turned the nucleus of many biochemical assays. Russian botanist Mikhail Tsvet invented column chromatography in 1906 while Arne Tiselius developed electrophoresis during the 1930s. The first immunoassay was designed by Rosalyn Sussman Yalow and Solomon Berson in the 1950s. J J Thomson in 1898 measured the mass-to-charge ratio of electrons and developed it in to a separation technique which was crafted in to a highly accurate analyzer in mass spectrometer by the subsequent work done by Francis William Aston, Wolfgang Paul, John Bennet Fenn and Koichi Tanaka.

Establishment of a clinical laboratory

Dr G. C. Uragoda in his book "History of medicine in Sri Lanka" states that the first hospital in the world was established in 9th century AD at Mihinthale, Sri Lanka which composed of rooms for sick, a refectory, and hot water baths room for making and storing medicines.[6] Uragoda has not mentioned anything on a clinical laboratory set up there.

The first hospital laboratory in Britain was set up at Guys Hospital. In the 19th century lay public, as well as many practitioners consider that medicine should not be moved out from the realm of clinicians in to the laboratories. With professional organizations such as American Society for Clinical Laboratory Science emerged as regulating authorities for laboratories in the early part of the 20th century and clinical laboratory turned an indispensable fixture in a hospital. Belk and Sunderman performed the first EQA scheme in the late 1940's which became an essential component of a laboratory's quality management system.[7]

Clinical chemistry came a long way from its primitive stage on to the current platform as a reliable tool in the diagnosis and patient management and the process of evolution is ongoing.

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Role of BNP & NT-proBNP in clinical practice

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The natriuretic peptide family mainly includes atrial natriuretic peptide (ANP), Brain or B-type natriuretic peptide (BNP), C-type natriuretic peptide (CNP) and urodilatin. [1]BNP was originally isolated from porcine brain tissue[1]. However, in humans the main sources of circulatory BNP are the ventricles of the heart. It is mainly synthesized and released by the myocytes of left ventricle in response to pressure and volume overload. [2]BNP is synthesized as proBNP comprising 108 amino acids. Once released into the circulation, it is cleaved into equal proportions of biologically active 32 amino acid BNP and biologically inactive 76 amino acid N-terminal fragment (NT-proBNP).[1]

BNP relaxes vascular smooth muscles to reduce ventricular preload and inhibits renin-angiotensin-aldosterone system and sympathetic nervous system.[3]

BNP is cleared from the plasma by receptor mediated clearance and through degradation by neutral endopeptidases. NT-proBNP is mainly cleared by renal excretion.[3]

Clinical utility

Large numbers of studies have found that BNP and NT-proBNP are elevated in patients with heart failure.[1] The role of BNP and NT-proBNP testing is included in the guidelines for the diagnosis and treatment of acute and chronic heart failure by the European Society of Cardiology (figure 1).[4] Several studies which evaluated the diagnostic performance of BNP and NT-proBNP demonstrated that in patients presenting to the emergency department with shortness of breath, BNP at a cut-off value of 100 pg/mL and NT-proBNP at a cut-off of 300 pg/mL had a very high negative predictive value to rule-out heart failure.[1]

In patients with acute coronary syndrome, both BNP and NT-proBNP are highly sensitive and specific indicators of the size of the myocardial infarction and valuable markers for predicting the prognosis and severity of ischaemic heart disease.[5]

Both BNP and NT-proBNP are found to be increased in patients with atrial fibrillation.[6] BNP and NT-proBNP are correlated directly with left ventricular end-diastolic dimension and left ventricular volumes and are inversely correlated with left ventricular ejection fraction in patients with dilated cardiomyopathy and hypertrophic cardiomyopathy.[7,8]

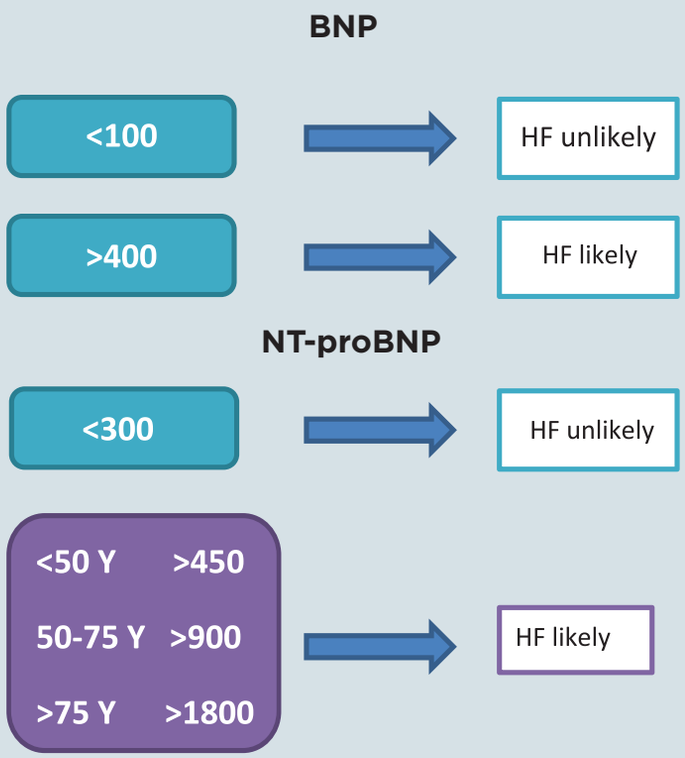

Figure 1: Recommended cut-offs of BNP and NT-proBNP (in pg/mL) for heart failure (HF) diagnosis in patients with acute dyspnoea.

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BNP and NT-proBNP are currently used in the evaluation of cardiac function status in forensic practice. Studies in postmortem individuals have demonstrated that BNP and NT-proBNP concentrations are significantly elevated in blood and pericardial fluid of the deceased who died from acute ischaemic heart disease and chronic congestive heart disease. However valuable postmortem cut-offs for both BNP and NT-proBNP in blood and pericardial fluid need to be established.[9]

Elevated BNP and NT-proBNP have been identified as risk markers in patients with acute pulmonary embolism.[10]

Recent studies have revealed that NT-proBNP levels of COVID-19 patients were significantly related to the severity of pneumonia. Therefore NT-proBNP testing helps to identify COVID-19 patients with coexisting heart failure and allow early management of cardiac failure.[11]

It is also recommended to use BNP and NT-proBNP to rule out chronic heart failure. In the non-acute setting BNP of <35 pg/mL and NT-proBNP of <125 pg/mL make a diagnosis of heart failure unlikely.[4]

There are many non-cardiac causes for elevated natriuretic peptides that might reduce their diagnostic accuracy (Table 1).[4]

Non-cardiac causes of elevated natriuretic peptides
Advanced age
Subarachnoid haemorrhage
Renal dysfunction
Liver dysfunction (mainly cirrhosis with ascites)
Paraneoplastic syndrome
Chronic obstructive pulmonary disease
Severe infections (pneumonia, sepsis)
Severe burns
Anaemia
Severe metabolic and hormone abnormalities (thyrotoxicosis, diabetic ketoacidosis)

Analytical considerations

Both BNP and NT-proBNP can be measured by commercially available assays (AxSYM BNP, Abbot; ADVIA centaur BNP, Bayer; Elecsys NT-proBNP, Beckman Access BNP, Roche Diagnostics).[1] Reliable point of care tests are also available for both markers (Triage BNP, Biosite; Cardiac Reader NT-proBNP, Roche Diagnostics).[1] As BNP and NT-proBNP assays are not yet standardized, values obtained with various assays are not comparable.

Blood for BNP should be collected in EDTA tube. Serum or plasma with additives of either EDTA or lithium heparin can be used for NT-proBNP assay. For BNP plasma samples stored at room temperature must be tested within 4 hours and at 2-8˚C within 24 hours.[1] Serum or plasma samples for NT-proBNP can be stored at room temperature for 3 days and at 2-8˚C for 6 days.[1] Both analytes are stable during freeze and thaw processes.

Biological variations

Both BNP and NT-ProBNP values show higher values in females and in older individuals.[1] There is inverse relationship of BNP and NT-proBNP with body mass index.[4] BNP and NT-proBNP values are increased with reduced renal function.[1] NT-proBNP is affected more by worsening renal function than BNP. There are no circardian variation and no marked influence of blood drawing conditions.[1,2]

BNP versus NT-proBNP

BNP is an active protein hormone with the half-life of 20 minutes whereas NT-proBNP is an inactive fragment has half-life of 120 minutes.[1] Therefore NT-proBNP shows higher circulating levels and slower fluctuations than BNP. Invitro stability of NT-proBNP is more than BNP.

Though the diagnostic and prognostic abilities of both markers are largely similar NT-proBNP is more sensitive than BNP in early diagnosis as it circulates at higher levels. In patients with heart failure who receive exogenous and synthetic BNP for treatment, BNP levels may be affected while NT-proBNP will not be affected. As NT-proBNP is primarily cleared by kidneys, its concentration is falsely elevated in severe renal disease.

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Congenital Disorders of Glycosylation: Medicine in a Nutshell

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Glycosylation

Glycosylation is a process in which glycans (i.e. carbohydrates or sugars) are covalently linked to the proteins or lipids forming different types of glycoconjugates (glycoproteins, glycolipids, glycosylphosphatidylinositol (GPI) anchors or proteoglycans).

The glycan parts of glycoconjugates contribute to diverse physical, biochemical and biological properties of glycoconjugates.

Glycosylation of both proteins and lipids occur in the endoplasmic reticulum (ER) and/or in the golgi apparatus (GA), depending on the specific type of glycosylation.[1]

The human genome consists of 30,000 -50,000 genes, but the human 'proteome' shows more than 500,000 proteins. The reason for the discrepancy between number of genes and proteins encoded for is the posttranslational modifications (PTMs).

PTMs of proteins occur once they have been synthesised. During PTMs molecules such as glycans and phosphate groups get attached to the proteins once proteins are synthesised. These are vital for the function and delivery to the site of actions of the proteins.

Analysis of the genetic code of a protein cannot predict this. A number of diseases require further testing such as mass spectrometric analysis to understand the cause of the malfunction of a protein.[2]

In humans, glycosylation can be divided into 4 main categories:

- N-linked (linkage to the amide group of asparagine),
- O-linked (linkage to the hydroxyl group of serine or threonine),
- C-linked (linkage to a carboxyl group of tryptophan) – very rare
- Formation of glycophosphoinositol (GPI) anchors.[2]

The processes of N- or O- glycosylation have numerous steps, any of which may be defective.

Congenital Disorders of Glycosylation

Congenital disorders of glycosylation (CDG) are a large and a highly heterogeneous group of genetic disorders. They include defects in the synthesis of glycoprotein and glycolipid, and their attachment to proteins and lipids.
It should be differentiated from congenital disorders of deglycosylation (CDDG) and enzymatic lysosomal storage disorders.
Diagnosis of CDG is challenging, because of their heterogeneity.

It has been described as 'nearly the whole medicine in a nutshell', because nearly all organs are involved and all symptoms have been reported. Majority of CDG are multisystem disorders.[3]

CDG should be considered in any unexplained disorder, particularly when neurological symptoms and signs are present, as most of CDG have a neurological component. However, many CDG have more or less specific features that are present in only one or a few of them.

Some symptoms or syndromes are even pathognomonic for a particular CDG.
Eg: Inverted nipples and fat pads in PMM2-CDG

Most CDG have an autosomal recessive inheritance except for EXT1-CDG, EXT2-CDG, GANAB-CDG, POFUT1-CDG, POGLUT1-CDG, PRKCSH-CDG, SEC63-CDG (autosomal dominant), and ALG13-CDG, ATP6AP1-CDG, ATP6AP2-CDG, OGT-CDG, PIGA-CDG, SLC9A7-CDG (very recently reported), SLC35A2-CDG, SSR4-CDG and VMA21- CDG (X-linked).

Several CDG show a number of biochemical abnormalities (of glycoprotein and other molecules) secondary to the hypoglycosylation. Some simple biochemical abnormalities can point to a particular CDG or to several CDG with defects in the same pathway.

Screening for CDG should be done in,

1. any unexplained neurological syndrome, particularly when associated with other organ disease

2. any unexplained syndrome even without neurological involvement.

Screening strategies for CDG

Screening often starts with serum transferrin (Tf) isoelectrofocusing (IEF), but capillary zone electrophoresis and high-performance liquid chromatography (HPLC) have the advantage of being more rapid and less labour-intensive.

Serum Tf -IEF does not pick up an important number of CDG namely:

1. O -glycosylation disorders that are not associated with an N-glycosylation defect
2. lipid glycosylation disorders
3. GPI anchor synthesis disorders
4. Several defects in the N-glycosylation pathway including those that do not show a deficiency of sialic acid.

False positive results can be found in conditions such as

1. transferrin natural polymorphic variants

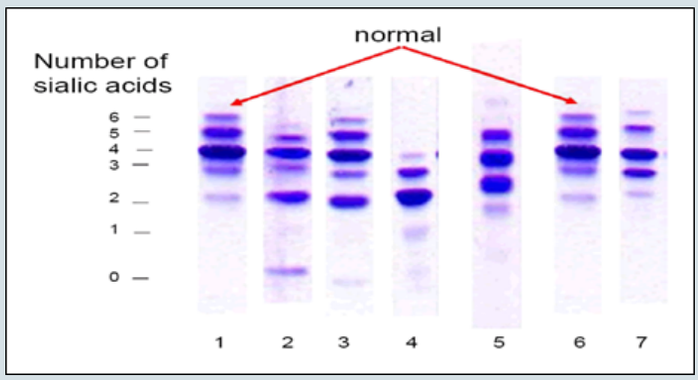
2. secondary glycosylation disorders (mainly galactosaemia and hereditary fructose intolerance).

IEF testing with pre-incubation with neuraminidase will remove the glycans.

A positive transferrin test leads onto further enzyme and genetic testing to identify the type of CDG.

When O-linked disorder is suspected, isoelectric focusing of apolipoprotein C III should be done.

Figure 1: An IEF pattern of serum glycoprotein transferrin. Lanes 1 and 6 show normal serum transferrin, composed



mostly of tetrasialotransferrin with small portions of mono, di, tri and pentasialotransferrin. Lanes 2 and 3 show IEF pattern from two CDG Ia patients. A reduction in tetrasialotransferrin is seen with a greater proportion of asialo and disialotransferrin, causing a cathodal shift in the IEF pattern. Lanes 4 and 5 show CDG IIx defects; the IEF pattern shows an increase in mono and trisialotransferrin fractions. Lane 7 shows a polymorphic variant eliminated by nuraminidase treatment.

Methods of Carbohydrate-Deficient Transferrin analysis

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1. Isoelectric focusing
2. Ion-exchange HPLC
3. Chromatography with radioimmunoassay (RIA)
4. Chromatography with immunoturbidimetry (TIA)
5. Capillary electrophoresis
6. Mass spectrometry
7. Protein chip arrays

An ideal test

Although transferrin has proven to be a useful marker of defective N-glycosylation, it can show a normal IEF profile in some cases of CDG. In addition, IEF only shows changes in charge but no information on changes in molecular weight. It is difficult to distinguish between type I and II defects in some patients.

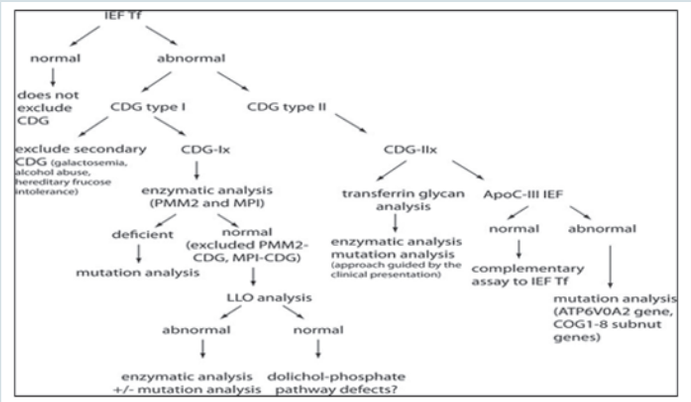
Additional and improved tests are needed for detecting and characterising various glycosylation disorders, leading to the most appropriate subsequent tests at an early stage of diagnosis.

Challenge for diagnostic strategies is to find a single method that can be used to detect aberrant glycosylation in both N- and O- linked disorders. Glycosylation analysis can be done by three different routes

1. Characterisation of glycans on intact proteins

2. Structural analysis of chemically or enzymatically released glycans

3. Characterisation of glycopeptides



Schematic illustration of the strategy for CDG laboratory diagnostics (for N-glycosylation, core 1 mucin-type O-glycosylation and combined N- and O-glycosylation disorders). IEF – isolectric focusing; Tf – transferrin, ApoC-III apolipoprotein C-III).4

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Figure 2. Flowchart for diagnosis.

A patient with recurrent episodes of muscle weakness

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Case presentation

A 62-year-old female presented with weakness in all four limbs and extreme fatiguability which recovered spontaneously. She had similar episodes two weeks before the admission. Recently she has noticed dry eyes which made her to use artificial tears. On examination, an eczema like rash over the dorsum of hands was noted. Muscle strength in the upper limbs and lower limbs were 2/5 and 3/5 respectively. Deep-tendon reflexes were normal in both upper and lower limbs, without any sensory impairment.

Investigation	Results	Unit	Reference interval
Haemoglobin	12.1	g/dL	12 – 17.5
WBC	6450	$10^6/mm^3$	4000 - 11000
Platelets	260,000	$/mm^3$	150, 000 – 450, 000
Serum sodium	138	mmol/L	135 - 145
Serum Potassium	2.0	mmol/L	3.5 – 5.5
Serum Chloride	116	mmol/L	98 - 106
Serum creatinine	1.07	mg/dL	0.6 – 1.1
Serum urea	35	mg/dL	15 - 45
Arterial blood gas analysis	pH – 7.2 PCO_2 - 23.9 HCO_3 - 10.9	 mmHg mmol/L	7.35 – 7.45 35 – 45 22 - 28
Anion gap	12		Up to 16 normal
Urine pH	6.0		4.5 – 8.0
Fasting plasma glucose	99	mg/dL	65 - 110
Serum total calcium	8.6	mg/dL	8.6 – 10.3
Serum phosphate	2.7	mg/dL	2.5 – 4.6
Urine Ca/Cr ratio	0.357		0.14 – 0.20
Urine 24-hour Ca excretion	143	mg/24 hours	100 - 300
Urine 24-hour phosphate excretion	384	mg/24 hours	400 - 1300
Urine 24-hour potassium excretion	52	mmol/24 hours	25 - 125
CRP	<5	mg/L	<5
Rheumatoid factor	20	IU/mL	<14
CPK	71	U/L	<170
iPTH	50	pg/mL	18 - 80

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Questions

1. What is the most probable diagnosis in this patient?
2. What biochemical features support your answer?
3. What is the test performed to confirm the disease?
4. What is the basis of the test mentioned above in the diagnosis of the disease?
5. What are the underlying causes of the disease you mentioned?
6. Subsequent investigations of the patient revealed positive anti-nuclear antibody (ANA - >1/100) with a positive Ro/SSA antibody. What could be the associations for the presentation of the patient?

Answers

1. Distal renal tubular acidosis (dRTA)
2. Distal renal tubular acidosis is due to a defect in hydrogen excretion by the cortical collecting duct system of the distal nephrons resulting in inability to acidify urine.
   The results are suggestive of a normal anion gap metabolic acidosis. Hypokalemia is unusual in the face of an acidosis, one of the exceptions being renal tubular acidosis type I or II. The urine pH is > 5.5 in the presence of metabolic acidosis which implies impaired urinary acidification. An alkaline urine in the presence of systemic metabolic acidosis is suggestive of dRTA.
3. Ammonium chloride loading test
4. The ammonium chloride is converted to urea in the liver with the consumption of bicarbonate. The bicarbonate is normally replaced by renal generation with excretion of hydrogen ions. This test stresses the kidneys to excrete acid and any failure will result in metabolic acidosis
5. Inherited, idiopathic, autoimmune disorders such as systemic lupus erythematosus (SLE) and Sjögren syndrome, amyloidosis, Wilson disease, sickle cell disease, hypercalcaemia
6. SLE, Sjögren syndrome SS/SLE overlap syndrome, subacute cutaneous lupus erythematosus, neonatal lupus, primary biliary cirrhosis, systemic sclerosis (SSc), polymyositis/ dermatomyositis, rheumatoid arthritis (RA), and mixed connective tissue disease (MCTD)

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A 14-year-old boy with acute onset muscle weakness

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Case presentation

A 14-year-old boy presented to local hospital with swollen neck and upper chest for four days duration. He had severe arthralgia, myalgia and a history of cold and fever two weeks prior to the admission.

Patient was transferred to a tertiary care hospital and there he gradually developed difficulty in walking and sitting, difficulty in breathing and swallowing.

On examination he was afebrile, had oedematous neck, upper chest and perioral region with painful oral ulcers. Neurological examination revealed tenderness over upper and lower limbs with normal muscle tone and weak muscle power (grade 4). Reflexes and sensory examination findings were normal.

Investigations

Initial biochemical investigations in blood were as follow:

Investigation	Results	Unit	Reference interval
ALT	333	U/L	<34
AST	1057	U/L	<31
ALP	185	U/L	50-162
CPK	39729	U/L	<145

Questions

1) What is the next most appropriate investigation?

Other investigations in blood revealed following results.

Investigation	Results	Unit	Reference interval
WBC	19	10^3/uL	4-10
Neutrophils %	78	%	40-70
Lymphocytes%	8	%	20-40
Haemoglobin	13	g/dL	11-16
ESR	44	mm/hour	<10
CRP	<6	mg/L	<6

Radiological and EMG:

Ultra sound scan of the neck and chest - Suggestive of myositis and fasciitis. Enlarged bilateral cervical lymph nodes.

EMG - severe generalized myositis

2) What is the possible diagnosis of this patient?
3) What is the pathophysiology of this condition?
4) What are the complications of this condition? What further investigations would you suggest?
5) What are the possible causes for this pathology in this patient?

Answers

1) Urine dipstick for myoglobin
   Urine was tea coloured and dipstick was positive for haemoglobin/myoglobin
2) Rhabdomyolysis
3) Rhabdomyolysis results from breakdown of skeletal muscles with release of its contents including myoglobin, potassium, phosphate, urate and creatine kinase.
4) Hyperkalaemia, acute renal failure and disseminated intravascular coagulation are the most critical complications. Myoglobin is filtered through the glomeruli and precipitated obstructing the renal tubules. Following investigations were done in blood to screen for the complications.

Investigation	Results	Unit	Reference interval
Creatinine	30.1	µmol/L	65-120
Sodium	118	mmol/L	136-146
Potassium	4.2	mmol/L	3.5-5.6
Ionized calcium	0.97	mmol/L	1.15-1.33
Magnessium	0.91	mmol/L	0.7-1.0
Phosphate	1.59	mmol/L	0.8-1.4

Patients' urine output was maintained at a level more than 100 mL/hour. Alkaline diuresis was continued for 48 hours.

5) Post ischaemia, trauma, drugs, toxins, infections, metabolic causes and inherited muscle disorders are the most common causes for rhabdomyolysis. In this patient, possible causes include infections, myositis and inherited muscle disorders. Following investigations were carried out to find a possible etiology.

Muscle biopsy of the right quadriceps muscle -Muscle fibers are normal, no atrophy or regeneration. No inflammation.

Viral antibodies -COVID19 IgG isolated (rapid antigen test negative), EBV IgM -negative, CMV IgM - negative, VDRL non -reactive, ANA -negative, Anti Jo1 -negative
Whole-body MRI -Not successful due to poor compliance
Other investigations in blood:

Investigation	Results	Unit	Reference interval
TSH	3.61	mIU/L	0.46-4.68
fT4	14	pmol/L	10-28
C3 complements	93.5	mg/dL	90-180
C4 complements	28	mg/dL	10-40

Patient was initially managed with steroids with a tentative diagnosis of post COVID multi system inflammatory syndrome leading to rhabdomyolysis. He recovered within 2 weeks except for the poor tolerance to oral feeds.

After a period of 1 month, ALT and AST activity in serum was normalized and CPK activity declined up to 1596 U/L. Since initial response to steroids was satisfactory, he was started on methotrexate and currently being managed as juvenile polymyositis/mixed connective tissue disorder.

A child with neurological manifestations

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Case presentation

An 11-year-old girl, born to consanguineous parents, presented with dystonic movements and swallowing difficulty for 2 weeks duration. She had a history of increased dark complexion and weight loss for one year duration.

Investigations

Her biochemical investigations in blood were:

Investigation	Results	Unit	Reference interval
AST	57	U/L	0-40
ALT	49	U/L	9-48
Total Protein	75	g/L	64-83
Albumin	42	g/L	34-50
Total Bilirubin	8	µmol/L	3-20
Direct Bilirubin	2	µmol/L	0-3
ALP	221	U/L	60-425
GGT	57	U/L	2-30
Ceruloplasmin	2	mg/dL	18-45
CRP	<5	mg/L	<5
Haemoglobin	11.9	g/dL	11.5-15

Questions

1. What further investigations would you request to help elucidate the cause for her altered biochemical test results?

2. What clues do the clinical features and laboratory investigations offer as to an underlying diagnosis?

3. What is your interpretation of her serum copper studies? (See below)

Investigation	Results	Unit	Reference interval
Ceruloplasmin	2	mg/dL	18-45
CRP	<5	mg/L	<5
24-hour urine copper excretion	4.16	mol/24 hours	0.23-1.09

4. What are the other causes for a similar level of ceruloplasmin?

5. Discuss further diagnostic tests that would support a diagnosis of Wilson disease (WD)?
This patient further underwent slit lamp examination of the eye, that was positive for Kayser -Fleischer (KF) Rings

6. Are the KF rings pathognomonic of WD?

7. What is the diagnostic score used in the diagnosis of the disease you mentioned?

8. What are the treatment options for the disease you mentioned?

9. What investigations would you request to follow-up this patient?

Answers
1. Viral serology to exclude infectious etiologies such as hepatitis A, B, C, Epstein-Barr virus (EBV) or cytomegalovirus (CMV)
∝1-antitrypsin to exclude ∝1-antitrypsin deficiency
Creatine kinase to exclude muscular dystrophy
Copper studies to exclude Wilson disease
Auto immune liver panel (antinuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody) to exclude autoimmune hepatitis
2. Clinical presentation with neurological manifestations and biochemically found to have elevated AST, ALT GGT and very low ceruloplasmin
3. Ceruloplasmin is an acute phase protein, it stores and carries the copper in the body. Due to the reduced ceruloplasmin, serum free copper concentration will be high, which will lead to increased 24-hour urine copper excretion. The serum copper studies are suggestive of Wilson disease.

4. Malnutrition
Liver diseases
Malabsorption
Nephrotic syndrome
Menkes syndrome

5.

Investigation	Features suggestive of WD
Free serum copper	>25 µg/dL
Penicillamine challenge test Urine copper (pre-penicillamaine) Urine copper (post-penicillamaine)	>1.25 µmol/24hours >25 µmol/24hours
Liver histology	Hepatic steatosis, inflammation, fibrosis, Mallory Denk Bodies, copper staining
Liver copper	>250 mg/g dry weight (normal <55)
MRI brain (T1and T2 weighted)	Detect atrophic changes and changes of putamen, giant panda's sign.
Genetic testing	

Penicillamine challenge test is undertaken by giving two doses of penicillamine 500 mg at each time, at the beginning and 12 hours apart following the commencement of urine collection.

6. No. KF rings are also seen in other chronic cholestatic disorders such as primary biliary cirrhosis and neonatal cholestasis.

7. Wilson Disease Scoring System (Leipzig score)

KF rings Present Absent	 2 0	Liver copper (in the absence of cholestasis) >5 x ULN (>4 µmol/g) 0.8-4 µmol/g Normal (<0.8µmol/g) Rhodanine -positive granules	 2 1 -1 1
Neurological symptoms Severe Mild Absent	 2 1 0	Urinary copper (in the absence of acute hepatitis) Normal 1-2 x ULN >2 x ULN Normal, but >5 x ULN after D-penicillamine	 0 1 2
Serum ceruloplasmin Normal (>0.2g/L) 0.1-0.2 g/L <0.1 g/L	 0 1 2	Mutation analysis On both chromosomes detected On 1 chromosome detected No mutations detected	 4 1 0
Coombs-negative haemolytic anaemia Present Absent	 1 0		

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Total score	Evaluation
4 or more	Diagnosis established
3	Diagnosis possible, more tests needed
2 or less	Diagnosis very unlikely

The score in this patient was more than 4.

8. Drug therapy for WD will target on removal of excess copper either through promoting copper excretion by chelating agents such as D-penicillamine and trientine, or by blocking intestinal copper absorption with zinc salts, or both.

9.
- In patients on penicillamine and/or trientine, a 24-hour urinary copper excretion should be monitored periodically.
- Patients on zinc monotherapy should have regular monitoring of serum and urinary Zinc levels. Which should be maintained above 125 µg/dL and 1.5-2 g/day respectively. Urinary copper levels below 30 µg/24 hours suggest Zinc overdose.

This patient was treated only with oral penicillamine and monitored using 24-hour urine copper level.

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Utility of HbA_{1c} as a tool for diagnosis of gestational diabetes mellitus and study of the correlation between HbA_{1c} and OGTT in a tertiary care setting in Sri Lanka.

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Introduction

Gestational diabetes mellitus (GDM) has adverse maternal and fetal outcomes. Its prevalence is increasing throughout the world as well as in Sri Lanka. Diagnosis of GDM based on oral glucose tolerance test (OGTT) is cumbersome and time consuming. Purpose of this study is to assess the utility of HbA_{1c} in the diagnosis of GDM.

Objectives

The aim of this study is to evaluate the relationship between plasma glucose values in OGTT and HbA_{1c} values of pregnant mothers between 24-28 weeks of period of amenorrhea (POA) and to assess the utility of HbA_{1c} in the diagnosis of GDM.

Methods

Hospital based cross sectional study was conducted among 154 pregnant mothers with (62) and without (92) GDM with a POA of 24 – 28 weeks. Diagnosed type 2 diabetes mellitus, multiple pregnancies, GDM in previous pregnancies, renal pathology, heamoglobinopathies, and anaemia (Hb < 10.5 g/dL) were excluded. GDM was diagnosed by OGTT according to 2018 ADA guidelines. HbA_{1c} was measured using Sebia 2 flex capillary electrophoresis analyser. Independent t test, correlation coefficient, receiver operating characteristics (ROC) curve were used in data analysis.

Results

HbA_{1c} values varied from 4.6 to 7.0%. Mean HbA_{1c} in mothers with GDM was 5.77% (95% CI 5.65 – 5.89). It is significantly higher compared to the mean HbA_{1c} value of mothers without GDM which was 5.19% (95% CI 5.13 – 5.25).p< 0.05. (Figure 1)

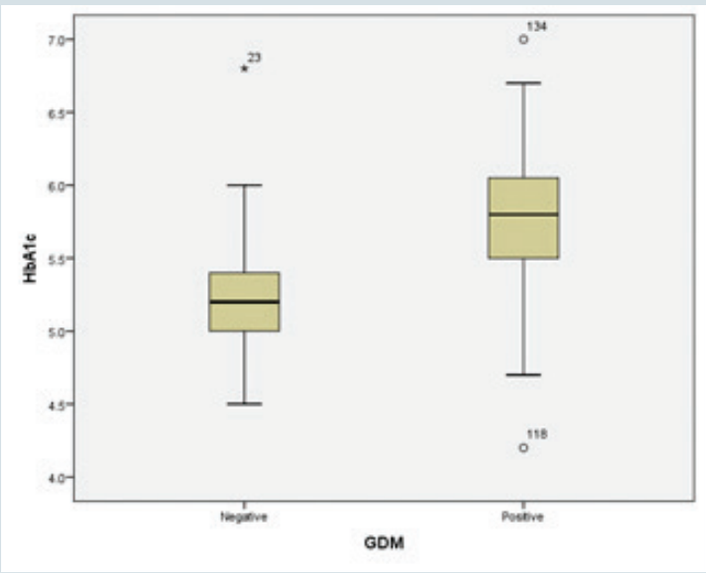

Figure 1: Distribution of HbA_{1c} values among mothers with and without GDM

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Pearson correlation between HbA_{1c} and plasma glucose values obtained from OGTT [Fasting plasma glucose (FPG), 1 hr, 2hr value] were 0.604, 0.683 and 0.66 respectively. Area under the ROC curve was 0.845. (Figure 2) Cut-off value with best equilibrium of the sensitivity and specificity (80% and 82%) was 5.45%. Sensitivity is increased to 92% (with only 8% of false negatives) by reducing the cutoff to 5%. Specificity is increased to 96% (with only 4% of false positives) by increasing the cut off to 5.9%.

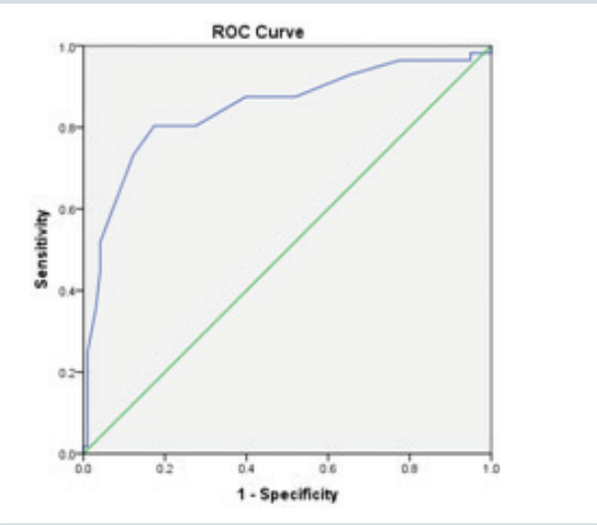

Figure 2: ROC curve according to the HbA_{1c} values of pregnant mothers with and without GDM

Conclusion

HbA_{1c} cannot be replaced for OGTT for the diagnosis of GDM. Cut off value of 5.4% will have 20% false negatives. Therefore, single HbA_{1c} value cannot be used to diagnose GDM. HbA_{1c} less than 5% can be used to rule out while value more than 5.9% can be used to rule in GDM. When it is between 5.0 – 5.9%, OGTT should be done to exclude GDM.

Evaluation of the short-term prognostic value of B-type natriuretic peptide in patients with acute decompensated heart failure

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Introduction
Acute decompensated heart failure (ADHF) is a global health problem characterized by frequent readmissions, poor prognosis, and reduced quality of life.

Objectives
This study was aimed to evaluate the short-term prognostic value of B-type Natriuretic Peptide (BNP) in patients with ADHF.

Methods
Seventy two patients (aged 18 to 75 years) diagnosed with ADHF who were admitted to the Cardiology Unit, National Hospital of Sri Lanka were recruited on a consecutive basis. Patients were excluded if they had renal insufficiency, acute myocardial infarction, and severe valvular heart disease. Plasma BNP was measured on admission, and pre-discharge. Other clinical and investigation findings were recorded from the clinical records. Survivors were monitored for 30 days for cardiovascular related re-admission or death.

Results
Majority of patients admitted with ADHF had a past history of diabetes (70.8%). Infection was the commonest identified aetiology. Non-compliance to treatment was not a common cause of decompensation.

Median plasma BNP level (pg/mL) on admission was 649.10 (IQR 344.6-1333.1) and pre-discharge was 183.90 (IQR 101.0-646.8). Of 72 patients studied, 15 patients (20.8%) were re-admitted and none of them died. Mean time for rehospitalization was 17±7.6 days.

None of the BNP measurement strategies showed a significant difference between the hospital readmitted and not readmitted groups (table 1).

Baseline characteristics of patients with ADHF according to the outcome (hospital readmitted vs. not admitted), and their association with risk of re-admission.

Variables	Not re-admitted n(%) or median (IQR)	Hospital Readmitted n(%) or median (IQR)	Odds ratio	95% CI	p value
Gender					
Male	43 (75.4%)	11 (73.3%)	1.117	0.306 - 4.072	0.867
Female	14 (24.6%)	4 (26.7%)			
Ischemic heart disease	39 (68.4%)	11 (73.3%)	1.269	0.355 - 4.535	0.713
Hypertension	34 (59.6%)	9 (60%)	1.015	0.318 - 3.239	0.980
Myocardial infarction	38 (66.7%)	1 (73.3%)	1.375	0.386 - 4.896	0.622
Diabetes	39(68.4%)	12 (80%)	1.846	0.463 - 7.360	0.380
Cardiomyopathy	9 (14.8%)	3 (20%)	1.531	0.352 - 6.656	0.568
COPD	1(1.8%)	9 (6.7%)	4.000	0.235 - 67.98	0.303
Valvular heart disease	20 (35.1%)	1 (6.7%)	0.132	0.016 - 1.080	0.031
Arrhythmia	12 (21.1%)	2 (13.3%)	0.577	0.114 - 2.913	0.502
An a emia	5 (8.8 %)	0 (0%)	0.776	0.682 - 0. 883	0.234
Age (year)	59.5 (50.25 - 67.5)	69.0 (63.0 - 72.7)			0.527
hsTroponin I (ng/mL)	0.085 (0.495-0.233)	0.057 (0.013-0.127)			0.069
Serum creatinine (µmol/L)	131.5 (89.25-143)	117.0 (93.2-5-149.0)			0.038
eGFR (ml/min/1.73m2)	51.2 (42.6-82.5)	55.4 (42.4-70.2)			0.116
Hb (g/dL)	11.3 (10.4-12.1)	11.5 (10.1-14.1)			0.231
LVEF (%)	36.2 (28.1-42.5)	32.5 (21.8-41.2)			0.517
LVEDD (mm)	57.5 (54.7-62.0)	57.0 (42.25-66.65)			0.308
LVESD (mm)	47.0 (40.5-50.5)	46.5 (42.25-50.0)			0.947
Admission BNP (pg/mL)	600.7 (347.1-1205.5)	1182.5 (394.9-3710.1)			0.766
Pre - discharge BNP (pg/mL)	249.3 (163.5-813.5)	119.0 (97.5-780.2)			0.332
Absolute change in BNP (pg/mL)	178.3 (103.1-289.3)	636.6 (297.3-3356.7)			0.467
Percent change in BNP (%)	38.1 (11.05-68.4)	76.4 (54.0-92.3)			0.210
Duration of hospital stay (days)	6.0 (5.0-8.7)	6.0 (3.5-7.7)			0.506

Table 1: Baseline characteristics of patients with ADHF according to the outcome (hospital readmitted vs. not admitted), and their association with risk of re-admission. (COPD - Chronic obstructive pulmonary disease; Hb – haemoglobin; LVEF – left ventricular ejection fraction; LVEDD – left ventricular end-diastolic volume; LVESD – left ventricular end-systolic diameter)

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A median reduction of 237.7 (IQR 84.8-433.1), (44%) from admission BNP level was seen during 5.4 days of mean hospital stay. Patients who died during the initial hospital stay, had heart failure complications or needed intravenous inotropes showed a higher admission BNP level (2542, 1728.08, 1603.5 respectively). Compared to patients with admission BNP<649.10, patients with admission BNP>649.1 had significantly higher high sensitivity troponin I (p=0.015) and serum creatinine (p<0.001), and low eGFR (p=0.003) and haemoglobin (p=0.041).

Cox analysis did not show a significant predictor capacity of BNP on rehospitalization (table 2).

Varibale	HR	95%CI	P value
BNP admission {pg/mL}	1.00	0.99 - 1.00	0.988
BNP on discharge {pg/mL}	0.99	0.99 - 1.00	0.310
BNP percentage change {%}	1.01	0.99 - 1.03	0.263
hsTroponin I {ng/mL}	0.84	0.59 - 1.18	0.311
Serum creatinine {µmol/L}	0.08	0.97 - 1.00	0.085
eGFR {ml/min/1.73m2}	1.00	0.99 - 1.02	0.326
Haemoglbin {g/dL}	1.30	0.95 - 1.79	0.093
LVEF {%}	0.97	0.92 - 1.02	0.302
LVEDD {mm}	0.94	0.87 - 1.01	0.108
LVESD {mm}	0.96	0.90 - 1.04	0.382

Table 2: Univariate cox analysis showing the association between various variables and the risk of re-admission during the 30 days of follow-up.(hsTroponin I – high sensitivity troponin I; eGFR – estimated glomerular filtration rate)

Conclusion

A significant association was not demonstrated for BNP in predicting cardiovascular related readmissions within 30 days after discharge. However, the potential of using plasma BNP to assess severity of ADHF and titrating therapy was highlighted which needs further research. A high rate of readmissions suggests that patients are discharged without sufficient cardiovascular stability.

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