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The future of neurology in the era of the artificial intelligence boom

The practice of neurology over the centuries has had as its basic approach, a good history and examination that guide the relevant investigations to reach diagnoses. With the expansion of the armamentarium of investigations, the emphasis on clinical methods has lessened. The rapid and unprecedented development of artificial intelligence (AI) which is known as the "AI boom" in recent years, has the potential to make a serious impact on this time-tested approach to making a clinical diagnosis. This editorial attempts to explore the future of neurology in the AI boom.

Although AI applications came to the limelight recently, AI models like machine learning (ML) methods have been around since the 1950s. AI has been featured in medical sciences, especially radiology, neurophysiology, genetics, etc. for years. AI algorithms are made to learn the patterns inherent in large clinical data sets such as Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI) scans or electrophysiological recordings and make predictions compared to determinations made by humans. This is referred to as supervised learning where ML algorithms are trained by previously labelled datasets into classifying data or predicting outcomes accurately. In contrast to supervised learning, unsupervised learning uses ML algorithms to analyse and cluster unlabelled data sets. They can discover hidden patterns in data without human input.

Although AI technology is encroaching into the medical field like wildfire, a machine replacing a clinician would still be a part of science fiction.

AI has several applications in current neurology practice. In the field of neuroimaging, AI can differentiate a haemorrhage from an infarction, quantify the Alberta Stroke Program Early CT Score in CT scans, and interpret the mismatch of infarction from hypoperfused areas in CT/MRI perfusion images in stroke patients. Machine learning (ML) algorithms have also been developed to learn the MRI images of patients with multiple sclerosis to define its subtypes. In epilepsy, AI applications are available to define focal cortical dysplasias. AI can also determine active epilepsy from that in remission by observing MRI charac-

teristics (fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity in diffusion tensor imaging data). It also can lateralize temporal lobe epilepsies.

There are ML algorithms to differentiate Alzheimer disease (AD) from vascular dementia by observing neuroimaging datasets. Another AI algorithm that was trained using AD neuroimaging data is capable of making predictions on the radiological diagnosis of AD. The accuracy of that algorithm was closely related to the post-mortem histopathological diagnosis of AD in that cohort and exceeded the accuracy of the clinical diagnosis. In Parkinson disease (PD) there is an AI algorithm to study neuromelanin sensitive magnetic resonance imaging which detects abnormalities in the substantia nigra pars compacta. This algorithm has good accuracy in diagnosing PD as well as in differentiating PD from atypical Parkinson syndromes. Neuro-electrophysiology has also not escaped from AI. There are AI applications to detect epileptiform discharges from scalp and intracranial electroencephalograms (EEGs), detect the epileptogenic zone in presurgical evaluation, and predict seizure localization using the patients' long-term scalp EEG data. The accuracies of these applications are eyebrow-raising. In the field of coma, AI applications are using scalp EEG data working on the prediction of six-month functional outcomes.

The retinal examination is also an area encroached on by AI. There are ML algorithms to detect papilloedema and diabetic retinopathy, using retinal photographs. The accuracies of these applications are favourable compared to that of experienced clinicians. AI could also revolutionize pharmacology, especially in new drug development. Sheffield Institute of Translational Neuroscience, UK has recently used an AI platform to identify 100 existing compounds that are potentially useful in amyotrophic lateral sclerosis. Their scientists have worked on five potential compounds and one was found to be effective in retarding symptoms in mice. Neuralink, the multimillion-dollar investment project since 2016, has researched a brain-computer interface where human brains achieve a symbiosis with AI. The project would broaden the horizons of neurorehabilitation therapeutics in the future.

Although it is fascinating to see the scope of AI applications in the field of neurology, significant limitations also do exist. For instance, an AI application trained to detect papilloedema may fail miserably when there is optic atrophy. Also, the accuracy of the AI applications depends on the training they had with the data provided to them. The complexity of the AI tool is proportionate to the inexplicability of its data processing. This is being referred to as the black box problem in AI (human inability to explain the precise steps which lead to predictions of AI applications). The situation is further complicated by the condition known as AI hallucination, where the AI tool generates outputs that are unrelated and unexpected and could lead to multifaceted impacts, including medicolegal issues. To assure the credibility and accountability of the AI tools, the U.S. Food and Drug Administration has reviewed and authorized several medical devices that utilize ML and published an approved AI/ML-enabled medical devices list.

Although AI technology is encroaching into the medical field like wildfire, a machine replacing a clinician would still be a part of science fiction. While the clinical methods would remain the pillars of future neurology practice, newer AI applications would certainly complement the traditional clinical methods. To be up in the game, the neurologist must understand the applicability of relevant AI applications and their limitations. Charles Darwin's famous quote "It is not the most intellectual of the species that survives; it is not the strongest that survives, but the species that survives is the one that is able to adapt and adjust to the changing environment in which it finds itself" would be equally applicable not only to neurologists but also to any professional in the AI era.

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Anaemia due to chronic kidney disease

A cross-sectional analysis from a tertiary referral centre in Sri Lanka

Introduction

Chronic kidney disease (CKD) is a leading cause of death and disability globally.[1] The Sri Lankan health system currently faces a major challenge with CKD, which has a higher prevalence locally than in neighbouring countries.[2] Studies conducted regionally show a high CKD prevalence of around 20% in certain districts of Sri Lanka,[3] although country-wide prevalence rates are not known. Diabetes is the leading cause of CKD in many,[4] although there is an increasing incidence of CKD of uncertain aetiology (CKDu) in some provinces, with a relatively young population from rural communities mostly affected.[5]

Anaemia is a well-recognized complication of CKD that has a significant impact on cardiovascular health and the quality of life of patients.[6,7] Anaemia in CKD is usually seen from stage 3 onwards and is multi-factorial in etiology. Erythropoietin deficiency is a major contributing factor. Nutritional deficiencies, losses related to dialysis and anorexia, disordered iron metabolism, occult blood losses, and hepcidin up-regulation are other factors contributing to anaemia in CKD.[8,9] Research evidence suggests an increasing prevalence of anaemia with advanced stages of CKD, race, diabetes, and female sex.[10-14]

There is inadequate data available on the prevalence of anaemia in Sri Lankan patients with CKD.

This study was conducted to determine the prevalence and associations of anaemia in a cohort of patients with CKD attending a tertiary referral centre in an urban area of Sri Lanka.

Materials and methods

A descriptive cross-sectional study was conducted in wards and clinics of the University Medical Unit of Colombo North Teaching Hospital, Ragama, Sri Lanka, over four months. Consecutive patients aged 18 years or more, attending medical clinics or admitted to medical wards with stable CKD for at least 3 months, giving informed written consent were included. CKD was defined as eGFR < 60 ml/min/1.73m^2.

Data collection was carried out using an interviewer-administered pretested questionnaire, where the interviewer was one of the investigators. Demographic and clinical data were extracted by interviewing patients and examining clinical records. Haemoglobin levels and other relevant laboratory investigations done within 3 months of enrollment were collected.

Data were analyzed from SPSS software package. Chi square and odds ratio were used to compare categorical variables. ANOVA was used to compare categorical and continuous variables. Significant value was set at a cut-off value of 0.05 for all statistical tests.

Ethical approval for the study was obtained from the Ethics Review Committe, Faculty of Medicine, University of Kelaniya.

Results

Characteristics of the study population

A total of 149 participants were enrolled; 86 (57.7%) were males. Mean age of the study population was 64.7 (SD 11.72) years. Table 1 shows socio-demographic characteristics and comorbidities of the study population.

In patients with diabetes, the mean duration of diabetes was 12.3 years and a majority had micro- and macro-vascular complications with 82 (78%) having diabetic retinopathy. Forty-one participants (39%) had ischaemic heart disease (IHD) and 15 (14.2%) had a history of stroke.

The mean duration since diagnosis of CKD in the study population was 2.68 years. 71 (47.7%) participants were in stage 3 CKD, while 38 (25.5%) and 40 (26.8%) were in stage 4 and stage 5 CKD, respectively. Ultrasound scans for the assessment of kidneys had been performed in all subjects. The majority (77.1%) had evidence of small kidneys with poor cortico-medullary demarcation.

All patients had undergone urine analysis. One hundred and four participants (69.7%) had overt proteinuria. Data on urine albumin /creatinine and protein/creatinine ratios were only available in a limited number of subjects.

Nineteen participants (12.6%) were on regular haemodialysis, 21/40 in CKD stage 5 were on conservative management. Among the 19 patients on dialysis, 8 had transplant plans.

Table 1. Characteristics of the study population

	Number (n = 149)	Percentage
Formal education	142	95.3%
Household income < USD 115/month	11	7.4%
Diabetes	105	70.5%
Hypertension	125	83.9%
Ischemic heart disease	56	37.6%
COPD/bronchial asthma	12	8.1%
Chronic liver cell disease	16	10.7%
Stroke	18	12.1%

Anaemia

Anaemia is defined by the World Health Organization (WHO) as Hb <13g/dL for males and <12g/dL for females.[15] Anaemia is classified as mild (Hb>10g/dL), moderate (Hb 8-9.9g/dL) and severe (Hb <7.9g/dL) in the National Cancer Institute (NCI/NVH) classification, which was used for data analysis in this study.

The overall prevalence of anaemia using the above cut-off values was 138 (92.6%). 93% of males (80/86) and 92% of females (58/63) had anaemia. 47(31.5%) had mild anaemia, 40(26.8%) had moderate anaemia and 51(34.2%) had severe anaemia.

Hb cut-off of 11g/dL was used as a cut-off value in assessing the associations with anaemia. Anaemia was significantly associated with female gender, advancing stages of CKD, presence of diabetes, higher degrees of proteinuria, co-existent chronic liver cell disease (CLCD) and being on hemodialysis (Table 2).

Table 2. Associations of anaemia

	Odds ratio (95% CI)	Significance
Female sex	2.2 (1.04-4.6)	P = 0.02
Stage 4 and 5 CKD	2.4 (1.6-7.1)	P < 0.001
Presence of diabetes	3.06 (1.4-6.5)	P = 0.003
Proteinuria	6.24 (2.7-14)	P < 0.001
Co-existent CLCD	4.7 (1.03-22)	P = 0.03
Being on dialysis	3.1 (1.1-9.5)	P = 0.03

Ninety-one (61%) had documented blood film reports. The commonest finding was iron deficiency with anaemia of chronic disease [55/91 (60.4%)] while 25/91 (27.5%) had anaemia of chronic disease only. Mixed deficiency was present in only 5/91 (5.5%) participants.

Further assessment of anaemia with folate and vitamin B12 levels had not been done, with iron studies being performed in only a limited number, due to the limited availability of these investigations in the government sector hospitals.

Evaluation for other possible causes of anaemia

To assess the contributing factors for anaemia, dietary intake of animal based food products rich in haem iron, evidence of gastro-intestinal (GI) or other blood loss and anthelminthic treatment were assessed.

Overall, consumption of animal based products in the study group was once a day or less in 82/149 (55%) participants. Low animal protein intake was significantly associated with anaemia (odds ratio 3.027 (95% CI-1.5-6), p=0.001). Twelve participants (8%) had a history of GI bleeding and seven of them had anaemia, while 48/149 (32.2%) reported dyspeptic symptoms. All those with a history of GI bleeding had undergone endoscopic evaluation but only 8/48 with dyspeptic symptoms had undergone endoscopy. Only 7 out of 149 (4.6%) subjects were treated with antihelminths during the preceding year.

Treatment of anemia

Sixty-nine participants were on oral iron, while 6 were on intravenous iron at the time of study. 56 were receiving folic acid and 4 were taking vitamin B12 injection. Of those on oral iron, 12/69 (17%) were poorly compliant with treatment, and the majority (11) claimed GI side effects as the reason. 40/88 (45.4%) participants with hemoglobin <10g/dL were on erythropoietin therapy. None had experienced adverse events with erythropoietin and the majority (36/40) claimed that erythropoietin improved their symptoms. 50/88 participants (56.8%) with hemoglobin <10g/dL had previously received at least one blood transfusion. We were unable to collect data regarding the exact indication for transfusion in each of these cases. 67/88 (76.1%) participants who had hemoglobin <10g/dL at treatment initiation, continued to have hemoglobin below the target of 10g/dL during follow up (Figure 1).

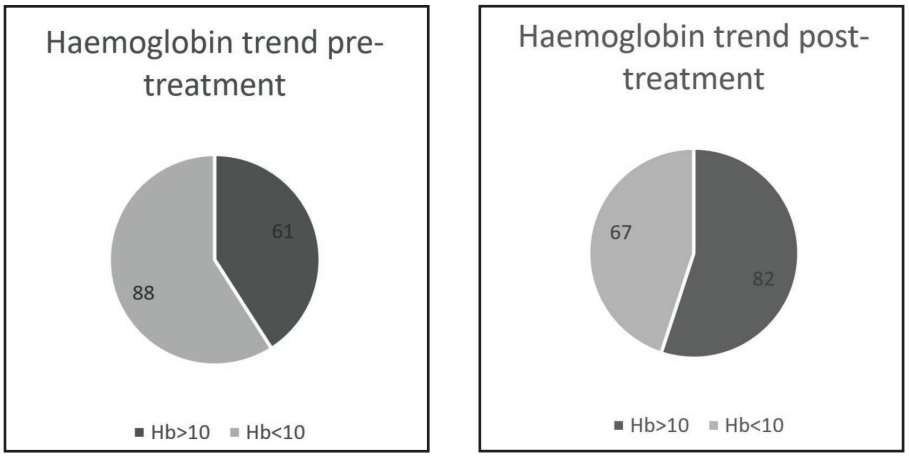

Figure 1. Haemoglobin trend in the population pre and post treatment.

Discussion

Anaemia was highly prevalent in this cohort of Sri Lankan patients with CKD, and was significantly associated with female gender, co-existing diabetes and advancing stages of CKD. A majority had co-existing iron deficiency. Most were not evaluated during the early stages of anaemia, leading to a delay in initiating appropriate treatment. Most qualifying participants were not on erythropoietin and a significant number had undergone blood transfusions.

Hypertension was the commonest co-morbidity in the study population, being present in 83.9%, which was consistent with previous findings showing high blood pressure being commonly associated with CKD.[16] More than 70% of the subjects were diabetic, which is likely to be the leading cause of CKD in this population. This is consistent with epidemiological studies locally and internationally showing a high prevalence of diabetes among CKD patients.[4,17] However, an aetiological study of CKD in Sri Lanka in 1998 showed that only 30% of the study population had diabetic nephropathy leading to CKD.[4] Our study population had a higher prevalence of diabetes, which may be explained by changing demographics and disease patterns over the past decades and the select nature of our study cohort (patients followed up in a medical clinic).

The overall prevalence of anaemia in the study population was 92.6%, which is significantly higher than noted in similar studies from other countries. Research from the USA has shown a prevalence of 47.7%6 and a study in the UK demonstrated a prevalence of 17% and 41% among non-diabetic and diabetic CKD patients respectively.[12] There are no Sri Lankan studies on the prevalence of anaemia in patients with CKD. Studies from developed countries have shown widely variable results, with some showing a prevalence >40%[6] while others demonstrated a prevalence of around 10%.[11]

Data on mean haemoglobin levels in the general population and the overall prevalence of anaemia in Sri Lanka is lacking. WHO estimates that 29.3% of females of childbearing age have haemoglobin levels below 11g/dL[18], which points to a much higher prevalence than in developed countries.

Female gender, advancing stages of CKD and co-existing diabetes were positively linked with the development of anaemia in our study. This is consistent with previous evidence.[10-14] Co-existent chronic liver cell disease was also associated with anaemia. Studies have shown a prevalence of more than 70% of anaemia among patients with cirrhosis with an independent link between chronic liver cell disease and anaemia.[19]

Blood films were not available in patients with milder degrees of anaemia. The usual clinical practice in many local medical clinics is to order a blood film if haemoglobin is less than 10-11g/dL. This practice should be reviewed, since early evaluation by blood film of milder degrees of anaemia is helpful to prevent further deterioration and to avoid the need for aggressive management later.

The commonest blood film finding in the study cohort was anaemia of

chronic disease with co-existent iron deficiency. In CKD patients from developed countries blood films are likely to show anaemia of chronic disease since adequate nutritional supplementation prevents manifestations of co-existent deficiency anaemias.[7] Iron deficiency co-existing with anaemia of chronic disease in the study cohort highlights the need for evaluating blood films and performing further investigations to identify co-existent deficiencies.

Iron deficiency was mostly evaluated by blood film only and a majority of study participants did not have further iron studies performed, due to the limited availability and cost of such investigations. Evaluation of the causes of iron deficiency suggested that the intake of animal-based products was significantly low in the study sample. Animal-based food sources provide heme iron, which is more readily absorbed compared to non-heme iron. However, quantification of the intake of plant-based sources of iron was not done. Patients with CKD have certain dietary restrictions, including limitation of protein and potassium-rich food, which makes them more vulnerable to nutritional deficiencies. Also, most study participants had diabetes mellitus for long periods, which may contribute to malabsorption. Evaluation of iron status is important in patients with anaemia and CKD, even in resource-poor settings, followed by advice on an iron rich diet.

GI blood loss is an important aetiology that should be evaluated in adults with iron deficiency anaemia, which may be contributed by antiplatelets and anticoagulants. Also, in tropical countries, parasitic infestations should be actively looked for and treated, since such infestations may be causative or contributing to anaemia.

Endoscopic evaluation was not undertaken in most study participants with iron deficiency anaemia, although it is a recommended investigation. Also, attributing anaemia to CKD per se may lead to a delay in the diagnosis of GI malignancies and other sinister pathologies. However, endoscopic evaluation of all CKD patients with co-existing iron deficiency may not be feasible, particularly in a resource-poor setting. Since there are no clear guidelines, clinicians should take a comprehensive history for any evidence of GI bleeding and for symptoms which warrant early endoscopic evaluation. The examination should include a per rectal digital examination.

Almost 60% of the study cohort had suboptimal levels of haemoglobin while on treatment. Although anaemia associated with CKD is difficult to treat, optimization of treatment leads to achieving target haemoglobin levels, which will enhance the quality of life and reduce cardiovascular complications.

Erythropoiesis stimulating agents (ESAs) and iron are the recommended primary treatments for anaemia of CKD. These modalities improve anaemia, leading to a better quality of life, reduced morbidity and reduced need for transfusion.[20] Iron supplementation was the commonest treatment modality in the study population, and most were on oral iron therapy. Although erythropoietin is recommended after replenishing irons stores in CKD[20], most eligible patients were not on erythropoietin.

In the study cohort, a significant number had low haemoglobin needing transfusions and the rate of blood transfusions was quite high. This could have multiple consequences including reactions, fluid overload and adverse impact on future renal transplantation. Transfusions could have been avoided by early treatment of anaemia. Most patients who required transfusions and were not on erythropoietin were also not on regular follow-up or were mainly attending clinics at non-specialized centres.

There were certain limitations to this study. This was a cross-sectional study and data was collected from existing clinic records. Since no long-term follow-up was undertaken, subsequent investigations were not recorded. Some participants were patients referred to the tertiary centre on their first visit with incomplete investigations.

Conclusions

Based on the findings of this study, we recommend that all patients with CKD in Sri Lanka should be periodically screened for anaemia. Even when anaemia is mild, patients

should be evaluated, and an individualized management plan should be implemented by the caring physician. Protocol based investigations, adequate iron and nutritional supplementation and timely commencement of ESAs are recommended to minimize the need for future blood transfusion.

Prospective studies with follow-up are necessary to assess the response to treatment in the long term. Further studies are also needed to formulate a protocol for evaluating iron deficiency in patients with CKD in resource-poor settings.

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