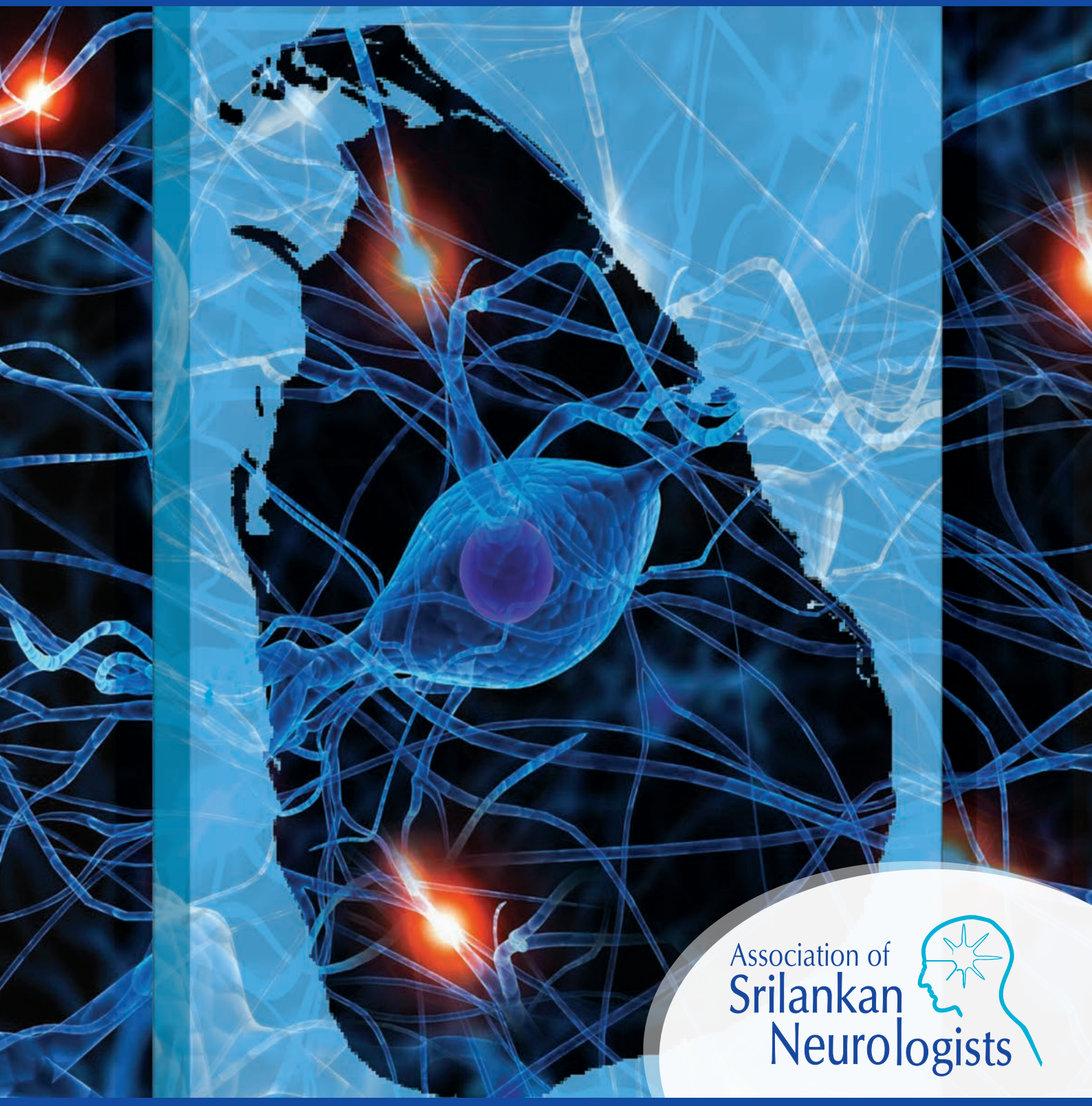
Sri Lanka Journal of Neurology

Official Journal of The Association of Srilankan Neurologists

Volume 4, Number 1, 2015



SRI LANKA JOURNAL OF NEUROLOGY

AIMS AND SCOPE

The *Sri Lanka Journal of Neurology* (*SLJN*) is a forum for debate, education and entertainment for health professionals interested in Clinical Neurology, Neurosurgery and Neurosciences. The Journal is aimed at practicing Neurologists, Neurosurgeons and Neuroscientists with commitments in Sri Lanka and has relevance to all those working in the health sector. The Journal's prime responsibility is to the members of the Association of Sri Lankan Neurologists (ASN) and its objective is to promote good clinical practice and influence policy making across the medical world through publication of original research and peer reviewed articles on current issues and to foster responsible and balanced debate on issues that affect medicine and health care in Sri Lanka. Contributions to the *SLJN* reflect its national and multidisciplinary readership and include current thinking across a range of medical specialties and the Journal assists the ASN in its continuing medical education programme.

While members of the ASN receive the *SLJN* as one of the benefits of membership, it will be available to other health professionals on paying a subscription fee. The Journal has full editorial independence.

Printed by **Ananda Press**
82/5, Sir Ratnajothi Saravanamuttu Mawatha, Colombo 13, Sri Lanka.
Tel: 0112 435975 E-mail: anpress@sltnet.lk

SRI LANKA JOURNAL OF NEUROLOGY

Official publication of the Association of Srilankan Neurologists

Volume 4, Number 1, 2015

CONTENTS

(Continued)

ISSN 2279-2295

Editorial

Acute stroke management – exciting times ahead

Sri Lanka Journal of Neurology, 2015, **4**, 1

Past decade made significant progress in acute stroke management. Wider use of thrombolysis in acute ischaemic stroke, place of surgery in intracerebral bleeds, organization of better acute stroke services, use of newer anticoagulants, and most recently the recognition of the efficacy of endovascular thrombectomy in appropriate cases of acute ischaemic strokes are some of these significant advances.

Latter part of 2015 saw the publication of five major trials that conclusively showed that endovascular thrombectomy improves outcomes in patients with disabling acute ischaemic strokes caused by a proximal intracranial vessel occlusion. This followed the publication in 2013 of three thrombectomy trials (IMS III, SYNTHESIS Expansion and MR RESCUE) using early generation devices that showed no improvement in outcomes. The latter five studies used a more modern device – retrievable stents. MR CLEAN a Dutch trial was the first of these to complete and it enrolled 500 patients who received the intervention within six hours of onset. CT angiography was used to select the patients with a thrombus in the distal intracranial internal carotid artery or M1/M2 branches of middle cerebral artery. Only about 10% of all stroke patients would fall into this category. Functional independence was seen in 33% of patients in the endovascular arm vs 19% in the control group. About 90% in both groups received intravenous thrombolysis. The other four trials ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT were terminated early when interim analyses demonstrated a clear difference in favour of thrombectomy. Majority of patients were treated within six hours in these trials. Therefore it is believed that endovascular treatment with retrievable stents should now be considered the standard of care for severe stroke patients similar to ones treated in these studies and that the hospital services should revise their treatment protocols to face this new challenge. To apply this treatment strategy to developing countries like ours will raise very important questions. Basic requirements for stroke management like stroke units and thrombolysis services are at a minimum in Sri Lanka despite the enthusiasm of practicing neurologists and initiatives taken by the Association of Srilankan Neurologists and the National Stroke Association, and one would wonder how feasible thrombectomy is going to be in our state hospitals. Success of thrombectomy would depend on many factors. They are, achieving the short window period of less than six hours, access to urgent CT angiogram with expertise in interpretation to select the correct patient, use of latest type of device because one reason for the failure of the earlier trials was the inappropriate devices used.

2015 also saw the publication of another interesting study on stroke rehabilitation. A Very Early Rehabilitation Trial (AVERT) is the largest randomized trial conducted in stroke rehabilitation to date. It compared very early mobilization within 24 hours after symptom onset with usual care. The trial compared a group of 1042 patients mobilized after 18.5 hours versus 1036 patients mobilized after 22.4 hours. The results were a surprise. The findings suggested that early rehabilitation may be worse than usual care. A favourable outcome (primary outcome = modified Rankin Scale 0-2) at 3 months was achieved in 46% of patients in the early and 50% of patients in the late mobilization group. These results have to be interpreted carefully because though the trial was of a high quality with a large cohort, the time difference between the two groups was only 4 hours, and 92% of patients in the early group and 59% in the control group were mobilized within the first 24 hours. Progression of the stroke in the early stages is also more likely to have occurred in the early group affecting their recovery. However these results should not lead to keeping patients in bed immobile and inactive for a prolonged period of time. Very early mobilization within 24 hours after stroke has to be considered with caution and should be avoided in those who are severely affected or had intracerebral haemorrhage.

Saman B Gunatilake
Editor

Paper

Stroke subtypes and risk factors in the Jaffna district – A hospital based study

A Arasalingam[1], T Kumanan[2], K Kamalakkannan[3], M Visvakumar[4], R M M P Wimalawardhana[4]

Sri Lanka Journal of Neurology, 2015, **4**, 2-6

Abstract

***Objective*:** To determine the stroke subtypes and risk factors in the Jaffna district and to determine if it differed from the rest of Sri Lanka.

***Methods*:** A hospital based prospective, cross sectional study was carried out in 448 stroke patients admitted to the Jaffna Teaching Hospital, from December 2014 to August 2015. Diagnosis of stroke was made according to the WHO definition and confirmed by a CT brain. The patients were investigated for conventional risk factors. The data was statistically analyzed using SPSS.

***Results*:** There were a total of 448 cases included in the study of which 226 (50.45%) were males and 222 (49.55%) were females. The mean age of the patients was 66.0 ± 12.23 for males and 67.25 ± 12.12 for females. Stroke subtypes showed preponderance for ischaemic strokes (84.15%). Hypertension was the commonest risk factor (56%) and the other risk factors were ranked as follows; past history of stroke (39.4%), smoking (30.8%), diabetes mellitus (26.05%), dyslipdaemia (15.8%), family history of stroke (12.3%) and ischaemic heart disease (11.9%).

***Conclusions*:** Ischaemic stroke was the commonest subtype and lacunar stroke was the commonest presentation according to the OCSP classification. Hypertension was the commonest risk factor. Preventive strategies to detect hypertension and diabetes early and public awareness of the ill effects of smoking should contribute significantly in the reduction of stroke burden.

Index words: haemorrhagic stroke, ischaemic stroke, risk factors, stroke subtypes, Northern Province, Jaffna, Sri Lanka

Introduction

Stroke is the second most common cause of death and third most common cause of disability worldwide. Several population studies focusing on epidemiology and risk factors have been carried out internationally and regionally [1]. However the risk factor profile for strokes vary in different population groups. Detailed assessment of risk factors in stroke of a country is relevant to understand the aetiology and helps in planning preventive strategies to reduce future stroke burden. Regional and ethnic variation within the country should also be taken into consideration when advocating preventive measures.

Published data on stroke subtypes and risk factor profiles in Sri Lanka is sparse. The demographic pattern of Sri Lanka shows a transition towards an ageing population [2, 3, 4]. There have been no published data from the Northern Province of the country, which was a war torn area for the last 3 decades. The demographic changes in the region due to the war, and migration of youth post war also can contribute to change in incidence of non-communicable diseases such as stroke. Thus we carried out a hospital-based study at the Jaffna Teaching Hospital, the only tertiary care hospital in the Northern Province. This is the first ever study on stroke from the Northern Province of Sri Lanka.

Methodology

This is a hospital based prospective study conducted at the Jaffna Teaching Hospital, carried out from 01/12/2014 to 31/08/2015. Situated in the Jaffna district, this is the only tertiary care hospital in the Northern Province of Sri Lanka. The Jaffna district is one of the 25 administrative divisions of Sri Lanka and has a population of 583,378.

Consecutive patients admitted with a stroke to the 8 medical wards during the study period were recruited to the study. A diagnosis of stroke was made according to the WHO definition and transient ischaemic attacks (TIAs) were excluded from the study. Detailed clinical history was obtained and clinical examination was performed as per a standard proforma. Full blood count, blood glucose, lipid profile, urea, creatinine, electrolytes and a 12 lead ECG were performed in all patients and echocardiography was done in selected patients. The patients were categorized as infarctions or haemorrhages based on CT findings.

[1] *Consultant Neurologist, Teaching Hospital, Jaffna,* [2] *Senior Lecturer and Consultant Physician, Department of Medicine, University of Jaffna,* [3] *Resident House Officer, Medicine, Teaching Hospital, Jaffna,* [4] *Resident House Officer, Neurology, Teaching Hospital, Jaffna, Sri Lanka.*

Risk factors were evaluated in all cases. Hypertension, diabetes mellitus, dyslipidaemia and atrial fibrillation were considered to be present if there was a history or they were on treatment for the condition. Smoking and alcohol use was defined according to international standards.

Data was corroborated by documented evidence in medical records, scans and medication history in addition to interviewing patients and carers.

The data was compiled and entered in excel sheet and analysed using SPSS.

Results

There were a total of 448 cases included in the study of which 226 (50.45%) were males and 222 (49.55%) were females. The mean age at presentation was 66.0 ± 12.23 for males and 67.25 ± 12.12 for females. Of the 448 cases 377 (84.15%) were ischaemic strokes while 71 (15.85%) were haemorrhagic strokes. Of the ischaemic strokes 49 (13.0%) were total anterior circulation strokes (TACS), 93 (24.7%) were partial anterior circulation strokes (PACS), 202 were lacunar strokes (LACS), 14 (3.7%) were posterior circulation strokes (POCS) and 17 (4.8%) were not classifiable. The cardiovascular risk factors for ischaemic and hemorrhagic strokes are shown in Table 1.

There were no statistically significant differences between the studied cardiovascular risk factors between ischaemic and haemorrhagic strokes.

Hypertension was the commonest risk factor amongst both ischaemic (56.5%) and haemorrhagic (56.3%) strokes. We compared the stroke risk profiles between hypertensive and non-hypertensive stroke patients.

253/448 (56.47%) were hypertensive. There were 53.8% females in the hypertensive group vs 44.1% females in the non hypertensive group (p = 0.043). The mean age at presentation of hypertensives vs non hypertensives is 67.80 ± 11.19 vs 65.1 ± 13.22 (p=0.020). The pattern of stroke subtypes and risk factors amongst hypertensives and non hypertensives are in Table 2.

The statistically significant differences included more females in the hypertensive group and non-hypertensive patients presented at a younger age. Other cardiovascular risk factors including past history of stroke, diabetes mellitus, dyslipidaemia and ischaemic heart disease were more common in the hypertensive group.

Diabetes was the third commonest risk factor, behind smoking which ranked second. Thus we did a sub analysis comparing the stroke risk profiles amongst diabetic and non-diabetic stroke patients. 132/448 (29.46%) were diabetic and of the diabetics 70 (53%) were male and 152 (49.4%) were males in the non-diabetic group (p = 0.481). Mean age at presentation in the diabetics vs non-diabetics was 67.16 ± 9.67 vs 66.40 ± 13.09 (p = 0.547). The pattern of stroke subtypes and risk factors amongst diabetic and non-diabetic patients are shown in Table 3.

Table 1. Cardiovascular risk factors in ischaemic and haemorrhagic strokes

	Ischaemic stroke N = 377	*Intracerebral haemorrhage N = 71*	*p value*
Gender –			
Male	187 (49.6%)	39 (54.9%)	> 0.05 (0.411)
Female	190 (50.4%)	32 (45.1%)	> 0.05 (0.411)
Past history of stroke	90 (23.9%)	11 (15.5%)	> 0.05 (0.122)
Family history of stroke	45 (11.9%)	9 (12.7%)	> 0.05 (0.416)
Hypertension	213 (56.5%)	40 (56.3%)	> 0.05 (0.980)
Diabetes mellitus	117 (31.0%)	15 (21.1%)	> 0.05 (0.093)
Dyslipidaemia	66 (17.5%)	10 (14.1%)	> 0.05 (0.482)
ischaemic heart disease	47 (12.5%)	8 (11.3%)	> 0.05 (0.778)
Other heart disease	18 (4.8%)	3 (4.2%)	> 0.05 (0.718)
Smoking	126 (33.4%)	20 (28.2%)	> 0.05 (0.387)
Alcohol	87 (23.1%)	16 (22.5%)	> 0.05 (0.921)
Hormonal therapy	1 (0.3%)	0 (0%)	> 0.05 (0.665)
Drug abuse	0 (0%)	0 (0%)	

Past history of stroke, hypertension, dyslipidaemia and ischaemic heart disease were more common among the diabetics.

A sub analysis of the influence of gender on the pattern of stroke showed that 226 (50.45%) were males. The mean age at presentation in males vs females is 66 ± 12.23 vs 67.26 ± 12.12 years (p=0.275). The pattern of stroke subtypes and risk factors are shown in Table 4.

Of the studied cardiovascular risk factors hypertension was more common amongst the females while past history of stroke, smoking and alcohol consumption were more common amongst the males.

Of the 448 patients 26 (5.8%) were young strokes (below the age of 45 years), of whom 16 (61.5%) were males and 10 (38.5%) were females. The stroke subtypes and frequencies of the risk factors amongst young stroke and comparison with other strokes are shown in Table 5.

Hypertension was the commonest risk factor amongst young strokes followed by a past history of stroke and smoking. The risk factors were same in both groups except for diabetes which was more common in the elderly.

Table 2. Pattern of stroke subtypes and risk factors amongst hypertensive and non-hypertensive stroke patients

	Hypertensive stroke patients N = 253	*Non-hypertensive stroke patients N = 195*	*p value*
Stroke subtypes –			
Ischaemic stroke	213 (84.2%)	164 (84.1%)	> 0.05 (0.980)
Haemorrhagic stroke	40 (15.8%)	31 (15.9%)	
Past history of stroke	74 (29.2%)	27 (13.8%)	< 0.05 (0.000)
Family history of stroke	35 (13.8%)	19 (9.7%)	> 0.05 (0.342)
Diabetes mellitus	94 (37.2%)	38 (19.5%)	< 0.05 (0.000)
Dyslipidaemia	62 (24.5%)	14 (7.2%)	< 0.05 (0.000)
Ischaemic heart disease	41 (16.2%)	14 (7.2%)	< 0.05 (0.004)
Other heart disease	14 (5.5%)	7 (3.6%)	> 0.05 (0.677)
Smoking	79 (31.2%)	67 (34.4%)	> 0.05 (0.484)
Alcohol	62 (24.5%)	41 (21%)	> 0.05 (0.387)

Table 3. Pattern of stroke subtypes and risk factors amongst diabetic and non-diabetic stroke patients

	Diabetic stroke patients N = 132	*Non-diabetic stroke patients N = 316*	*p value*
Stroke subtypes			
Ischaemic stroke	117 (88.6%)	260 (82.3%)	>0.05 (0.093)
Haemorrhage stroke	15 (11.4%)	56 (17.7%)	
Past history of stroke	39 (29.5%)	62 (19.6%)	<0.05 (0.022)
Family history of stroke	19 (14.4%)	35 (11.1%)	> 0.05 (0.168)
Hypertension	94 (71.2%)	159 (50.3%)	< 0.05 (0.000)
Dyslipidaemia	51 (38.6%)	25 (7.9%)	< 0.05 (0.000)
Ischaemic heart disease	31 (23.5%)	24 (7.6%)	< 0.05 (0.000)
Other heart disease	9 (6.8%)	12 (3.8%)	> 0.05 (0.319)
Smoking	40 (30.3%)	106 (33.5%)	> 0.05 (0.506)
Alcohol	32 (24.2%)	71 (22.5%)	> 0.05 (0.685)

Table 4. The influence of gender on the pattern of stroke subtypes and risk factors of stroke

	Male N = 226	*Female N = 222*	*p value*
Stroke subtypes –			
Ischaemic stroke	187 (82.7%)	190 (85.6%)	> 0.05 (0.411)
Haemorrhage stroke	39 (17.3%)	32 (14.4%)	
Past history of stroke	62 (27.4%)	39 (17.6%)	< 0.05 (0.012)
Family history of stroke	24 (10.6%)	30 (13.5%)	> 0.05 (0.235)
Hypertension	117 (51.8%)	136 (61.3%)	< 0.05 (0.043)
Diabetes mellitus	70 (31%)	62 (27.9%)	> 0.05 (0.481)
Dyslipidaemia	35 (15.5%)	41 (18.5%)	> 0.05 (0.402)
Ischaemic heart disease	32 (14.2%)	23 (10.4%)	> 0.05 (0.221)
Other heart disease	8 (3.5%)	13 (5.9%)	> 0.05 (0.512)
Smoking	110 (48.7%)	36 (16.2%)	< 0.05 (0.000)
Alcohol	97 (42.9%)	6 (2.7%)	< 0.05 (0.000)

Table 5. The stroke subtypes and risk factors amongst young strokes and other stroke patients

	Young strokes N = 26	*Other strokes N = 422*	*p value*
Stroke subtypes –			
Ischaemic strokes	20 (76.9%)	357 (84.6%)	> 0.05 (0.299)
Haemorrhage strokes	6 (23.1%)	65 (15.4%)	
Past history of stroke	6 (23.1%)	95 (22.5%)	> 0.05 (0.947)
Family history of stroke	4 (15.4%)	50 (11.8%)	> 0.05 (0.654)
Hypertension	12 (46.2%)	241 (57.1%)	> 0.05 (0.275)
Diabetes mellitus	3 (11.5%)	129 (30.6%)	< 0.05 (0.039)
Dyslipidaemia	3 (11.5%)	73 (17.3%)	> 0.05 (0.449)
Ischaemic heart disease	0 (0%)	55 (13%)	> 0.05
Other heart disease	2 (7.7%)	19 (4.5%)	> 0.05 (0.561)
Smoking	5 (19.2%)	141 (33.4%)	> 0.05 (0.135)
Alcohol	3 (11.5%)	100 (23.7%)	> 0.05 (0.153)

Discussion

The mean age of presentation in our study was 66.0 ± 12.23 for males and 67.25 ± 12.12 for females which was slightly higher than the population study in an urban area where the mean ages were 64.7 ± 11.9 for males and 61.6 ± 13.0 for females[2] and other hospital based studies where the mean ages varied from 55.8 years to 64.5 years [4,5,6], however the mean age is less than those reported in the Western populations. The difference could be either due to differences in methodology or due to the widely spoken of demographic transition and migration of youth post war.

In our study there were almost equal number of males and females (50.45% males and 49.55% females). This differs from the population-based study conducted in Colombo [2] where there was a 2:1 male to female ratio and the hospital based study in Colombo [4] where the male to female ratio was approximately 1.475:1. Other hospital-based studies done at Colombo also show a male predominance [5,6]. This difference may be due to the

post war effect, demographic transition and death and migration especially of the males during the war and the post war period.

The distribution of the stroke subtypes in our study showed a preponderance for ischaemic strokes (84.15%). This is similar to the global trend but slightly higher than one of the hospital based study in Colombo where 74.7% had ischaemic strokes and the rest had haemorrhagic strokes [4]. Another hospital based study showed a similar distribution to our study with 83.3% ischaemic strokes and 16.7% haemorrhagic strokes [6].

In the population based study in Colombo [2] risk factors were ranked as hypertension (62.5%), smoking (45.8%), diabetes mellitus (33.3%), past stroke (29.2%), family history of stroke (20.8%) and ischaemic heart disease (8.3%). Hypertension was the commonest risk factor in our study, however the other risk factors were ranked as follows past history of stroke (39.4%), smoking (30.8%), diabetes mellitus (26.05%), dyslipdaemia (15.8%), family history of stroke (12.3%) and ischaemic heart disease (11.9%). The difference could be explained by the fact that the study in Colombo was a population based study while our study is a hospital based study. However hypertension was also the commonest risk factor in the population based study as well as the other hospital based study in Colombo [4].

An interesting finding was that hypertension occurred in nearly equal number of patients in iscahemic and haemorrhages strokes in our study, however in another hospital based study in Colombo hypertension occurred in 97.6% of patients with haemorrhagic strokes and 59.6% patients with ischaemic strokes.

Since hypertension was the commonest risk factor, the sub analysis between hypertensives and non hypertensives showed that there is no significant difference in the stroke subtypes. Hypertension was a significant risk factor in females, but this differed from the study in Colombo where hypertension occurred equally in males and females [2]. Past history of stroke and smoking were significant risk factors in males and this correlates well with the population study from Colombo [2].

Our study had 26 young strokes. Hypertension was the commonest risk factor even amongst young strokes. The risk factor profile was the same amongst young strokes as well as the older patients except that diabetes was significantly more common in the elderly.

Conclusion

The mean age at presentation was slightly higher in our study population and the males and females were equally affected in our study. Ischaemic stroke was the commonest subtype and lacunar strokes were the commonest ischaemic stroke sub type. Ischaemic stroke was the commonest amongst the young strokes as well. Hypertension was the commonest risk factor followed by past history of stroke, smoking and diabetes mellitus.

Preventive strategies to detect hypertension and diabetes in the community, and public awareness of the ill effects of smoking can contribute significantly in the reduction of stroke burden. Suitable measures should be adopted as primary and secondary prevention to reduce stroke risk. A population-based study should be carried out in the Jaffna district to further evaluate the prevalence of stroke and the risk factors. Though the differences when compared with other studies from other parts of Sri Lanka mainly Colombo are minor, population based studies from North and the South are needed to establish the true burden of stroke in the country.

References

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al; Global burden of Diseases, Injuries and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2014; **383**; 245-54.
2. Chang T, Gajasinghe S, Arambepola C. Prevalence of stroke and it's risk factors in urban Sri Lanka: Population based study. *Stroke* 2015; **46**: 2965-8.
3. Ranawaka U, Balasuriya J, Ranawaka N, Jayasekara B, Wickramasinghe R, Wijesekera J. Prevalence of stroke in a Sri Lankan community. Abstract presented at: The Sri Lanka Medical Association Annual Scientific Sessions; 2003; Colombo, Sri Lanka.
4. Gunatilake SB, Jayasekara BAS, Premawardene P. Stroke subtypes in Sri Lanka – a hospital based study. *Ceylon Medical Journal* 2001; **1**: 19-20.
5. Arasalingam A, Alagiyawanna AMALR, Gunaratne PS. Intracerebral haemorrhage (ICH) – A study of patient characteristics / profile and risk factors. Abstract presented at: The Association of Sri Lankan Neurologist Annual Scientific Sessions; 2011; Colombo, Sri Lanka.
6. Arasalingam A, Alagiyawanna AMALR, Gunaratne PS. Intracerebral haemorrhages vs Ischaemic Strokes – patient profile and risk factors. Abstract presented at: The Association of Sri Lankan Neurologists Annual Scientific Sessions; 2011; Colombo, Sri Lanka.

Paper

Improvement in stroke care after establishment of the Stroke Unit

U K Ranawaka[1], A T Alibhoy[1], S Puvanendiran[1], D J S Fernando[2], J C Wijesekera[1]

Sri Lanka Journal of Neurology, 2015, **4**, 7-11

Abstract

***Objective*:** To determine whether there was an improvement in stroke care after the establishment of the Stroke Unit at the Institute of Neurology, National Hospital of Sri Lanka.

Design: The process of acute stroke care was evaluated by retrospective case record analysis of 192 patients with stroke admitted to the Stroke Unit. These results were compared with a previous audit of 263 patients treated in the neurology wards. The two audits used identical methodology, and were conducted using an audit package developed by the Royal College of Physicians of London.

***Methods*:** Sixty audit items related to stroke care were assessed, and compared between the two audits. Performance for each item was recorded as a percentage, and was graded from 'very poor' to 'very good'. The difference between the two audits for each item was expressed as an odds ratio (OR).

***Results*:** Care was graded as 'very good' or 'good' for 56.7% of audit items, compared to 20% in the first audit. Significant improvements in care (OR>1.0, p<0.05) were noted in 50 out of the 60 audit items. Large improvements were seen in assessment of risk factors, CT scanning, rehabilitation oriented clinical assessments and initiation of secondary preventive measures.

***Conclusion*:** Establishment of the Stroke Unit has led to significant improvements in the process of stroke care.

Index words: audit, stroke care, stroke unit, developing country, Sri Lanka

Introduction

Stroke is the second leading cause of death worldwide, and the fourth leading cause of global disease burden[1]. In Sri Lanka, where hospital statistics are the only reliable source of morbidity and mortality data, it ranks fourth among the leading causes of in-hospital deaths[2]. It continues to be a major global health problem in the 21st century, causing significant morbidity, mortality, and disability.

After years of therapeutic nihilism, there is renewed enthusiasm in facing the challenge of stroke. Rapid pre-hospital transport systems, advanced neuroimaging techniques and an emergency approach have revolutionised stroke care, aimed at delivering thrombolytic therapy or endovascular treatment for acute ischaemic stroke. Thrombolysis and endovascular treatment, however, are indicated only in ischaemic stroke, require enormous logistic support to be administered within narrow therapeutic time windows, carry inherent risks of complications, and are costly. Even in developed countries, only about 1.4-12% of eligible patients reportedly receive such treatment[3,4,5,6,7,8,9]. They remain therapeutic options that cannot be widely used in many of the developing countries, where more than two-thirds of strokes and 87% of stroke-related deaths in the world occur[10,11].

Management of patients in a stroke unit is an effective and cost-effective intervention after acute stroke[12,13,14]. It produces significant improvements in short term and long term outcome measures[12,14], and is one of the few interventions of proven benefit available for all types of patients, including those with haemorrhagic stroke[15]. Importantly, it is an intervention that can be easily made available in developing countries with limited resources. Even though there is a large evidence base highlighting the benefits of stroke unit care, data regarding such benefits from the developing countries are extremely limited[16].

Over the past two decades, audits of stroke care have driven quality improvement efforts in many parts of the world, but these initiatives have been largely confined to developed countries. They continue to highlight deficiencies of stroke care, even in these settings[4,17,18,5,19,20,21,6,8,22,23,24].

We previously carried out an audit of acute stroke care at the Institute of Neurology, National Hospital of Sri Lanka, Colombo (NHSL) in 1997 which highlighted

[1] *Institute of Neurology, National Hospital of Sri Lanka, Colombo,* [2]*Faculty of Medical Sciences, University of Sri Jayawardenepura, Nugegoda, Sri Lanka.*

serious deficiencies[25]. Following this, many changes were made in the structure and process of stroke care, and the most important of these was the establishment of the first stroke unit in the country at the NHSL in 1998. The objective of the present study was to determine whether there was an improvement in acute stroke care after the establishment of the Stroke Unit.

Methodology

We evaluated the process of acute stroke care by retrospective case record analysis of 192 consecutive patients with stroke admitted to the Stroke Unit of the Institute of Neurology over a period of two years (1998-2000) (**Audit 2**). These results were compared with the results of the previous audit (**Audit 1**) which analysed 263 consecutive stroke patients treated in the neurology wards over a period of 3 years (1994-1997)[25]. The two audits employed identical methodology, with similar inclusion and exclusion criteria. Both were conducted using the same audit package developed by the Royal College of Physicians of London and the UK Stroke Audit Group (the RCP Audit Package)[26].

The audit consisted of 60 audit items categorised under 13 care domains, each related to a particular aspect of stroke care. The result for each audit item was expressed as a percentage value, which was an indication of the quality of documentation of care. For the purpose of this study, we graded quality of care for each audit item as; Very good (81-100%), Good (61-80%), Average (41-60%), Poor (21-40%) and Very poor (0-20%). Results from the two audits were compared using a software programme provided with the audit package. The difference between the two audits for each audit item was expressed as an odds ratio (OR). The significance of this difference at the 5% level was expressed as a p value. An odds ratio of greater than unity (OR>1) indicated that the quality of care in the group of patients audited after the establishment of the Stroke Unit (Audit 2) was better than in Audit 1, whereas an OR<1 indicated that care in the second audit was comparatively poorer. Statistical non-significance (p>0.05) was denoted as OR=NS. The odds ratios and the p values were derived directly from the software package. The detailed methodology of the audit has been previously described[26,27].

Results

Care was graded as 'Very good' or 'Good' for 56.7% of audit items, compared to 20% in the first audit. 'Very poor' care was observed for only 13.3% of the audit items in Audit 2, compared to 50% in Audit 1. (Table 1) Significant improvements in care (odds ratio >1.0, p<0.05) were noted with regard to 50 (83.3%) of the 60 audit items tested. There was no statistically significant difference in care for the other ten items (p>0.05). None of the audit items showed a decline in care (odds ratio <1.0, p<0.05) (Table 2).

Table 1. Comparison of quality of care between the two audits

Quality of care		*Audit 1*	*OK%1*	*Audit 2*	*OK%1*
Very good	(91 – 100%)	04	6.7%	21	35%
Good	(76 – 90%)	08	13.3%	13	21.7%
Average	(51 – 75%)	11	18.3%	08	13.3%
Poor	(26 – 50%)	07	11.7%	10	16.7%
Very poor	(0 – 25%)	30	50%	08	13.3%

There were large improvements in relation to certain aspects of care that had scored poorly in the first audit. These included clinical parameters such as recording of certain risk factors (previous stroke or TIA, hyperlipidaemia, peripheral vascular disease), and neurological assessment including conscious level, mental state and visuospatial function. Performing CT scans, rehabilitation oriented clinical assessments and initiation of secondary preventive measures showed marked improvements.

No significant differences were noted in recording of blood pressure and fundoscopy as they were adequately performed in both audits. Improvements were not seen in discharge planning and some aspects of rehabilitation oriented assessment. Advice regarding smoking remained poor.

Discussion

Audit is a powerful tool for change. The purpose of audit is to identify deficiencies of care, and to introduce remedial interventions. Audit should then be repeated to evaluate the effectiveness of the interventions made. We were able to achieve this by completing the two audits before and after the establishment of the Stroke Unit, thus completing the audit cycle and demonstrating improvement in stroke care. This is the first such report from Sri Lanka, and to our knowledge, only the second report of stroke unit related improvements in care from a developing country.

We used a previously validated audit instrument, the RCP audit package, for this study. The RCP stroke audit package had been successfully used by several investigators previously[27,28]. This audit was based on retrospective case record evaluation, with its inherent limitations in evaluating quality of care, but any such

Table 2. Documentation of audit items of stroke care

Audit item	*OK%1*	*OK%2*	*OR>1 (p<0.05)*	*OR<1 (p<0.05)*	*OR-NS (p>0.05)*
1. History					
Source of history	62	79	2.55		
Rate of onset of symptoms	82	96	5.71		
Record of admission drugs	19	41	2.93		
2. Risk factors					
Previous stroke or TIA	22	76	11.3		
History of hypertension	71	91	4.21		
History of heart disease	51	83	4.59		
Peripheral vascular disease	00	46	218.0		
History of diabetes	60	83	3.24		
History of hyperlipidaemia	01	44	99.5		
Smoking	32	77	7.23		
Alcohol	30	78	8.16		
3. Pre-stroke function					
Record of dependence	15	60	8.42		
Use of social services	04	32			13.3
Employment	32	57	2.85		
4. General examination					
Pulse rate and rhythm	42	86	8.8		
Blood pressure	96	96			1.0
Heart sounds	79	97	9.9		
Neck bruits	22	69	7.6		
Peripheral pulses	02	48	48.4		
Fundoscopy	89	95			1.16
5. Neurological examination					
Conscious level	82	99	20.6		
Eye movements	69	89	3.62		
Power in the limbs	94	97	2.14		
Communication	39	90	14.3		
Trunk control or gait	12	53	8.48		
Swallowing	20	59	5.57		
Formal mental test score	02	36	37.2		
Visuospatial function	02	24	20.8		
Visual fields	36	56	2.26		
Sensory testing	58	86	4.4		
6. Clinical diagnosis					
Clear diagnostic formulation	22	71	8.39		
7. Usual baseline investigations					
Full Blood Count	93	99	14.9		
ESR	73	98	22.5		
Urea and Electrolytes	89	99	11.9		

(Continued)

Audit item	*OK%1*	*OK%2*	*OR>1 (p<0.05)*	*OR<1 (p<0.05)*	*OR-NS (p>0.05)*
Glucose	97	98	2.16		
ECG	62	99	56.7		
8. Special investigations					
CT Scan	68	98	21.3		
Investigate rare causes	63	80	2.34		
9. Immediate management plan					
Hydration	09	18	2.37		
Urinary incontinence	04	15	4.72		
10. Management in the first week					
Consultant review	84	99	18.1		
Review of important deficits	82	97	7.97		
11. Rehabilitation					
Record of personal interests	01	08			9.09
List of patients' problems	02	25	13.1		
Rehabilitation goals	00	98	14.2		
Re-assess functional status	03	99	99.9		
Multidisciplinary meeting	00	95			0
Information given to patient/relatives	01	00	13.9		
12. Discharge planning					
Ownership of accommodation	00	81			0
Type of accommodation	00	32			0
Living alone/ not	01	33	92.5		
Stairs / ground floor / lift	00	28			0
Access to toilet	00	02			0
Informal support available	02	33	31.6		
13. Secondary prevention					
Blood pressure after 4 days	81	96	6.06		
Antihypertensive medication	52	94	14.2		
Long term aspirin	77	94	59.2		
Long term anticoagulation	07	65	24.3		
Advice about smoking	00	01			2.6
Non invasive carotid imaging	31	81	9.40		

OK% - quality of care, expressed as a percentage (see text)
OR>1 (p<0.05) - denotes significant improvement in care
OR<1 (p<0.05) - denotes significant decline in care
OR=NS - denotes no significant change in care (p>0.05)

limitation would apply equally to both audits. These audits evaluated the process of care, before and after the establishment of a stroke unit, rather than outcome. In auditing stroke care, audit of process is considered better than that of outcome as setting standards is easier, and deficient areas and remediable actions are easy to detect[29,30]. Variation in case mix between the two audits would affect outcome measures, but not process of care.

Conclusions

Even though the benefits of stroke unit care have been well documented, data regarding such benefits from the developing countries remain scarce. We have shown that establishment of a stroke unit can produce significant improvements in stroke care, even in a developing country like Sri Lanka. We hope these findings would serve as a catalyst for the establishment of stroke units in the country.

References

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006; **367**: 1747-57.
2. Ministry of Healthcare and Nutrition, Sri Lanka. *Annual Health Bulletin* 2012.
3. Wardlaw JM, Sandercock PAG, Berge E. Thrombolytic therapy with recombinant tissue plasminogen activator for acute ischaemic stroke. Where do we go from here? A cumulative meta-analysis. *Stroke* 2003; **34**: 1437-42.
4. Lau AH, Hall G, Scott IA, Williams M. Thrombolysis in acute stroke: ongoing challenges based on a tertiary hospital audit and comparisons with other Australian studies. *Aust Health Rev* 2015; 29. doi: 10.1071/AH14167. [Epub ahead of print]
5. Ganesh A, Camden M, Lindsay P, Kapral MK, Coté R, Fang J, Zagorski B, Hill MD; Canadian Stroke Audit Group. The quality of treatment of hyperacute ischemic stroke in Canada: a retrospective chart audit. *CMAJ Open* 2014; **2**: E233-9.
6. Bray BD, Campbell J, Cloud GC, Hoffman A, Tyrrell PJ, Wolfe CD, Rudd AG; Intercollegiate Stroke Working Party Group. Bigger, faster? Associations between hospital thrombolysis volume and speed of thrombolysis administration in acute ischemic stroke. *Stroke* 2013; **44**: 3129-35.
7. Bray BD, Campbell J, Hoffman A, Tyrrell PJ, Wolfe CD, Rudd AG. Stroke thrombolysis in England: an age stratified analysis of practice and outcome. *Age Ageing* 2013; **42**: 240-5.
8. Child N, Fink J, Jones S, Voges K, Vivian M, Barber PA. New Zealand National Acute Stroke Services Audit: acute stroke care delivery in New Zealand. *N Z Med J* 2012; **125**: 44-51.
9. Rudd AG, Hoffman A, Grant R, Campbell JT, Lowe D; Intercollegiate Working Party for Stroke. Stroke thrombolysis in England, Wales and Northern Ireland: how much do we do and how much do we need? *J Neurol Neurosurg Psychiatry* 2011; **82**: 14-9.
10. Johnston SC, Mendis S, Mathers CD. Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modelling. *Lancet Neurol* 2009; **8**: 345-54.
11. Mathers CD, Lopez AD, Murray CJL. The Burden of Disease and Mortality by Condition: Data, Methods, and Results for 2001. In: Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL (Eds). Global Burden of Disease and Risk Factors. Washington (DC): World Bank; 2006. Chapter 3.
12. Stroke Unit Trialists' Collaboration. Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke. *British Medical Journal* 1997; **314**: 1151-9.
13. Rudd AG, Hoffman A, Irwin P, Lowe D, Pearson MG. Stroke Unit Care and Outcome. Results from the 2001 National Sentinel Audit of Stroke (England, Wales, and Northern Ireland) *Stroke* 2005; **36**: 103.
14. Langhorne P, Dennis MS. Stroke units: the next 10 years. *Lancet* 2004; **363**: 834-5.
15. Ronning OM, Guldvog B, Staven K. The benefit of an acute stroke unit in patients with intracranial haemorrhage: a controlled trial. *Journal of Neurology, Neurosurgery and Psychiatry* 2001; **70**: 631-4.
16. Pandian JD, Joy SA, Justin M, Premkumar AJ, John J, George AD, Paul P. Impact of stroke unit care: an Indian perspective. *Int J Stroke* 2011; **6**: 372-3.
17. Lynch EA, Luker JA, Cadilhac DA, Hillier SL. Rehabilitation assessments for patients with stroke in Australian hospitals do not always reflect the patients' rehabilitation requirements. *Arch Phys Med Rehabi* 2015; **96**: 782-9.
18. Wiedmann S, Hillmann S, Abilleira S, Dennis M, Hermanek P, Niewada M, Norrving B, Asplund K, Rudd AG, Wolfe CD, Heuschmann PU; European Implementation Score Collaboration. Variations in acute hospital stroke care and factors influencing adherence to quality indicators in 6 European audits. *Stroke* 2015; **46**: 579-81.
19. Campbell JT, Bray BD, Hoffman AM, Kavanagh SJ, Rudd AG, Tyrrell PJ; Intercollegiate Stroke Working Party. The effect of out of hours presentation with acute stroke on processes of care and outcomes: analysis of data from the Stroke Improvement National Audit Programme (SINAP). *PLoS One* 2014; **9**: e87946.
20. Eissa A, Krass I, Bajorek BV. Use of medications for secondary prevention in stroke patients at hospital discharge in Australia. *Int J Clin Pharm* 2014; **36**: 384-93.
21. Cloud G, Hoffman A, Rudd A; Intercollegiate Stroke Working Party. National sentinel stroke audit 1998-2011. *Clin Med* 2013; **13**: 444-8.
22. Bray BD, Ayis S, Campbell J, Hoffman A, Roughton M, Tyrrell PJ, Wolfe CD, Rudd AG. Associations between the organisation of stroke services, process of care, and mortality in England: prospective cohort study. *BMJ* 2013; **346**: f2827.
23. Rudd AG, Lowe D, Hoffman A, Irwin P, Pearson M. Secondary prevention for stroke in the United Kingdom: results from the National Sentinel Audit of Stroke. *Age Ageing* 2004; **33**: 280-6.
24. Rudd AG, Irwin P, Rutledge Z, Lowe D, Wade DT, Pearson M. Regional variations in stroke care in England, Wales and Northern Ireland: results from the National Sentinel Audit of Stroke. Royal College of Physicians Intercollegiate Stroke Working Party. *Clin Rehabil* 2001; **15**: 562-72.
25. Ranawaka UK, Fernando MAH, Gunasekera TGSM, Senanayake BSN, Gunawardena DRR, Wijesekera JC, Fernando DJS. An audit of acute stroke care at the Institute of Neurology, National Hospital of Sri Lanka, 1994-1997. *Ceylon Medical Journal* 2002; **47**: 86-89.
26. Royal College of Physicians. Stroke Audit Package. London: *Royal College of Physicians* 1994.
27. Hancock RJT, Oddy M, Saweirs WM, Court B. The RCP audit package in practice. *Journal of the Royal College of Physicians of London* 1997; **31**: 71-78.
28. McNaughton H. Stroke audit in a New Zealand hospital. *New Zealand Medical Journal* 1996; **109**: 257-60.
29. Rudd AG, Irwin P, Rutledge Z, Lowe D, et al. The National Sentinel Audit for Stroke: a tool for raising standards of care. *Journal of the Royal College of Physicians of London* 1999; **33**: 460-64.
30. Dennis M. Stroke services: the good, the bad and the…….. *Journal of the Royal College of Physicians of London* 2000: **34**: 92-96.

Paper

The randomized prospective study of non-surgical management of patients with mild to moderate carpel tunnel syndrome

D D Wijegunasinghe[1], S T K Jayatunge[1], P M Kumarasinghe[1], A W P I Gunathilake[1], W N A Sriyani[1]

Sri Lanka Journal of Neurology, 2015, **4**, 12-17

Abstract

***Objective*:** To evaluate effectiveness of used oral medications such as diuretics, steroids and local steroid injections in the treatment of mild to moderate CTS.

***Methods*:** Prospective randomized study of patients with clinical symptoms and signs of CTS, confirmed by standard electrodiagnosis. Baseline assessments included a standardized Boston questionnaire to assess symptom severity score, functional severity score, total score, relevant clinical examination and necessary nerve conduction studies (NCS). After the baseline assessment, patients were randomized to following treatment arms:

1. Steroid local injection (n = 64)
2. Oral steroid for 28 days (n = 64)
3. Oral steroid + diuretics for 28 days (n = 69)

Boston questionnaire symptom severity score, functional severity score, total score and the NCS results were analyzed after 28 days of treatment.

***Results*:** Boston questionnaire scores (symptom severity score, functional severity score and total score) were significantly improved with all three treatment modalities after 4 weeks of treatment $p < 0.05$ the values of each indicator was more or less similar in each group at the baseline.

The percentage of improvement is highest with steroid injection and lowest with oral steroids and steroids + diuretic group falling in between. Sensory nerve conduction studies showed an improvement in all three treatment modalities. But a statistically significant improvement was seen in steroid injection and oral steroid + diuretic groups only $p < 0.05$.

***Conclusion*:** All three treatment modalities i.e. steroid injections, oral steroids, and oral steroid and diuretics are effective in treating mild to moderate CTS. The improvement seen with steroid injection is more than that is seen in the other two interventions.

Introduction

Carpal tunnel syndrome (CTS), an entrapment neuropathy of the median nerve at the wrist, is the most common peripheral nerve disorder, with a population prevalence of 9.2% in women and 6% in men[1,3]. This is because the anatomy of our wrists is less than ideal. The median nerve at the wrist travels through the carpal tunnel, and shares this space with 9 flexor tendons. The 'tunnel' is formed by the bones of the wrist posteriorly and laterally and the transverse carpal ligament anteriorly. Due to the limited space within the tunnel, swelling of the tendons, arthritic changes in the wrist, swelling or infiltration of the median nerve itself can compress the nerve[8,9,21]. The classic symptoms of CTS are numbness and paraesthesia in the first three fingers of the hand, which is commonly exacerbated at night. The diagnostic signs include sensory loss along the lateral aspect of the hand, motor weakness and wasting of abductor pollicis brevis (APB) muscle, and eliciting Tinel's and Phalen's sign at the wrist. The nerve conduction study (NCS) study is a definitive diagnostic test for CTS with high degree of sensitivity and specificity[2,6,7]. This test demonstrates a distal lesion of the median nerve at the wrist and excludes other peripheral conditions resulting in similar symptoms[2].

Non-surgical treatment options such as local steroid injections, oral steroids, diuretics, and splinting have been used to treat mild to moderate CTS[10,11,12]. However, there is no uniform consensus on the ideal treatment options.

Therefore we decided to compare the efficacy of the following treatment options.

1. Steroid local injection, Depo-Medrol (Methylprednisolone acetate) 40mg at the level of the carpal tunnel.
2. Oral steroid for 28 days, oral prednisolone 20mg daily for 14 days and 10mg daily for 14 days.
3. Oral steroid and diuretics, oral prednisolone 20mg daily for 14 days and 10mg daily for 14 days and oral frusemide 40mg daily for 28 days.

Methods

This study was conducted at the General Hospital,

[1]*Neurology Unit, General Hospital, Matara, Sri Lanka.*

Matara. All consecutive patients referred for evaluation of suspected CTS to the neurology unit from 1st of July to 31st September 2012, were clinically assessed using the following inclusion and exclusion criteria proposed by the AAN Quality Standards Subcommittee (1993) by a designated medical officer attached to the neurology unit.

Inclusion criteria

1. Sensory symptoms (numbness and/or tingling) in at least 2 of digits 1, 2, 3, and 4 for at least 1 month. The sensory symptoms may be intermittent or constant, but if constant, there must have been a period of time during which the symptoms were intermittent. The numbness and tingling may be accompanied by pain, but pain alone is not sufficient to meet this first inclusion criteria.
2. Sensory symptoms (numbness and/or tingling) aggravated by at least 1 of the following: sleep, sustained hand or arm positioning, or repetitive actions of the hand.
3. Sensory symptoms (numbness and/or tingling) mitigated by at least 1 of the following: changes in hand posture, shaking the hand, or use of a wrist splint.
4. If pain is present, the wrist, hand, and finger pain is greater than elbow, shoulder, or neck pain if there is pain in any or all of those locations.

Exclusion criteria

1. Sensory symptoms exclusively or predominantly in the digit 5 (little finger) (ulnar neuropathy).
2. Neck pain or shoulder pain preceded the paresthesia in the digits (cervical radiculopathy and/or brachial plexopathy).
3. Numbness and/or tingling in the feet which preceded or accompanied the sensory symptoms in the hands (polyneuropathy).
4. Findings on the problem focused history and physical examination which indicate an explanation for the sensory symptoms which is more probable than CTS, for example, digital neuropathy, median nerve pathology proximal to the carpal tunnel, ulna neuropathy, radial neuropathy, brachial plexopathy, cervical radiculopathy, spinal cord, brainstem or brain pathology, or a polyneuropathy.
5. History of carpel tunnel decompression in the past.

Those who had signs and symptoms compatible with CTS had nerve conduction studies performed on both hands by the consultant neurologist.

The temperature was maintained at >32°C during the procedure. For motor NCS, the median and ulnar motor nerves were stimulated at wrist 7 cm proximal to the active recording electrode. The sensory responses were obtained at digit II and digit V for the median and ulnar nerves, stimulating antidromically at 13 cm and 11 cm, respectively. Following were recorded.

1. Median-D2 sensory nerve action potential (SNAP).
2. Ulnar-D5 SNAP.
3. Median-APB compound muscle action potential (CMAP), stimulating at wrist and ante-cubital fossa.
4. Ulnar-ADM CMAP, stimulating at the wrist and elbow.

If the median studies show slowing across the wrist (prolonged peak SNAP latency, prolonged distal latency of CMAP), and ulnar studies are normal, then this is clear evidence of a median neuropathy at or distal to the wrist, as can be seen in carpal tunnel syndrome. When this is the case, no further nerve conduction studies are needed.

When the above studies are normal, or inconclusive, we performed additional studies such as the following median-ulnar comparisons:

1. Median-ulnar palmar comparison. This is a mixed nerve action potential (MNAP) study, in which stimulation is in the palm and recording is at the wrist. This study is more sensitive than the median-D2 Ulnar D5 SNAP. (In our laboratory, we consider a difference in peak latency of greater than or equal to 0.4 msec abnormal.)
2. Median-lumbrical and ulnar-interosseous CMAP comparison. The median and ulnar nerves are stimulated at the wrist, with a single recording electrode over the lumbrical-interosseous space between digits 2 and 3. This study is often obtainable even in very severe CTS, so it is most useful when a routine median-APB CMAP is unobtainable. (In our laboratory, a difference in distal motor latency of 0.4 msec or greater is considered abnormal.)
3. Median-ulnar-D4 SNAP comparison. Median and ulnar nerves are stimulated at the wrist, recording from digit 4 using ring electrodes.

Needle EMG is performed when the above NCS were not suggestive of CTS or suspect a proximal lesion (such as a C6-7 radiculopathy).

The following muscles were sampled

1. APB.
2. Two or more C6-7 muscles (e.g. Pronator Teres, Extensor Digitorum Communis) to exclude a C6-7 radiculopathy – a common cause of sensory disturbance in the radial hand/fingers. If PT is chosen, this also helps to exclude a proximal median neuropathy.

The patients were categorised to mild, moderate and severe depending on the NCS findings as given below.

Mild CTS: Median Motor – Sensory latency difference between median andulnar 0.5-0.9ms.

Moderate CTS: Sensory latency difference between median and ulnar> 1ms.

Severe CTS: Median motor TL> 5.0ms with normal ulnar nerve NCS.

Those who had severe CTS according to NCS criteria were excluded and referred for surgery. Those who had symptoms compatible with CTS and NCS evidence of mild to moderate CTS were recruited and informed written consent was obtained. Prior to treatment, the severity of symptoms was assessed using the Boston questionnaire translated into Sinhala. The form was filled by the interviewing medical officer after explaining and clarifying each question and examining both hands. Thereafter they were randomized to the three treatment options. All were evaluated after 4 weeks of treatment using the Boston questionnaire and a repeat nerve conduction study.

Statistical analysis

Data were processed using excel and later converted SPSS sav files for analysis. The treatment outcome, the severity of illness was assessed using Boston questionnaire and the nerve conduction study results. Paired T test was used to evaluate the difference in outcome indicators at the baseline and end line. The difference of values of each patient in symptom severity score, functional severity score and total score given by the Boston questionnaire[18,19,20] and Medial TL and sensory difference as given by nerve conduction tests across 3 treatment groups were compared using One Way Anova tests. Bonferroni method of post hoc assessments were used to compare subgroup differences. IBM SPSS version 20 was used.

Results

A total of 197 patients were randomized to steroid injection group (n=64), oral steroid group (n=64), and oral steroid and diuretics group (n=69). Patients age ranged from 17 years to 76 years and the age distribution between the treatment groups were comparable (p>0.05). The majority of patients were females (76.6%) and sex composition between treatment groups was similar. The outcomes were assessed for patients irrespective of which hand is affected. If both hands were affected (in 34% of cases), the hand which had mild to moderate CTS was considered for the analysis. Table 1 compares the pre and post test level measurements of each outcome indicator based on the Boston questionnaire.

Table 1. Pre and post levels of Boston Questionnaire and NCS indicators by 3 treatment types

Treatment type and outcome		*Pre*		*Post*		*P values (Pre past difference)*
		Mean	*Standard Deviation*	*Mean*	*Standard Deviation*	
Steroid injection	Symptom severity score	2.17	.85	1.41	.59	t= 6.4, df= 61, p <0.05
	Functional severity score	2.03	.84	1.35	.33	t= 7.3, df= 39, p <0.05
	Total score	4.21	1.52	2.78	.95	t= 7.4, df= 60, p <0.05
	Medial TL	4.2	0.48	3.9	0.66	t= 3.6, df= 54, p <0.001
	Sensory difference	1.2	0.41	0.91	0.35	t= 5.03, df= 40, p <0.001
Oral steroid	Symptom severity score	1.96	.61	1.53	.54	t= 6.3, df= 62, p <0.05
	Functional severity score	1.86	.68	1.60	.58	t= 3.7, df= 36, p <0.05
	Total score	3.85	1.22	3.04	1.14	t= 5.5, df= 62, p <0.05

(Continued)

Treatment type and outcome		*Pre*		*Post*		*P values (Pre past difference)*
		Mean	*Standard Deviation*	*Mean*	*Standard Deviation*	
	Medial TL	4.12	0.50	4.03	0.51	t= 1.07, df= 57, p > 0.05
	Sensory difference	1.1	0.43	0.94	0.54	t= 1.92, df=47, p > 0.05
Oral steroid & diuretics	Symptom severity score	2.16	.90	1.64	.70	t= 5.6, df= 63, p <0.05
	Functional severity score	2.11	.86	1.63	.58	t= 4.8, df= 38, p <0.05
	Total score	4.20	1.55	3.21	1.14	t= 7.8, df= 62, p <0.05
	Medial TL	4.2	0.43	4.1	0.50	t= 4.5, df= 61, p <0.001
	Sensory difference	1.12	0.33	0.99	0.29	t= 4.5, df=48, p <0.001

This table reveals that the Boston questionnaire scores (symptom severity score, functional severity score and total score) were significantly improved with all three treatment modalities after 4 weeks of treatment p <0.05 the values of each indicator was more or less similar in each group at the baseline.

The percentage of improvement was highest with steroid injection and lowest with oral steroids and steroids + diuretic group falling in between. Improvement in the NCS sensory difference was seen in all three treatment modalities. But statistically significant improvement was presentonly in the steroid injection and oral steroid + diuretic groups (p <0.05).

In order to assess the most effective treatment option the differences of the values of each outcome indicator were compared using One Way Anova test. Post hoc test with Bonferroni corrections were used to get the between group differences.

Steroid injections were more effective compared to oral steroids which was statistically significant. However, the difference between the steroid injection and combination of steroids and diuretics failed to show a statistically significant difference in outcomes.

Discussion

Any condition that reduces the cross-sectional area of the carpal tunnel or increases the volume of its contents will compress the median nerve against the flexor retinaculum and will result in distal motor and sensory dysfunction. Therefore, any medication that reduces the swelling of structures within the carpal tunnel may be effective in the treatment of CTS. Diuretics, oral steroids and steroid injections are commonly used to reduce the volume of the swollen tissue, resulting in the improvement of symptoms and signs of CTS.

Although surgical decompression offers the most effective management for CTS, conservative non-operative therapies are effective in the management of mild to moderate CTS.

The study showed that the Boston questionnaire scores (symptom severity score, functional severity score and total score) significantly improved with all three treatment modalities after 4 weeks of treatment. We used a short-term, low-dose oral steroid regimen to avert any possible side effects and used once daily dosing to improve patient compliance.

The repeat NCS at 28 days revealed an improvement in all three treatment modalities. But statistically significant improvement was present in steroid injection and oral steroid + diuretic groups only. Although the oral steroid group showed an improving trend it lacked the statistical power probably due to the inadequate sample size.

The comparison of the three treatment modalities using One Way Anova test revealed that there was a significant superiority of steroid injections over oral steroid as treatment for CTS. However the difference between the steroid injection and combination of steroids

Table 2. Average improvements of outcome indicators in different treatment groups

Indicator	*Treatment type*	*Mean improvement (reduction of score)*	*Significance*
Symptom Severity score	Steroid injection	0.770	F=3.871, df(2,186), p <0.05
	Oral steroid	0.437	
	Oral steroid & Diuretics	0.469	Post hoc comparison shows that difference is only between Steroid injection and oral steroids (p <0.05)
Functional severity score	Steroid injection	0.8543	F=4.03, df(2,113), p <0.05
	Oral steroid	0.3758	
	Oral steroid & Diuretics	0.6456	Post hoc comparison shows that difference is only between Steroid injection and oral steroids (p <0.05)
Total score	Steroid injection	1.5005	F=4.9, df(2,184), p <0.05
	Oral steroid	0.8047	
	Oral steroid & Diuretics	1.0016	Post hoc comparison shows that difference is only between Steroid injection and oral steroids (p <0.05)
Medial TL	Steroid injection	0.24	F=2.73, df(2,172), p > 0.05
	Oral steroid	0.06	
	Oral steroid & Diuretics	0.18	
Sensory difference	Steroid injection	0.32	F=1.109, df (2,137), p > 0.05
	Oral steroid	0.17	
	Oral steroid & Diuretics	0.22	

and diuretics failed to show a statistical significance. But it is likely that given a larger sample size, this difference is likely to reach statistical significance.

This study showed that all three treatment modalities i.e. steroid injections, oral steroids, and oral steroid and diuretics are effective in treating mild to moderate CTS. The most significant improvement was seen with the steroid injection group.

References

1. Mondelli M, Giannini F, Giacchi M. Carpal tunnel syndrome incidence in general population. *Neurology* 2002; **58**: 289-94.
2. Bland JD. et al. Do nerve conduction studies predict the outcome of carpal tunnel compression? *Muscle Nerve* 2001; **24**: 935-40.
3. Atroshi I, Gummesson C, Johnson R, Ornstein E, Ranstam J, Rosen I. Prevalence of carpal tunnel syndrome in a general population. *JAMA* 1999; **282**: 153-8.
4. Franzblau A, Werner RA. What is carpal tunnel syndrome? *JAMA* 1999; **282**: 186-7.
5. Practice parameter for carpal tunnel syndrome (summary statement). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1993; **43**: 2406-9.
6. Stevens JC. AAEM minimonograph 26: the electrodiagnosis of carpal tunnel syndrome. American Association of Electrodiagnostic Medicine. *Muscle Nerve* 1997; **20**(12): 1477-86.

7. Padua L, LoMonaco M, Gregori B, Valente EM, Padua R, Tonali P. Neurophysiological classification and sensitivity in 500 carpal tunnel syndrome hands. *Acta Neurol Scand* 1997; **96**(4): 211-7.

8. Armstrong T, Dale AM, Franzblau A, Evanoff BA. Risk factors for carpal tunnel syndrome and median neuropathy in a working population. *J. Occup. Environ. Med* 2008; **50**: 1355-64.

9. Maghsoudipour M, Moghimi S, Dehghaan F, Rahimpanah A. Association of occupational and non-occupational risk factors with the prevalence of work related carpal tunnel syndrome. *J. Occup*. *Rehabil* 2008; **18**: 152-6.

10. Chang MH, Chiang HT, Lee SSJ, Ger LP, Lo YK. Oral drug of choice in carpal tunnel syndrome. *Neurology* 1998; **51**: 390-3.

11. Herskovitz S, Berger AR, Lipton RB. Low dose, short term oral prednisolone in the treatment of carpal tunnel syndrome. *Neurology* 1995; **45**: 1923-5.

12. Hui AC, Wong SM, Wong KS, Li E, Kay R, Yung P, Hung LK, Yu LM. Oral steroid in the treatment of carpal tunnel syndrome. *Ann Rheum Dis*. 2001; **60**(8): 813-4.

13. Marshall S, Tardif G, Ashworth N. Local corticosteroid injection for carpel tunnel syndrome. *Cochrane Database Syst Rev*. 2007 **18**(2): CD001554. Review.

14. Girlanda P, Dattola R, Venuto C, Mangiapane R, Nicolosi C, Messina C. Local steroid treatment in idiopathic carpal tunnel syndrome: short- and long-term efficacy. *J Neurol* 1993; **240**(3): 187-90.

15. Wong SM, Hui AC, Tang A, Ho PC, Hung LK, Wong KS, Kay R, Li E. Local vs systemic corticosteroids in the treatment of carpal tunnel syndrome. *Neurology* 2001; **56**(11): 1565-7.

16. Verdugo RJ, Salinas RA, Castillo JL, Cea JG. Surgical versus non-surgical treatment for carpal tunnel syndrome. [update of Cochrane Database Syst. Rev. 2003; (3), CD001552;PMID: 12917909] Cochrane Database Syst. Rev. 2008; 4 CD001552

17. Pathirana KD, Kommalage M. Influence of age and the severity of median nerve compression on forearm median motor conduction velocity in carpal tunnel syndrome. *J Clin Neurophysiol* 2011; **28**(6): 642-6.

18. Mumcu EF, Heybeli N, Kutluhan S, Demirci S, Kerman M. Assessment of outcome of carpal tunnel syndrome: a comparison of eletrophysiological findings and a self-administered Boston questionnaire. *J Hand Surg* (Br). 2002; **27**: 259-64.

19. Padua L, Mondelli M, Reale F, Sicurelli F. Relationship between the self-administered boston questionnaire and eletrophysiological findings in follow-up lof surgically-treated carpal tunnel syndrome. *J Hand Surg* (Br). 2000; **25**: 128-34.

20. Greenslade JR, Mehta RL, Belward P, Warwick DJ. DASH and Boston questionnaire assessment of carpal tunnel syndrome: what is the responsiveness of an outcome questionnaire? *J Hand Surg* (Br) 2004; **29**: 159-64.

21. AnnicaBarcenilla, Lyn M March, Jian Sheng Chen, Philip N. Sambrook. Carpal tunnel syndrome and its relationship to occupation: a meta-analysis. *Oxford Journals, Medicine & Health, Rheumatology* 2011: **51**: 250-61.

22. Ann Marie Dale, Carisa Harris-Adamson, David Rempel, et al. Prevalence and incidence of carpal tunnel syndrome in US working populations: pooled analysis of six prospective studies. *Scand J Work Environ Health* 2013; **39**: 495-505.

23. Sarella LK, Rao DS. Neurological Disorders in Pregnancy and Puerperium. *Sri Lanka Journal of Obstetrics and Gynaecology* 2014: **36**(3): 74-78.

Review

An update on pharmacotherapy of post herpetic neuralgia

A Arasalingam[1], T Kumanan[2], S N Thiyahiny[3]

Sri Lanka Journal of Neurology, 2015, **4**, 18-21

Introduction

Post herpetic neuralgia (PHN), a chronic neuropathic pain persisting for more than 3 months after the rash of acute herpes zoster has healed, is debilitating and difficult to manage. It is the commonest complication of herpes zoster (shingles) occurring in 10 to 34% of patients. The increase in incidence and severity with age is a striking feature of PHN. The incidence varies depending on the definitions used to define post heretic neuralgia[1,2]. Globally precise figures on the incidence and prevalence of PHN are hard to obtain because of variable definitions and inadequate data. There is no published data from Sri Lanka on the incidence or prevalence of PHN or herpes zoster. However, herpes zoster and PHN are common conditions seen in primary and secondary health care settings with resistant PHN being referred to tertiary health care institutions.

Most experts agree that pain beyond 90-120 days after onset of rash is true chronic neuropathic pain[3,4]. The course of pain in herpes zoster has 3 phases: an acute herpetic pain that lasts approximately 30 days after onset of rash; a subacute phase that lasts 30-120 days after a rash; and PHN defined as pain that persists at least 120 days after the onset of rash[4,5]. Post herpetic neuralgia that continues six months after the onset of rash is more likely to be persistent for years[6]. PHN has an incidence of 10 to 20%[7]. The quality of life is affected by pain and associated symptoms such as fatigue and insomnia and decreased social activity[7,8].

Risk factors for PHN include older age, prodromal pain, extent and severity of rash and severity of acute herpes zoster pain[9]. Age older than 50 and a visual analogue scale over 5/10 are predictive of persistent pain at 3 months despite early treatment with antivirals[5].

In this update we have discussed different therapeutic options using number needed to treat (NNT) and number needed to harm (NNH). NNT is a measure of effectiveness of an intervention and is treatment specific and describes the difference between active treatment and control in achieving a particular clinical outcome. NNH is similar to NNT but describes adverse events.

Treatment of post-herpetic neuralgia

Post herpetic neuralgia is difficult to treat. There are a variety of treatment options. Randomised controlled clinical trials showed that 30 to 70% of patients with PHN do not achieve satisfactory relief[10]. No single treatment has been shown to be completely effective for all patients. Multimodal analgesic treatment strategy to balance efficacy and tolerability of medication regimen is often needed for the optimal management of post herpetic neuralgia.

Pain control is the mainstay of the treatment which depends on the type and nature of the pain. The nature of the neuropathic pain is variable and there are a variety of different pain mechanisms operating in different patients or in the same patient at different points of time. Therapeutic options could be drugs (oral or topical), nerve block / stimulation and prevention.

Antidepressants

Tricyclic antidepressants (TCAs) amitriptyline, nortriptyline and desipramine seem to be effective. They reduce the pain by inhibiting re-uptake of serotonin and norepinephrine at presynaptic nerve terminal and blocking calcium channels. According to clinical trials and meta-analysis the number needed to treat is 2.1 to 2.6[10]. Amitriptyline and nortriptyline are equally effective, with approximately 50% achieving a good response[11]. In a systematic review of studies in PHN patients minor adverse effects occured in 84% of the patients with a number need to harm (NNH) of 5.67 (3.34-18.58)[10]. Dizziness, sedation and anticholinergic effects were the most frequently reported adverse effects such as dry mouth, gastrointestinal discomfort, constipation, urinary retention, nausea, vomiting, blurred vision, confusion and orthostatic hypotension. Cardiac dysrhythmias such as QT prolongation, torsades de pointes and sudden cardiac death in patients with conduction abnormalities are also reported and review of baseline ECG especially in the elderly and those with a history of cardiovascular disease and hypokalaemia is recommended. These adverse effects are less pronounced at low doses. Starting at a low dose at bedtime and titrating gradually weekly to a target dose is recommended. Nortriptyline and desipramine are better tolerated compared to amitriptyline and considered a better option in the elderly[12]. Duloxetine and venlafaxine are selective serotonin and norepinephrine re-uptake inhibitors (SNRIs) and are used in acute herpes zoster pain and PHN. Clinically they are better tolerated than TCAs[13].

[1]*Consultant Neurologist, Teaching Hospital, Jaffna,* [2]*Consultant Physician and Senior Lecturer, Department of Medicine, University of Jaffna,* [3]*Senior Lecturer in Pharmacology, Faculty of Medicine, University of Jaffna, Sri Lanka.*

Anticonvulsants

The exact mechanism of action of pregabalin and gabapentin are unknown. They act at the alpha 2 delta subunits of the voltage gated calcium channels with a consequent release of excitatory neurotransmitters including glutamate. These drugs are excreted unchanged in the urine thus, dose need to be adjusted according to renal function[10]. Studies have shown that the number needed to treat (NNT) is 2.8 for gabapentin for moderate improvement of PHN[14]. Two parallel group studies comparing different dose of gabapentin ranging from 1200mg/day to 3600mg/day showed that gabapentin was efficacious with no significant difference between groups. Pooled results for gabapentin gave a NNT of 4.39 (3.34-6.07). Gabapentin is usually prescribed in 3 or 4 divided dose and side effects include somnolence, dizziness, peripheral oedema and ataxia. These side effects are generally short lived but may require dose adjustment [10]. The analgesic efficacy of pregabalin was established in trials and the pooled NNT for a 50% pain reduction was 4.93 (3.66 - 7.58)[10]. Analgesic efficacy and adverse effect profiles are comparable to gabapentin but occur at a much lower dose. Pregabalin has a more predictable and linear pharmacokinetic profile compared to gabapentin. Titration of dose is rapid and usually prescribed in 2 divided doses[15].

Opioids

Studies have shown that opioids are effective in neuropathic pain including post herpetic neuralgia[10,16]. In a crossover randomised controlled trial, opioids and tricyclic antidepressants significantly reduced pain in post herpetic neuralgia compared to placebo (38.2%, 31.9% and 11.2% pain relief respectively). The number needed to treat was 2.8 for opioids and 3.7 for TCAs[17]. Pooled data from a quantitative systematic review of opioids yielded a NNT of 2.67[10]. Adverse effects of opioids include nausea, pruritus, dizziness, sedation and constipation. Most adverse events improved with time except constipation. Generally use of opioids is not encouraged due to the risk of addiction.

Tramadol

Tramadol, a synthetic 4-phenyl-piperidine analogue of codeine acts on the mu opioid receptor and is also a serotonin and norepinephrine reuptake inhibitor. Thus it has the properties of an opioid and a tricyclic antidepressant. In a randomised clinical trial tramadol (average dose 275mg/day) significantly improved quality of life in patients with PHN and the NNT was 4.8 (2.6-26.9)[10,18]. The wide 95% CI indicates that replication of this study is required before efficacy can be firmly stated. Adverse effects include nausea, dizziness, constipation, somnolence and headache. Concomitant use of SSRIs or selective monoamine oxidase inhibitors may lead to serotonin syndrome and seizures.

Topical lidocaine

A 5% lidocaine patch produces local analgesia without causing anaesthesia and also provides protection from mechanical irritation. Clinical trials in PHN showed that topical lidocaine produces significant reduction of pain and allodynia. Systemic adverse effects are minimal with topical lidocaine. Localised skin reactions have been reported in a small number. Efficacious and long term pain relief is possible within 2-3 weeks of initiation of lidocaine patch[20].

Topical capsaicin

Capsaicin is an alkaloid extracted from hot chilli peppers and acts on afferent nociceptor terminals. The repeated use of topical capsaicin causes depletion of substance P and other neuropeptides form nociceptive fibres (unmyelinated C fibers) resulting in analgesia. The use of capsaicin is limited due to local irritation and burning sensation, especially in PHN with allodynia. It is recommended to apply capsaicin following pretreatment with local anaesthetics[12]. Two parallel group studies compared capsaicin cream (0.075% cream) to placebo and the pooled NNT was 3.26 (2.26-5.85)[10].

Invasive treatments

Nerve block is less commonly used due to the need for expertise and risk of invasion related adverse effects. Epidural block, intrathecal analgesia and sympathetic nerve blocks have limited evidence for efficacy in PHN.

Nerve blocks

Epidural block with local anaesthetics and steroids is not effective in providing long term pain relief in patients with post-herpetic neuralgia[21]. In a systematic review intrathecal treatment was associated with an efficacy in 92% of the patients while efficacy was seen only in 17% of patients with epidural treatment.

However the intrathecal administration of steroids has beneficial effects[22] but increases risk of development of adhesive arachnoiditis. Pooled data in a systematic review showed that intrathecal therapy with lidocaine/methylprednisolone was effective with a NNT of 1.13 (1.05-1.22), but not with intrathecal lidocaine alone[10].

Sympathetic nerve block has beneficial effects in acute herpes zoster but does not provide long term pain relief[21]. There are some reports of long-term pain relief with peripheral nerve block using local anaesthetics but evidence is limited[23].

Spinal cord stimulation

Spinal cord stimulation is useful for chronic neuropathic pain and provides significant long term pain

relief in patients with PHN[24]. Spinal cord stimulation can be a treatment option for the management of intractable pain from PHN.

Vaccination against herpes zoster

Herpes zoster occurs as a result of decreased cell mediated immunity and is more common in elderly. The immunity can be enhanced by endogenous boosting. An episode of zoster boosts the immunity against varicella zoster virus (VZV) and recurrent herpes zoster is uncommon in immunocompetent adults. This is the rationale for developing a zoster vaccine to boost the immunity against VZV in previously exposed individuals. The zoster vaccine is a lyophilized preparation of a live attenuated VZV and is administered as a single subcutaneous injection.

The Shingles Prevention Study, the main efficacy trial[25] showed that vaccination caused significant reduction in the incidence of herpes zoster (51.3%) and PHN (66.5%). The burden of illness (measure of incidence, severity, duration of pain and discomfort) of herpes zoster was reduced by 61.1% and there was a 73% reduction in the number of cases of herpes zoster with severe and chronic pain.

The safety sub-study of the Shingles prevention study showed that few adverse reactions occurred; the most frequent one is the injection site reaction. There were no serious adverse events reported. The vaccine was efficacious over a 4 year follow-up period. Interim analysis of a 10 year follow-up study at 7 years showed that the vaccine significantly reduces the incidence of herpes zoster and the incidence of PHN and the burden of the disease[26].

The vaccine can be administered concomitantly with the influenza vaccine with no reported interactions,[27] however immunogenicity of the zoster vaccine is reduced when administered with pneumococcal vaccine and this combination should be avoided[28].

Conclusion

The incidence of herpes zoster and PHN increases with advancing age. Post-herpetic neuralgia is difficult to treat and may require multiple medications and referral to a pain specialist. Early diagnosis and appropriate pharmacological intervention of herpes zoster decreases the risk of PHN. Results of studies on vaccination against herpes zoster are promising. Sri Lankan demographics show an increased proportion of ageing which may increase the risk of incidence of herpes zoster and PHN. Preventive strategy with herpes zoster vaccination may be a cost effective option in the future.

References

1. Gauthier A, Breuer J, Carrington D, Martin M, Remy V. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. *Epidemic Infect* 2009; **137**: 38-47.
2. Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population based study on the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc* 2007; **82**: 1341-9.
3. Cunningham AL, Dowrkin RH. The management of post-herpetic neuralgia. *BMJ* 2000; **321**: 778-9.
4. Desmond RA, Weiss HL, Arani RB, et al. Clinical applications for change-point analysis of herpes zoster pain. *J Pain Symptom manage* 2002; **23**: 510-6.
5. Jung BF, Johnson RW, Griffin DR, Dworkin RH. Risk factors for post-herpetic neuralgia in patients with herpes zoster. *Neurology* 2004; **62**: 1545-51.
6. Dworkin RH, Gann JW Jr, Oaklander AL, Raja SN, Schmader KE, Whitley RJ. Diagnosis and assessment of pain associated with herpes zoster and postherpetic neuralgia. *J Pain* 2008; **9**: S37-44.
7. Thyregod HG, Rowbotham MC, Peters M, Possehn J, Berro M, Petersen KL. Natural history of pain following herpes zoster. *Pain* 2007; **128**: 148-56.
8. Yawn BP, Gilden D. The global epidemiology of herpes zoster. *Neurology* 2013; **81**: 928-30.
9. Coen PG, Scott F, leedham-Green M, Nia T, Jamil A, Johnson RW. et al. Predicting and preventing post herpetic neuralgia: are current risk factors useful in clinical practice? *Eur J Pain* 2006; **10**: 695-700.
10. Hempenstall K, Nurmokko TJ, Johnson RW, A'Hern RP, Rice AS. Analgesic therapy in post herpetic neuralgia: a quantitative systematic review. *PLoS med* 2005; **2**: e164.
11. Watson CP, Vernich L, Chipman M, Reed K. Nortriptyline versus amitriptyline in postherpetic neuralgia: A randomised trial. *Neurology* 1998; **51**: 1166-71.
12. Sampathkumar P, Drag LA, Martin DP. Herpes zoster (shingles) and post herpetic neuralgia. *Mayo Clin Proc* 2009; **84**: 274-80.
13. Zin CS, Nissen LM, Smith MT, O' Callaghan JP, Moore BJ. An update on the pharmacological management of post herpetic neuralgia and painful diabetic neuropathy. *CNS Drugs* 2008; **22**: 417-42.
14. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of post-herpetic neuralgia: a randomised controlled trial. *JAMA* 1998; **280**: 1837-42.
15. Sabatowski R, Galvez R, Cherry DA, Jacquot F, Vincent E, Maisonobe P, et al. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain* 2004; **109**: 26-35.
16. Watson CP, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer J. Controlled-release oxycodone relieves neuropathic pain: a randomised controlled trial in painful diabetic neuropathy. *Pain* 2003; **105**: 71-8.

17. Raja SN, Haythornthwaite JA, Pappagallo M, Clark MR, Travison TG, Sabeen S, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomised placebo controlled trial. *Neurology* 2002; **59**: 1015-21.

18. Boureau F, Legallicier P, Kabir-Ahmadi M. Tramadol in post-herpetic neuralgia: a randomised, placebo-controlled trial. *Pain* 2003; **104**: 323-31.

19. Rowbotham MC, Davies PS, Verkempinck C, Galer BS. Lidocaine patch: double blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain* 1996; **65**: 39-44.

20. Galer BS, Jensen MP, Ma T, Davies PS, Rowbotham MC. The lidocaine patch 5% effectively treated all neuropathic pain qualities: results of a randomised, double blind, vehicle controlled, 3 week efficacy study with the use of the neuropathic pain scale. *Cli J Pain* 2002; **18**: 297-301.

21. Kumar V, Krone K, Mathieu A. Neuraxial and sympathetic blocks in herpes zoster and post-herpetic neuralgia: an appraisal of current evidence. *Reg Anesth Pain Med* 2004; **29**: 454-61.

22. Kotani N, Kushikata T, Hashimoto H, Kimura F, Muraoka M, Yodono M et al. Intrathecal methylprednisolone for intractable postherpetic neuralgia. *N Eng J Med* 2000; **343**: 1514-19.

23. Doi K, Nikai T, Sakura S, Saito Y. Intercostal nerve block with 5% tetracaine for chronic pain syndromes. *J Clin Anesth* 2002; **14**: 39-41.

24. Harke H, Gretenkort P, Ladleif HU, Koester P, Rahman S. Spinal cord stimulation in postherpetic neuralgia and in acute herpes zoster pain. *Ants Analg* 2002; **94**: 694-700.

25. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and post-herpetic neuralgia in older patients. *N. Engl. J. Med* 2005: **352**: 2271-84.

26. Schrader K, Oxman MN, Levin M. Persistence of zoster vaccine efficacy. Poster presented at: 48th Annual ICAAC/IDSA 46th Annual Meeting: 2008 Oct 25-28: Washington, DC.

27. Kerzner B, Murray AV, Cheng E, et al. Safety and immunogenicity profile of concomitant administration of Zostavax and inactivated influenza vaccine in adult aged 50 and older. *J Am. Geriatric. Soc*. 2007; **55**: 1499-1507.

28. Summary of Product Characteristics Zostavax, Sanofi Pasteur MSD (2009).

Case report

Basilar invagination due to rheumatoid spondylitis of servical spine

Harsha Gunasekara[1], Subashini Samaraweera[2], Maheshi Wijeratne[3], Wasana Thambawita[4]

Sri Lanka Journal of Neurology, 2015, **4**, 22-23

Introduction

Basilar invagination is a rare congenital or acquired craniocervical junction abnormality where the tip of the odontoid process projects above the foramen magnum. We report a patient with cervical cord compression due to basilar invagination caused by rheumatoid arthritis.

Case report

A 73-year-old female with rheumatoid arthritis developed insidiously progressive difficulty in walking over a year. She noticed weakness of upper limbs and retention of urine 6 months prior to admission. She had an emergency tracheostomy at the age of 64 years following stridor caused by bilateral arytenoid fixation due to rheumatoid arthritis.

There were no cranial nerve abnormalities. She had spastic quadriparesis with predominant left lower limb weakness and was unable to walk unaided. There was no sensory level. She had an indwelling catheter. She had evidence of asymmetrical oligoarthritis with deformities in her right hand.

Her ESR was 52 mm in the 1st hour, CRP, rheumatoid factor titres were normal. Cyclic citrullinated peptide (CCP) antibody titre was raised at 148.2 U/ml (normal range 0-5). CT of the cervical spine showed atlanto-axial subluxation with vertical displacement of the odontoid process leading to basilar invagination (Figure 1, see discussion below). Erosive changes were noted in the odontoid process and apophysial joint at C1/C2. Magnetic Resonance Imaging of the cranio-cervical region showed cervical cord compression at the foramen magnum (Figure 2). There was no evidence of myelomalacia, Klippel-Feil anomaly, syringomyelia or hydrocephalus on neuroimaging. She underwent posterior decompression and occipito-cervical stabilisation with screw fixation at C3-C5 after thorough pre-operative evaluation (Figure 3). Post-operatively, she underwent physiotherapy and was able to be mobilised with minor support.

Discussion

The prevalence of cervical spine involvement in rheumatoid arthritis (rheumatoid spondylitis) ranges from 25% to 80%, depending on the diagnostic criteria

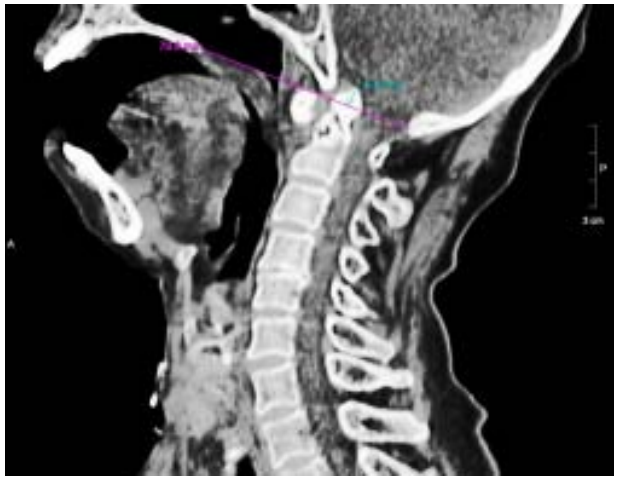


Figure 1. Reconstructed sagittal CT, cranio vertebral region: atlanto-axial subluxation with vertical displacement of the odontoid process 6.8mm above Chamberlain's line.

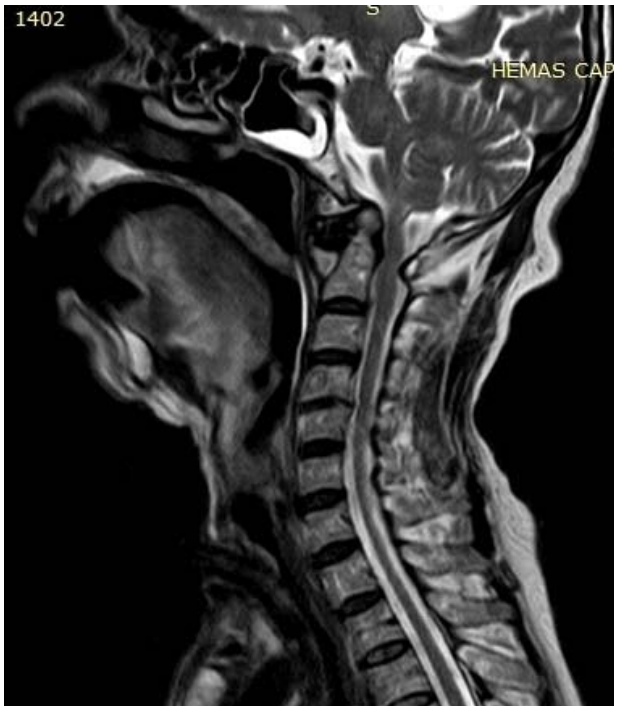


Figure 2. MRI (T2 weighted) of cranio vertebral region: cervical cord compression at foramen magnum.

[1]*Consultant Neurologist,* [2]*Consultant Radiologist,* [3]*Consultant Neurosurgeon,* [4]*Registrar in Radiology, Sri Jayewardenepura General Hospital and Postgraduate Medical Training Centre, Nugegoda, Sri Lanka.*

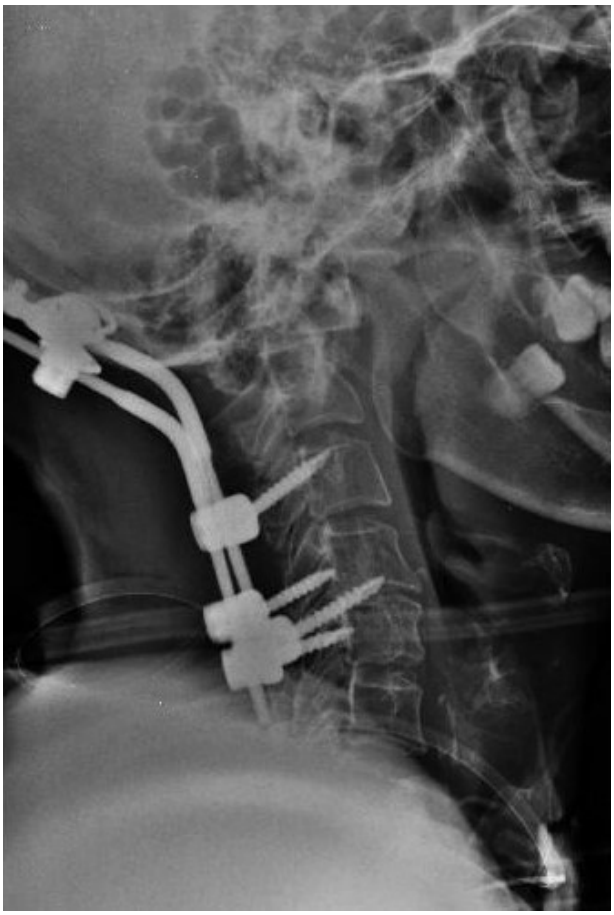


Figure 3. Lateral radiograph of cervical spine: occipito-cervical stabilisation with screw fixation at C3 to C5 levels.

applied[1]. However, only 7-34% of patients with rheumatoid arthritis have a neurologic deficit. The three major abnormalities which cause neurologic deficit include atlanto-axial subluxation (49%), basilar invagination (38%) and sub-axial subluxation (10-20%). Basilar invagination (also referred to as basilar impression, superior migration of the odontoid or cranial settling) is attributed to erosion and bone loss in the occipito-atlantal and atlanto-axial joints[2].

Radiological evidence of rheumatoid spondylitis may be present in asymptomatic patients. Compression of C2 sensory fibres can present with pain in the face or ear or as occipital neuralgia. Progressive radiculo-myelopathy and/or medullar compression may occur in advanced stages of the disease.

Diagnosis is established by demonstration of the odontoid tip at an abnormally higher level on plain radiography or CT of cervical spine. Usually the odontoid tip lies at or below a line extending from the posterior margin of the hard palate to the posterior edge of the foramen magnum (Chamberlain's line). Basilar invagination is generally considered present if the elevation is greater than 5 mm[3,4]. In this patient the odontoid tip was 6.8 mm above the Chamberlain's line (Figure 2). MRI of brain and cranio-cervical region is required to confirm/exclude cervical cord and brain stem compression.

Surgical intervention is indicated especially in the presence of neurological impairment or with radiological changes alone to prevent neurological disability. Cervical traction is sometimes used pre-operatively. If basilar invagination is reducible, it may be possible to treat with a posterior-only surgical approach, including decompression and fusion. Basilar invagination that is not reducible is treated with anterior decompression followed by posterior occipito-cervical stabilization[4,5]. Cervical traction was not used in this patient pre-operatively and anterior approach was avoided as she had a tracheostomy in situ.

Cervical spine involvement in rheumatoid arthritis should be diagnosed and treated as early as possible to minimize preventable morbidity. However, diagnosis at an advanced stage should not preclude consideration of surgical treatment, as surgical intervention has shown to improve function and preserve life even in severe grades of myelopathy[3].

References

1. Rajangam K, Thomas IM. Frequency of cervical spine involvement in rheumatoid arthritis. *J Indian Med Assoc.* 1995; **93**(4): 138-9, 137.
2. da Corte FC, Neves N. Cervical spine instability in rheumatoid arthritis. *Eur J Orthop Surg Traumatol* 2014; **24** Suppl 1: S83-S91.
3. Mukerji N, Todd NV. Cervical Myelopathy in Rheumatoid Arthritis. *Neurology Research International* 2011; **7**: 1-7.
4. Smith JS, Shaffrey CI, Abel MF, Menezes AF. Basilar Invagination. *Neurosurgery* 2010; **66**: A39-47.
5. Gillick JL, Wainwright J, and Das K. Rheumatoid Arthritis and the Cervical Spine: A Review on the Role of Surgery. *International Journal of Rheumatology* 2015; Article ID 252456: 12 pages.

Case report

Myeloneuropathy caused by nitrous oxide toxicity

D S Liyanage[1], L Flores[2], F Norwood[3]

Sri Lanka Journal of Neurology, 2015, **4**, 24-26

Keywords: myelopathy, peripheral neuropathy, nitrous oxide toxicity

Introduction

Nitrous oxide (N_2O) is a nonflammable gas with a sweet taste and odor which was first synthesized by English natural philosopher and chemist Joseph Priestley in 1772. It is used as an inhaled anesthetic and analgesic agent in medicine and dentistry. It is also used as a propellant in food industry (eg. in the whipped cream dispensers), nitrating agent for alkali metals and as a component in rocket fuel[1]. Abuse of nitrous oxide might cause significant neurological disability. The mechanism of N_2O neurotoxicity is the interference with vitamin B_{12} bioavailability and the resulting neurological syndromes are indistinguishable from vitamin B_{12} deficiency due to malabsorption or low dietary intake. We present a case of a young male who presented to a tertiary care center in London, United Kingdom with clinical, radiological and biochemical features of N_2O abuse.

Case report

A 26-year-old Afro Caribbean male presented with two week history of paraesthesiae – 'pins and needles' affecting both his lower limbs. He had been previously well without any medical comorbidities and paraesthesia started from soles of both legs two weeks prior to the admission which gradually progressed to up to knees. Two days before the admission his hands got involved. There were no pain, weakness or bladder / bowel involvement. Interestingly he was experiencing electric shock like sensation travelling through his limbs on bending of the neck for uncertain duration. Symptoms such as visual loss, double vision, vertigo, slurred speech or difficulty in swallowing were absent. Apart from that there were no joint pain, swelling, rashes or photosensitivity. He did not recall any recent chest infection or diarrhoeal illness. Family members were free of any neurological disorders. He worked as a customer care officer in a private establishment and had been using alcohol infrequently. He denied any substance or recreational drug abuse.

Neurological examination revealed normal mental state, speech and cranial nerves. Muscle power in limbs were normal. On sensory examination pain, joint position and vibration position was absent upto ankle joint. He had global hyporeflexia and plantar responses were flexor. However Romberg's test was negative. He was able to walk unaided but the gait was unsteady.

Initial haematological and biochemical parameters were within normal range including full blood count (FBC), inflammatory markers, random blood sugar, HbA1c, renal profile, liver profile and thyroid profile. However his vitamin B_{12} was marginally low (167 ng / L (180 – 1100)) with raised methylmalonic acid – 3800 nmol / L (0 – 280 nmol / L) and homocysteine -26.4 mic.mol / L (< 15 mic.mol /L). Magnetic resonance imaging (MRI) of spine demonstrated T2 signal hyperintensity extending from C1 to T2 vertebral segments (Figure 1). They were more prominent on posterior part of the cord on axial views (Figure 2). There was no cord swelling or enhancement with gadolinium. MRI brain was normal. Lumbar puncture had normal manometry and cerebrospinal fluid (CSF) analysis showed normal proteins, glucose and no cellular reaction. Nerve conduction studies (NCS) demonstrated moderately severe axonal type sensory neuropathy without any significant motor axon loss. He had a normal serum copper, negative autoantibodies (Anti-Nuclear Antibodies (ANA), Anti Neutrophil Cytoplasmic Antibodies (ANCA), antibodies to Extractable Nuclear Antigens (ENA), Anti Parietal Cell Antibodies, Anti Tissue Transglutaminase Antibodies and was negative for HIV, syphilis and hepatitis serology.

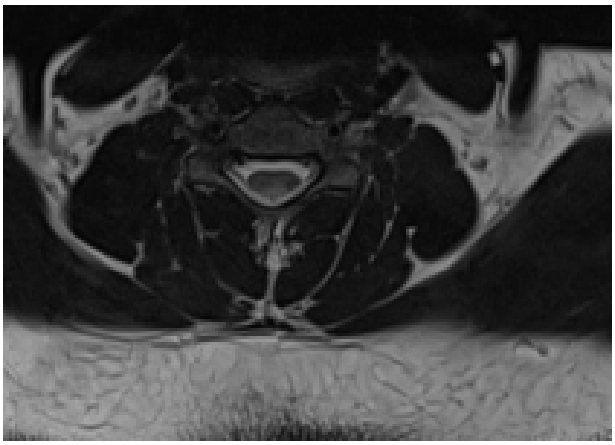


Figure 1. MRI Spine (Sagittal section). T2 hyperintensities extending from C1 to T2 vertebral segments.

[1,2]*Registrar in Neurology,* [3]*Consultant Neurologist, Kings College Hospital, London, United Kingdom.*

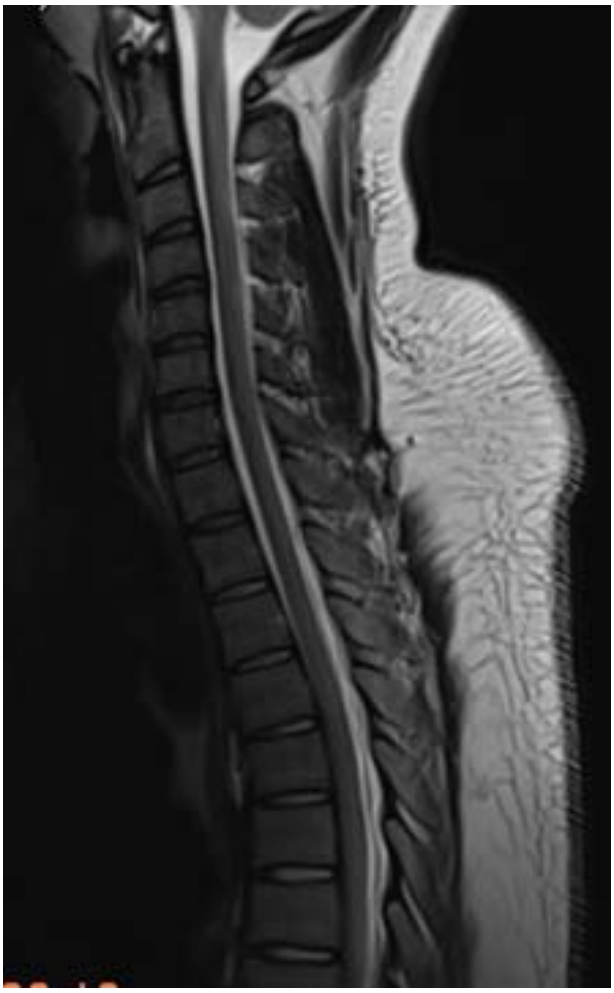


Figure 2. MRI Spine (Axial section). T2 hyperintensities mostly affecting posterior columns of spinal cord.

During hospital stay his symptoms progressed with numbness extending upto buttocks and inguinal region, loss of vibration upto knee and development of faecal incontinence and urinary urgency. Once the vitamin B_{12} deficiency was confirmed, he was started on intramuscular vitamin B_{12} replacement. At this stage he revealed the fact that he had been abusing nitrous oxide (N_2O) every weekend for 2 years. This varied from 2 to 200 canisters per weekend. Finally the diagnosis of myeloneuropathy secondary to nitrous oxide toxicity was made.

Discussion

Nitrous oxide (N_2O) is also known as "laughing gas" due to the euphoric effects of inhaling it, a property that has led to its recreational use as a dissociative anaesthetic since 1800s. Even though N_2O abuse is uncommon in Sri Lanka, it is not the case in western countries. Its misuse was previously largely restricted to and widespread among medical professionals (a survey in 1979 reported that 20% of medical and dental students used it recreationally). However for the last two to three decades it has gained popularity in clubs, parties and music festivals. The 2012 Global Drug Survey – an international online survey of drug use in mainly young adults with over 22000 respondents – reported that almost half of UK respondents had used nitrous oxide recreationally at some point. This is in large part due to its free availability in nightclubs and low cost in the form of 'whippits' (aerosol chamber used in canisters of whipped cream). As reported by Advisory Council on the Misuse of Drugs (ACMD) in the UK, the most common method of inhalation among 2014 users was from a balloon (94%), followed by whipped cream dispensers (5%)[2].

The toxic effects of nitrous oxide are mediated through oxidation of cobalt ions in vitamin B_{12} making it inactive – impaired vitamin B_{12} bioavailability[3]. This inhibits the conversion of homocysteine to methionine, which is needed for methylation of myelin proteins, causing demyelination of central and peripheral nervous system. This reaction is necessary for the production of tetrahydrofolate (which is essential for DNA synthesis) as well. Apart from that vitamin B_{12} is necessary for the conversion of methylmalonyl CoA to succinyl CoA. Because of these two vitamin B_{12} dependent pathways, impaired metabolism of that causes elevation of methylmalonic acid and homocysteine. Resulting neurological syndromes (subacute combined degeneration of cord, peripheral neuropathy, cognitive decline, optic atrophy and psychiatric manifestations such as depression and anxiety) are indistinguishable from B_{12} deficiency caused by malabsorption or low dietary intake[3]. Diagnosing nitrous oxide induced neurological disease may be difficult if the patient does not disclose inhalational activity or the examiner fails to inquire about it. Elevated serum concentrations of Methylmalonic Acid (MMA) or Homocysteine may be the only clues as vitamin B_{12} can be normal. There is no correlation between haematological (megaloblastic anaemia, elevated mean corpuscular volume (MCV)) and neurological features.

Our patient presented with clinical features compatible with subacute peripheral neuropathy (glove and stocking type sensory symptoms and signs, hyporeflexia). Apart from that he had evidence of myelopathy – positive Lhermitte's and sphincter disturbance. This was confirmed by nerve conduction studies (NCS) and MRI of spine which demonstrated axonal type sensory neuropathy and T2 high signal intensities extending throughout the cervical cord (features compatible with subacute combined

degeneration of cord) respectively. Vitamin B_{12} levels were reduced and the homocysteine and methylmalonic acid levels were raised pointing towards abnormality in vitamin B_{12} metabolism. Initially he didn't disclose his inhalational activity which made some delays in definitive diagnosis.

In the literature there are numerous case reports of myeloneuropathy caused by N_2O abuse or occupational exposure (as that is used as anaesthetic agent and analgesic in medicine and dentistry). One of the first cases was of a patient inhaling whipped cream propellant although the authors did not associate N_2O toxicity with disturbed vitamin B_{12} metabolism[4]. Treatment of nitrous oxide induced neurotoxicity is abstaining from the exposure and high dose vitamin B_{12} replacement. There is limited evidence that replacing methionine also helps[2,5]. Methylmalonic acid and homocysteine levels return to normal after starting vitamin B_{12} replacement. Recovery may be slow and incomplete – depending on the extent of damage. This case highlights an important cause of potentially avoidable cause of neurological disability.

Competing Interests

The authors declare that they have no competing interests.

References

1. Van Amsterdam J, Nabben T, van den Brink W. Recreational nitrous oxide: Prevalence and risks. *Regulatory Toxicology and Pharmacology* 2015. http://dx.doi.org/10.1016/j.yrtph.2015.10.017
2. Thompson AG, Leite MI, Lunn MP, Bennett DL. Whippits, nitrous oxide and the dangers of legal highs. *Practical Neurology* 2015; **15**: 207-9.
3. Waclawik AJ, Luzzio CC, Juhasz-Pocsine K, Hamilton V. Myeloneuropathy from nitrous oxide abuse: Unusually high methylmalonic acid and homocysteine levels. *Wisconsin Medical Journal* 2003; **102**: 43-5.
4. Sahenk Z, Mendell JR, Gouri D, Nachtman J. Polyneuropathy from inhalation of N_2O cartridges through a whipped cream dispenser. *Neurology* 1978; **28**: 485-7.
5. Pema PJ, Horak HA, Wyatt RH. Myelopathy caused by nitrous oxide toxicity. *Am J Neuroradiol* 1998; **19**: 894-6.

Case report

Cockayne syndrome: picture story

M N P Perera[1], J Wanigasinghe[2]

Sri Lanka Journal of Neurology, 2015, **4**, 27-29

Introduction

Cockayne syndrome is a rare autosomal recessive neurodegenerative disorder with multisystem involvement, described by Edward Alfred Cockayne in 1936[1]. It is caused by a defect in DNA repair system. There are two gene mutations reported; *ERCC6* in 65% of individuals and *ERCC8* in 35%. It is characterized by progeria, cachectic dwarfism, progressive intellectual disability with leukodystrophy, photosensivity, sensorineural deafness and progressive pigmentary retinopathy[2].

We report a 12-year-old boy diagnosed with this rare syndrome, based on clinical, ophthalmological and radiological features.

Case report

A 12-year-old male child was evaluated for progressive difficulty in walking due to unsteadiness. He is the third child of second degree consanguineous parents with unremarkable family history of any neurological disorder. Antenatal, birth and neonatal history were uneventful. However, his birth weight was only 1.8 kg. Since birth his growth was significantly affected in spite of normal nutrition and absence of any systemic illness. His development was globally affected since birth; only mildly initially. The signs of unsteadiness of gait with tremor around 6 years of life were the first clinical signs noticed by the parents. This progressively worsened over the years with significant impairment of manual functions such as feeding and writing due to the tremor. Later he was noted to have a dysarthria. Appearance of lentigines over the sun exposed areas of his face was noted around 6 years which also gradually increased in number. Though he commenced school in main stream he had to be moved to special education.

He presented to us at 12 years, at which point appeared as a progeric and examination revealed a cachectic dwarf. All his growth parameters were well below third centile. The examination of face revealed a small skull with large sunken eyes, a beaked nose, large prominent ears, relatively small mandible, dental crowding, evidence of cutaneous photosensitivity and dry scaly skin with facial lentigenes (Figure 1). His neurological examination revealed cerebellar signs. He was hypotonic with muscle power of grade 4 and normal reflexes. His cognitive function at current age of 12 years was compatible to that of 6 years according to the TONI 3 (Test of nonverbal intelligence). Eye examination revealed a pigmentary retinopathy, bilateral pale discs, poorly defined fovea ([Figure 2) and a refractive error. Other system examination was normal.

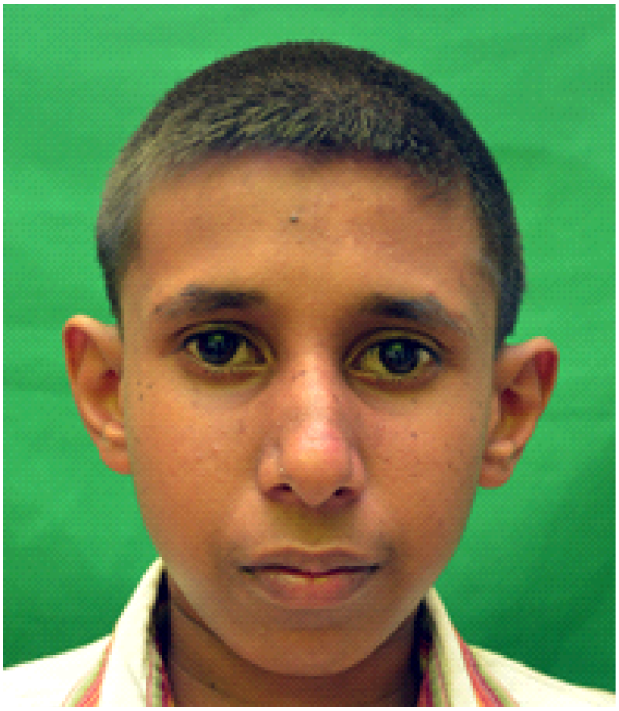


Figure 1. Characteristic facial appearence

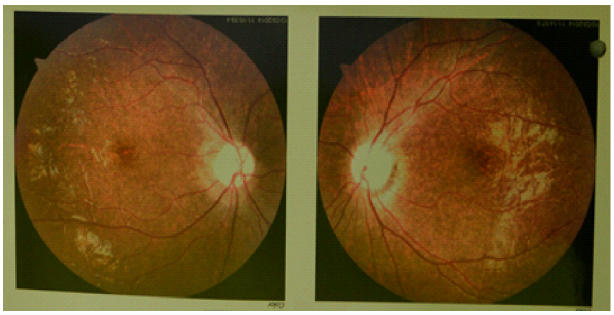


Figure 2. Fundal photograph showing pigmentary retinopathy

[1]*Lady Ridgeway Hospital for Children, Colombo,* [2]*University of Colombo, Sri Lanka.*

Basic investigation revealed elevated liver enzymes with normal fasting blood sugar and renal functions. Computerized tomography (CT) showed evidence of bilateral basal ganglia calcification ([Figure 3) and his magnetic resonance imaging (MRI) brain showed evidence of early leukodystrophy characterized by T2 and flair hyperintensities in the white matter and cerebral and cerebellar atrophy (Figure 4). Audiogram and renal ultra-sonogram were normal.

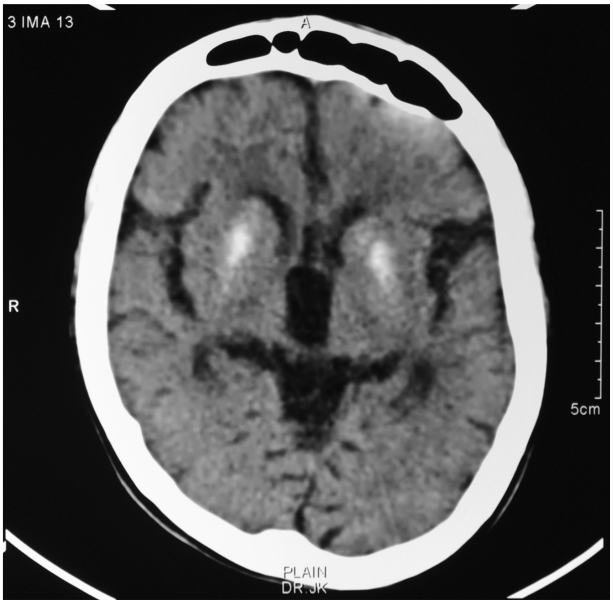


Figure 3. CT showing bilateral basal ganglia calcification

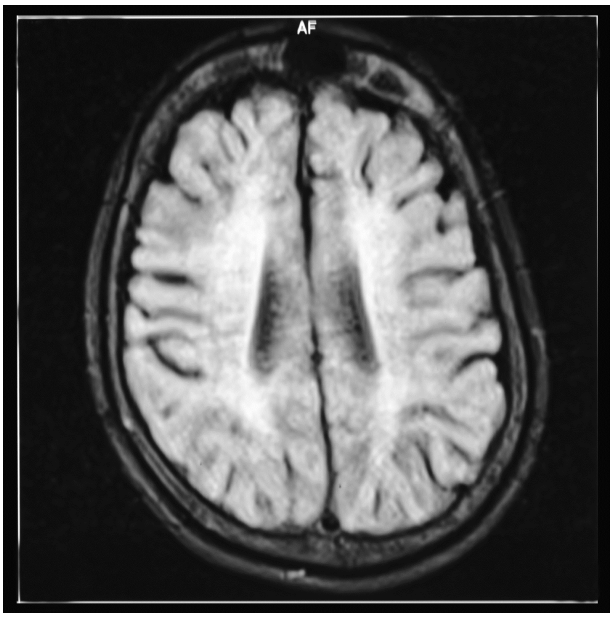


Figure 4. MRI T2 flair showing leucodystrophy

Discussion

Cockayne syndrome is a rare condition with a variable age of onset and rate of progression[2]. The degeneration begins in the second or third year of life. The mean age of death in reported cases is 12 years and three months[5]. The phenotypic spectrum of Cockayne syndrome can be divided into four general clinical presentations: Type 1 (intermediate/ classic form), Type 2 (severe early onset form), Type 3 (mild/ atypical form) and Type 4 (adult form)[6]. CS type I which is characterized by postnatal growth failure with early developmental delay, followed by progressive behavioral and intellectual deterioration is the most likely spectrum in this child. Premature aging is the cardinal feature and is due to defect in DNA repair system. Characteristic cutaneous findings include photosensitivity, thin skin, dry scaly skin and thin dry hair. Ophthalmologic changes are pigmentary degeneration of the retina (pepper and salt appearance); the hallmark of the disease and cataracts, optic atrophy or optic disk pallor[2,6]. Most patients have mild to moderate sensory neural hearing loss.

Neurocognitive decline with variable onset is due to pericapillary calcifications in the cortex and basal ganglia at an early age, severe neuronal loss in the cerebral cortex and cerebellum, leukodystrophy and demyelinating neuropathy[4,6]. These changes correlate with the physiologic changes of aging. Characteristic neurological findings are increased or decreased muscle tone and reflexes, unusual gait resulting from leg spasticity, ataxia, and contractures of the hips, knees, and ankles.

Less frequently found symptoms in Cockayne syndrome include major structural anomalies of the renal system, cryptorchidism or testicular hypoplasia, delayed puberty, irregular menstrual cycles, arteriosclerotic disease, hepatomegaly and hypertension. Our patient did not have any of these.

There is no definite treatment for Cockayne syndrome[6,2]. However, physical therapies, sunscreen, avoiding excessive sun exposure, hearing aid, visual aid, gastrostomy tube feeding, psychological therapy and genetic counseling are some important aspects in the management.

Conclusion

The characteristic facial features, cachectic progeric dwarfism, microcephaly, intellectual disability, cerebellar signs, photosensitivity, pigmentary retinopathy, characteristic CT and MRI findings lead us to the diagnosis of Cockayne syndrome in this child.

References

1. Cockayne EA. Dwarfism with retinal atrophy and deafness. *Arch Dis Child* 1936; **11**: 143-8.
2. Vincent L. Cockayne syndrome. Gene Review 2012. http://www.ncbi.nlm.nih.gov/books/NBK1342/
3. Kleijer WJ, Laugel V, Berneburg M, et al. Incidence of DNA repair deficiency disorders in Western Europe: Xeroderma-pigmentosum, Cockayne syndrome and trichothiodystrophy. *DNA Repair (Amst)* 2008; **7**: 744-50.
4. Joshi RM, Kallapur SG, Gandhi RK, et al. Cockayne syndrome (a case report). *J Postgrad Med* 1987; **33**: 43-4.
5. Nance MA, Berry SA. Cockayne syndrome: review of 140 cases. *Am J Med Genet* 1992: **42**: 68-84.
6. Cockayne syndrome. The Swedish information Centre for Rare Disease. 2012. https://www.socialstyrelsen.se/rarediseases/cockaynesyndrome

Case report

Mucormycosis – deadly disease and deadly treatment

P Weeratunga[1], G Rathnayake[1], T Chang[1,2]

Sri Lanka Journal of Neurology, 2015, **4**, 30-31

Introduction

Mucormycosis is an emerging angioinvasive mycosis caused by the filamentous fungi of the Mucorales order of the class of Zygomycetes. The clinical spectrum extends from cutaneous infection to rhinocerebral, and sino-pulmonary to frequently fatal disseminated infections, especially in immunocompromised hosts. Life-saving measures include surgical debridement, high-dose amphotericin B and treatment of the underlying immuno-deficiency. Amphotericin B is the most effective antifungal therapy for mucormycosis, but has potentially fatal adverse effects. We report a patient with rhinocerebral mucormycosis who unexpectedly died while improving on treatment to highlight the potentially fatal adverse effects of amphotericin B.

Case report

A 60-year-old man with type 2 diabetes mellitus and hypertension for 10 years complicated with non-proliferative diabetic retinopathy and diabetic nephro-pathy, presented with left-sided facial paralysis of 6 hours duration. He had developed dull intermittent left-sided maxillary and temporal facial pain and numbness associated with malaise and anorexia one month prior to presentation. There was no history of fever, family or contact history of tuberculosis. His past glycaemic control was poor.

On examination, he was noted to have a partial 3rd nerve palsy with mild pupillary dilatation, a lower motor neuron facial nerve palsy, and a palatal palsy on the left. Sensory loss was demonstrable in the left trigeminal territory with involvement of the ophthalmic, maxillary and mandibular divisions. Optic fundi showed evidence of non-proliferative diabetic retinopathy. Rest of the systems and general examination was unremarkable. His pulse rate was regular and blood pressure was 170/90 mmHg. After admission to hospital the patient developed 6th and 8th nerve palsies on the left while the initial 3rd, 5th and 7th nerve palsies worsened.

His white cell count was 16,900/cumm with 80% neutrophils. Inflammatory markers were elevated with an ESR of 136 mm/h and a CRP of 96 mg/dl. Renal and liver function tests were normal. Non-contrast enchanced cranial computerized tomography scan was normal apart for opacities in the left ethmoid and maxillary sinuses. Cerebrospinal fluid analysis was normal. Gadolinium-enhanced magnetic resonance imaging of the brain demonstrated contrast enhancing invasive lesions in the left ethmoid and maxillary sinuses eroding into the surrounding bones (Figure 1). Nasal endoscopy found significant debris in the left ethmoidal sinus and gram stain was positive for fungal hyphae.

The patient underwent surgical debridement of the left ethmoid and maxillary sinuses and was commenced on amphotericin B. Over the next days to weeks, the patient demonstrated progressive clinical improvement with resolution of cranial nerve palsies, return of appetite and feeling generally well. During the course of treatment with amphotericin B, the patient developed a transient rise in serum creatinine, which stabilized with adequate hydration and conversion to amphotericin B lipid complex preparation. The serum potassium level remained normal and there was no evidence of renal tubular acidosis. However, he developed hypomagnesaemia with a serum magnesium level of 0.5 mmol/l (reference range 0.7-1.5mmol/l), which was corrected with intravenous magnesium sulphate. Serum magnesium and calcium levels were tested every third day of amphotericin B treatment. However, this monitoring could not be con-tinued in the third week of treatment due to the unavailability of reagents. Despite neurological and general improvement, the patient developed torsades de pointes and subsequent refractory monomorphic ventricular tachycardia and died 21 days after com-mencing amphotericin B.

Discussion

We describe a patient with mucormycosis who made a good recovery due to early diagnosis and initiation of appropriate treatment, but died possibly as a result of amphotericin B (AmB) related toxicity.

Although AmB is the only pharmacological pre-paration licensed for the management of mucormycosis it has an unfavorable adverse effect profile, including infusion related adverse effects and renal toxicity. The spectrum of renal toxicity encompasses acute kidney injury, interstitial nephritis, renal potassium and magnesium wasting and renal tubular acidosis. Cardiac toxicity with ventricular arrhythmias and bradycardia is reported in adults with preexisting cardiac disease,

[1]*University Medical Unit, National Hospital of Sri Lanka,* [1,2]*Department of Clinical Medicine, Faculty of Medicine, University of Colombo, Sri Lanka.*

even when administered in conventional dosages and infusion rates. Reports of arrhythmias in patients with normal concentration of potassium and magnesium who were given AmB intravenously suggest that it may be directly cardiotoxic[1]. Nephrotoxicity is notably low with the lipid formulations of AmB[2].

Our patient had extensive sinus disease with cranial nerve involvement and diabetes as poor prognostic features, but had an initial good recovery with surgical intervention and AmB therapy. Nephrotoxicity was noted with AmB but was non-progressive with the use of the lipid complex preparation of AmB. Hypomagnesaemia associated with AmB therapy is common by the second week of therapy and maximal by the fourth week of treatment with AmB. The hypomagnesemia is usually mild, but a severe decrease in plasma magnesium levels requiring magnesium supplements may develop in some patients[3]. It is curious that our patient developed significant hypomagnesemia relatively early during therapy. The fatal complication of refractory ventricular arrhythmia and torsades de pointes are postulated to have occurred as a consequence of hypomagnesemia as well as the direct cardiotoxic effect of the drug. Inability to measure magnesium levels as recommended during treatment due to resource limitation is likely to have contributed to the mortality of this patient.

Mucormycosis is potentially fatal, especially in patients with disseminated disease and in those with central nervous system involvement. Recent estimates of mortality range from 44 -80% (4-6) with variation noted based on the extent of involvement, comorbidities and duration of response to therapy. Factors such as prolonged neutropenia or underlying hematological malignancy are also noted to predispose to mortality[7]. Furthermore, the disease is gaining increasing significance especially in the developing world due to its predilection in patients with diabetes mellitus. Data from a study in a tertiary care center in India demonstrate that 74% of patients with mucormycosis had uncontrolled diabetes[8]. The noted mortality of the disease among patients with diabetes mellitus is 40% with 80% of deaths occurring in low- to middle-income populations[9].

Conclusions

Mucormycosis is a disease with high mortality but the drug treatment of the disease is equally deadly as highlighted in our case. The need for stringent cardiometabolic monitoring during treatment with amphotericin B cannot be more emphasized.

References

1. Burke D, Lal R, Finkel KW, et al. Acute amphotericin B overdose. *Ann Pharmacother* 2006; **40**: 2254-9.
2. Luber AD, Maa L, Lam M, Guglielmo BJ. Risk factors for amphotericin B induced nephrotoxicity. *J Antimicrob Chemother* 1999; **43**: 267-71.
3. Barton CH, Palh M, Vaziri ND, Cesario T. Renal magnesium wasting associated with amphotericin B therapy. *Am J Med* 1984; **77**: 471-4.
4. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis.* 2005; **41**: 634-53.
5. Spellberg B, Kontoyiannis DP, Fredricks D, et al. Risk factors for mortality in patients with mucormycosis. *Med Mycol.* 2012; **50**: 611-8.
6. Lanternier F, Dannaoui E, Morizot G, et al. French Mycosis Study Group. A global analysis of mucormycosis in France: the RetroZygo Study (2005-2007) *Clin Infect* Dis. 2012; **54** (Suppl 1): S35-S43.
7. Singh N, Aguado JM, Bonatti H, et al. Zygomycosis in solid organ transplant recipients: a prospective, matched case-control study to assess risks for disease and outcome. *J Infect Dis.* 2009; **200**: 1002-11.
8. Chakrabarti A, Das A, Mandal J, et al. The rising trend of invasive mucormycosis in patients with uncontrolled diabetes mellitus. *Med Mycol.* 2006; **44**: 335-42.
9. Arce-Salinas CA, Pe´rez-Silva E. Mucormycosis complications in systemic lupus erythematosus. *Lupus* 2010; **19**: 985-8.

Case report

Zellweger syndrome

M N P Perera[1], P D Rathnayaka[1], E A Jasinge[1], S K Arulmoli[2]

Sri Lanka Journal of Neurology, 2015, **4**, 32-33

Introduction

Zellweger syndrome, also known as "cerebro-hepato-renal syndrome" is the most severe and common peroxisomal disorder which presents in the neonatal period with multisystem involvement[1]. It is a rare inherited disorder and estimated incidence is 1 in 50 000 to 100000 live births[1]. We present the first reported case of Zellweger syndrome in Sri Lanka.

Case report

A 10-month-old male child with global developmental delay, seizures and facial dysmorphism was admitted to the neurology unit for further evaluation and management. He was the only child of second degree consanguineous parents with unremarkable family history of neurological disorder. His antenatal and perinatal periods were uncomplicated except for a transient period of poor sucking and lethargy. Since birth, he exhibited significant developmental delay and at 10 months of age his development age was 6/52. He had been having myoclonic seizures from 6/52 of age.

His growth parameters were well below the third centile and he exhibited distinctive facial features including flat face, high forehead, wide anterior fontanelle, broad nasal bridge, micrognathia, high arched palate and flat occiput. He had nystagmoid eye movement and significant hypotonia with reduced reflexes. Systemic examination revealed hepatomegaly.

A clinical diagnosis of Zellweger syndrome was made and further supported by presence of bilateral profound sensorineural deafness, renal cyst, acetabular dysplasia, gross EEG (electro encephalogram) abnormality (Figure 1) and cerebral hypomyelination. Elevated blood levels of very long chain fatty acids confirmed the diagnosis (Table 1).

Table 1. Plasma – very long chain fatty acid

	Patient results ugm/ml	Normal controls ugm/ml	Zellwager ugm/ml
C26:0	1.43	0.23+/-0.09	1.0+/-1.5
C24/C22	0.73	0.84+/-0.10	2.07+/-0.28
C26/C22	0.21	0.01+/-0.004	0.5+/-0.16

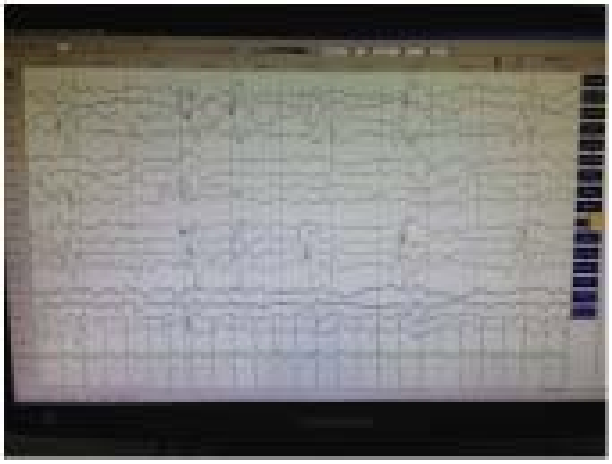


Figure 1. EEG showing poorly formed background with multifocal epileptiform activity

Discussion

Zellweger syndrome was first described in 1964 by Ulrich Zellweger a Swiss-American professor of pediatrics and genetics[2]. Itis the most severe form of peroxisome biogenesis disorders (PBDs) which are characterized by the failure of the body to produce functional peroxisomes which play a vital role in numerous biochemical processes in the body, especially in the beta oxidation of very long chain fatty acids (VLCFAs)[1,3]. Peroxisomal dysfunction and the resultant derangement in metabolism result in a multisystem disorder which mainly affects the brain, liver and kidneys. Zellweger syndrome is a lethal disease and survival beyond one year is unusual. Diagnosis could be made based on clinical, biochemical, radiological, histological and genetic studies.

Characteristic dysmorphism of Zellweger syndrome includes flat face, high forehead, large fontanelles, broad nasal bridge, small nose with anteverted nares, micrognathia, high arched palate, extra folds of skin on the neck, shallow bony ridges of the eye socket and flat occiput[1]. They develop a spectrum of neurological complications: frequent seizures, profound hypotonia, poor or absent reflexes, mental retardation and developmental delay. Among them profound hypotonia is characteristic and acts as a guide towards the diagnosis[3]. In addition, diagnosis is supported by a variety of eye abnormalities

[1]*Lady Ridgeway Hospital for Children, Colombo,* [2]*Teaching Hospital, Jaffna, Sri Lanka.*

(hyperteleorism, cataracts, corneal opacities, optic atrophy, nystagmus, glaucoma) hearing loss, splenomegaly and hepatomegaly[1]. Minor skeletal abnormalities like clubfoot and camptodactyly and certain heart defects such as septal defects and patent ductus arteriosus have been reported[1]. Our patient had many of these clinical features which assisted us in the diagnosis.

Radiological evaluation gives further supportive evidences to arrive at the diagnosis. Neuronal migration defects and cerebral hypomyelination are highly suggestive of Zellweger syndrome[1,3]. For example, all the 6 Zellweger syndrome cases reported by James and Wallace (1997) had impaired myelination, diffusely abnormal cortical gyral patterns and germinolytic cysts in the caudothalamic groove[4]. X ray can be used to identify characteristic chondrodysplasia punctata and acetabular dysplasia[1,3]. In addition, routine abdominal ultrasound shows renal cysts in 70% of cases[5]. The radiological features seen in our patient were acetabular dysplasia, isolated renal cyst and cerebral hypomyelination.

Microscopic evidence of reduction in number of peroxisomes on hepatic and renal biopsy helps to arrive at the diagnosis[6]. However, the most commonly used and most informative initial screen test is the measurement of VLCFA concentrations in plasma[7]. Elevation of C26:0 and C26:1 and the ratios C24/C22 and C26/C22 are consistent with a defect in peroxisomal fatty acid[3].

Definitive diagnosis is based on genetic studies. Zellweger syndrome is an autosomal recessive disorder that is caused by mutation in anyone of 13 genes, termed PEX genes that encode peroxins which are proteins required for the normal peroxisome assembly. A majority of the patients exhibit either a mutation in PEX1 or PEX6[3] gene. We were not able to perform genetic studies in the described patient due to limited access and cost factors.

Conclusion

Etiological diagnosis of development delay is a tedious process as the differential diagnosis is extremely wide. Diagnosis is important for possible therapeutic intervention and genetic counselling. Careful clinical evaluation will help in directing investigations. Characteristic facial appearance, profound hypotonia, nystagmoid eye movements and hepatomegaly of described patient point towards the diagnosis of Zellweger spectrum disorder.

References

1. Zellweger Spectrum disorders. National Organization of Rare disorders. 2008.http://rarediseases.org/https://rarediseases.org/rare-diseases/zellweger-spectrum-disorders/

2. Bowen P, Lee CSN, Zellweger H, et al. A familial syndrome of multiple congenital defects. *Bull Johns Hopkins Hosp* 1964; **114**: 402-14.

3. Steinberg SJ, Raymond GV, Braverman NE, et al. Peroxisome Biogenesis Disorders, Zellweger Syndrome Spectrum. GeneReviews.2012.http://www.ncbi.nlm.nih.gov/books/NBK1448/

4. James A, Wallace W. MRI of Zellweger Syndrome. *AJNR Am J Neuroradiol* 1997; **18**: 1163-70.

5. Abdelmoneim EM. Zellweger syndrome: cause of neonatal hypotonia and seizures. *Journal of Paediatrics* 2011; **11**: 54-8.

6. Wolter JM, Koert PD, Marius AV, et al. Ultrastructure of the Liver in the Cerebro Hepato Renal Syndrome of Zellweger. *Ultrastruct Pathol* 1983; **5**: 135-44.

Case report

Isolated sphenoidal fungal sinusitis in a patient with ulcerative colitis on steroids

D D K Abeyaratne[1], K A S Bandara[1], C Liyanapathirana[1], M G C P Marasinghe[1], S B Gunatilake[1]

Sri Lanka Journal of Neurology, 2015, **4**, 34-35

Background

Isolated sphenoid sinus lesions are rare, and account for 1-2.7% of all paranasal sinus lesions[1]. These lesions are sphenoid cyst, sphenoid sinusitis, fungal disease, inverted papilloma, sphenochoanal polyp, foreign body, malignant tumors. Isolated sphenoidal sinusitis can be bacterial or fungal and the incidence of fungal infection is about 25-30% of all and this is categorized as non-invasive, invasive indolent and fulminant[2]. Noninvasive fungal sinusitis usually involves only one sinus and out of all para-nasal sinuses, commonest to be involved is the maxillary sinus and the commonest organism being aspergillus[3]. Isolated sphenoidal sinus fungal disease is rare as a result of the unfavorable anatomic location of the sphenoids and decreased nasal airflow in that region[4]. This disease is more common in immune-compromised patients, but there are cases reported in immune-competent individuals as well[5].

Since isolated sphenoidal fungal sinusitis is rare, and also because it presents with a range of non specific symptoms, such as headache, visual symptoms or cranial nerve palsies, the diagnosis can be easily missed if not for a higher degree of suspicion. The diagnosis of isolated sphenoidal fungal sinusitis usually requires advanced imaging because, nasal endoscopy and sinus X-ray can be normal in these patients. Due to all these reasons, the literature reveals, that the diagnosis of fungal sinusitis in sphenoid sinus is often delayed, where the patients suffer for years with headache or deteriorate with complications.

We report a case of isolated sphenoidal sinus fungal sinusitis, in a patient with ulcerative colitis in remission, presenting with severe unilateral headache and facial numbness leading to a diagnostic dilemma in the initial stage. This elaborates the importance of a high degree of suspicion of this rare disease in this type of a clinical presentation, to image early and prevent further serious complications.

Case presentation

A 43-year-old female presented with a severe unbearable right frontal headache for two weeks duration. It had been persistent and progressive, associated with right orbital pain and facial numbness. She complained of photophobia, and the headache was not associated with tearing or vomiting. The pain did not resolve with simple conventional analgesics. She had no similar episodes in the past. She had no features suggestive of sinusitis such as nasal blockage, discharge or a history of sinusitis. In hospital she continued to have episodic excruciating right sided headache, with a persistent background dull headache. She had been diagnosed with ulcerative colitis 10 yrs back, now in remission and also having sero-negative arthritis for which she is on long term treatment with a small dose of oral prednisolone and sulfasalazine.

On examination, she had no sinus tenderness or intranasal abnormalities. Pupils were normal and there was no papilloedema. But on neurological examination, there was a marked sensory loss over the area of right maxillary sensory division, where she complained of numbness. Other divisions of fifth cranial nerve were found to be normal along with the motor component. Corneal reflex was present and all other cranial nerves were normal. On eye screening, intra ocular pressures of both eyes were normal.

The initial differential diagnosis considered for her presentation were severe migraine, pseudo tumor cerebri, space occupying lesion, or venous sinus thrombosis. Her blood counts showed an elevated WBC ($12x10^3$/uL) and a high ESR (91mm/1st hour). But CRP was normal. Non contrast CT of brain did not reveal any specific abnormality. Considering severe sinusitis as a possibility for unilateral headache, even without other features of sinusitis, an x-ray sinus view was done and was normal. Nasal endoscopy performed was also normal. Negative results of initial procedures and CT imaging, created a diagnostic dilemma at this point.

Therefore a contrast enhanced CT scan of sinuses was performed with a high degree of suspicion because of severe persistant unilateral pain with trigeminal nerve involvement. It revealed, probable sphenoidal sinusitis. MRI scan of brain with skull base, with infra-temporal views was performed and this confirmed right sided isolated sphenoid sinusitis (Figure).

[1]*Department of Medicine, University of Sri Jayewardenepura and Colombo South Teaching Hospital, Sri Lanka.*

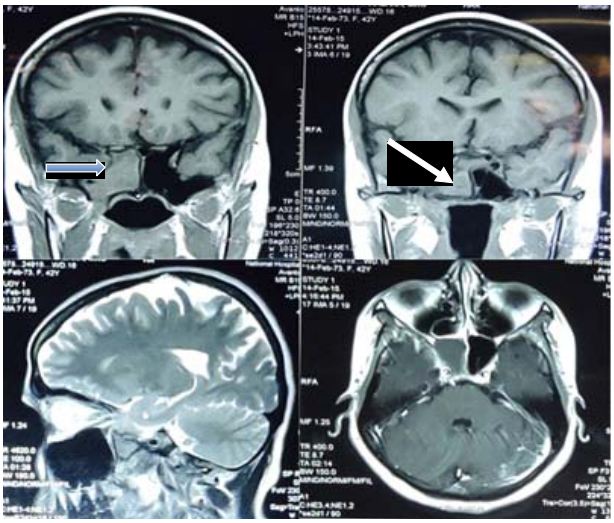


Figure. MRI showing the right sphenoid sinus opaque indicated by arrow

She underwent functional endoscopic sinus surgery where a freely movable mass was identified in sphenoid sinus suggestive of a fungal growth and it was completely removed. Histo-pathological diagnosis confirmed fungal sinusitis with fungal hyphae in tissue. Patient completely recovered after surgery without any complications, even without systemic antifungal therapy. Now, at five months of follow up, she has no headache and the numbness of face had resolved over one month following surgery.

Discussion

Isolated sphenoidal fungal sinusitis is a rare clinical entity and is often misdiagnosed due to lack of specific features in the presence of a non-resolving headache. Headache is the most common presentation of this disease and is mostly deep seated and retro-orbital. The mucous membrane of the sphenoid sinus receives sensory innervation by the posterior ethmoidal nerves (branch of the ophthalmic nerve), and post-ganglionic parasympathetic fibers of the facial nerve that synapsed at the pterygopalatine ganglion which control secretion of mucus. Retro-orbital pain is likely as a result of this innervation[5]. But other variants of headache such as vertex, referred occipital or diffuse are commonly seen[3].

Our patient had a deep right sided frontal headache which was throbbing in nature and in the background of dull persistent headache. Other symptoms of isolated sphenoidal fungal sinusitis include visual disturbances including unilateral vision loss, diplopia, blurring of vision due to involvement of optic nerve. Also nasal obstruction, rhinorrhea, hyposmiaare some other features reported[5]. Involvement of cranial nerves especially ophthalmic and maxillary branches of trigeminal nerve that was evident in our patient had been reported in 4 patients in a case series of 15 patients[2].

Depending on the severity of the fungal infection the treatment methods vary. Our patient was falling into non-invasive fungal sinusitis, where hyphae were seen in histology but the fungal culture was negative. She had complete cure of headache and numbness after endoscopic nasal surgery. Therefore she was not treated with systemic anti-fungal medications.

The sphenoid sinus is anatomically closely related to a set of vital structures including the dura, pituitary, optic nerve, pterygoid canal and nerve, internal carotid artery and the cavernous sinus with its associated cranial nerves (III, IV, V1, V2, and VI). Therefore, early diagnosis and management of sphenoid sinus lesions is crucial to prevent devastating complications that can occur due to involvement of these structures.

Conclusion

Isolated sphenoidal sinus fungal sinusitis is rare and that should be considered with priority in patients presenting with severe deep seated headache, even if the usual features of sinusitis are absent, with normal initial brain imaging and nasal endoscopy. This case emphasizes the importance of awareness of this rare clinical entity and the need for appropriate imaging.

References

1. Alazzawi S, Shahrizal T, Prepageran N, Pailoor J. Isolated sphenoid sinus lesion: A diagnostic dilemma. *Qatar Med J* 2014: 57-60.
2. Thery A, Espitalier F, Cassagnau E, Durand N, Malard O. Clinical features and outcomes of sphenoid sinus aspergillosis: A retrospective series of 15 cases. *Eur Ann Otorhinolaryngol Head Neck Dis* 2012; **129**(4): 179-84.
3. Moon Oh Kwon, Kyung Soo Kim. Headache induced by isolated sphenoid fungal sinusitis: sinus headache? *J Headache Pain* 2009; **10**(6): 473-6.
4. Wang ZM, Kanoh N, Dai CF, Kutler DI, Xu R, Chi FL. Isolated sphenoid sinus disease: An analysis of 122 cases. *Ann Otol Rhinol Laryngol* 2002; **111**: 323-7.
5. AyseIriz, Muharrem Dagli, Halit Akmansu, Özge Ha, Bengi Arslan, Adil Eylmaz. Isolated fungal sinusitis of the sphenoid sinus. *Turk J Med Sci* 2009; **39**(3): 453-6.

Picture quiz

Neuromuscular disorders

Sri Lanka Journal of Neurology, 2015, **4**, 36-38

(Compiled by A Arasalingam[1] and Saman B Gunatilake[2])

Q1

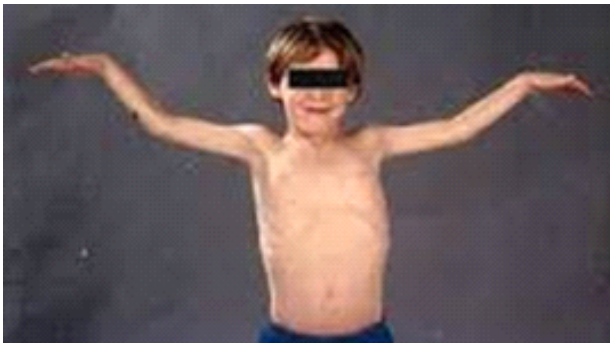
A 45-year-old male presented with progressive exercise induced muscle cramps, myalgia and stiffness over the last 20 years. There was no significant family history. On examination there was generalised muscle hypertrophy especially of the calf, but no weakness. Tapping or brief application of pressure to the upper arm produced short lasting muscle contractions. He had elevated serum CK levels. Western Blot pattern is shown:

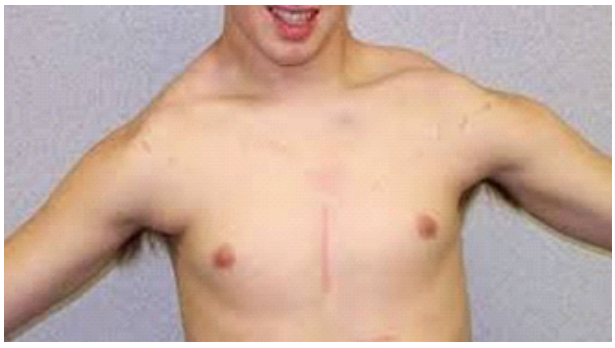
What is the diagnosis?

Q2

A 24-year-old male presented with a rigid spine and neck, contractors at the elbow and shortening of the Achilles tendon, scoliosis and increased lumbar lordosis. The muscles of the lower arms and legs and the scapular muscles were atrophied. There was mild weakness of the triceps and iliopsoas muscles. He had generalised areflexia. Cardiac investigations revealed a first degree AV block. Serum CK activity was elevated 6 times the upper limit of normal. He had noticed that he was unable to extend his arm fully and that his Achilles tendon was taut from the age of five. He had an elder brother with the same presentation.

What is the diagnosis?



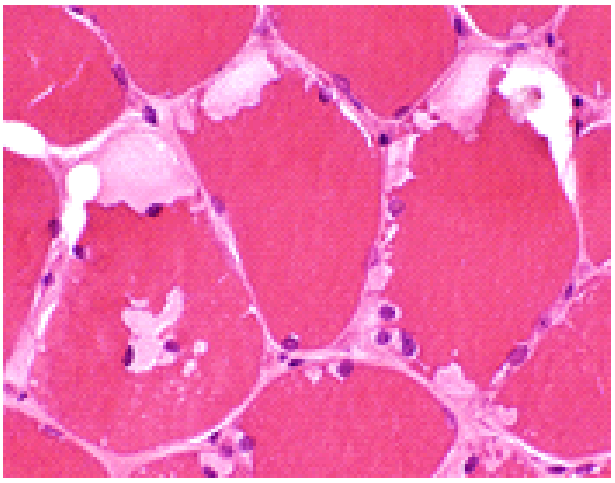


[1]*Consultant Neurologist, Jaffna,* [2]*Consultant Neurologist and Professor of Medicine, University of Sri Jayewardenepura, Sri Lanka.*

Q3

A 40-year-old female presented with cramps and swelling of the hands for more than 4 years. She had never had episode of passing dark urine nor had she noticed muscle weakness. Her past medical history was unremarkable except for a goiter. Her family history was negative for neuromuscular disorders. Her neurological examination was normal.

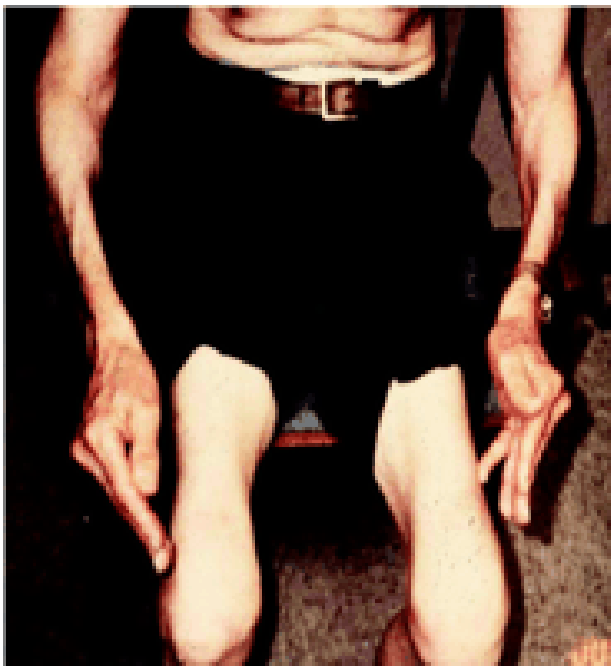
Initially she had a markedly elevated serum CK activity of > 13000 IU/L. Repeat measurements showed activities of 3389 IU/L and 1550 IU/L respectively. The ischaemic forearm test showed only a minimal increase in serum lactate but ammonia showed a considerable rise from 14 to 489 micromol/l. A skeletal muscle biopsy was done. Histology shown.



What is the diagnosis?

Q4

A 66-year-old man presented with progressive muscle weakness for more than 6 years. Had been treated for polymyositis with steroids without any benefit. Patient complained of difficulty going up and down stairs and turning door knobs and handles. Serum CK was 360 IU/L (normal <200).

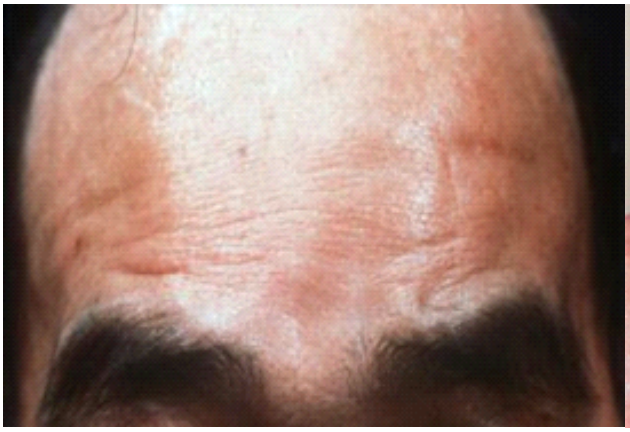
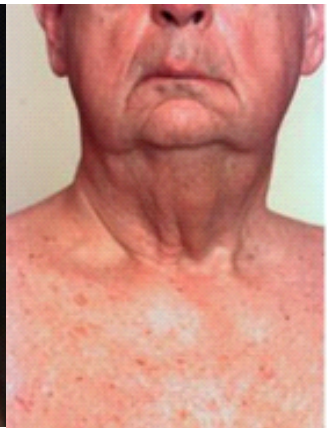
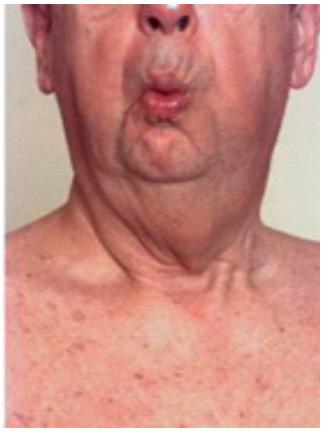
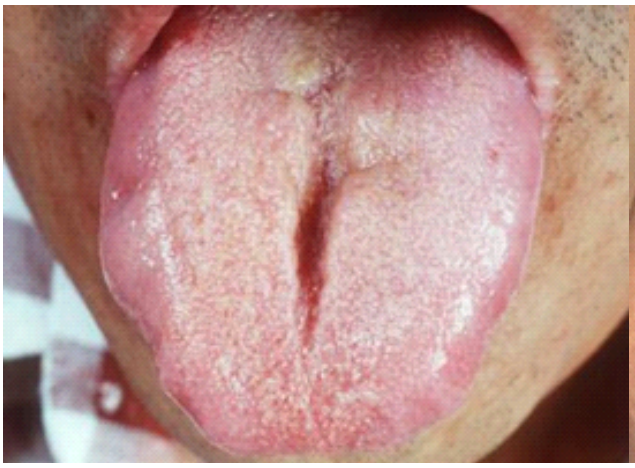
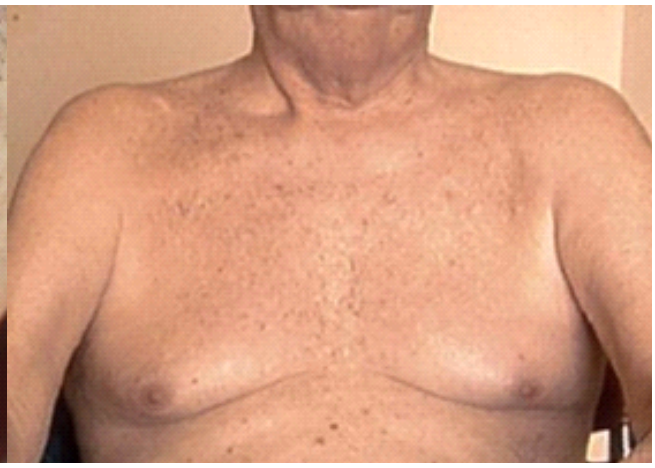


What is the diagnosis?

What is seen in a muscle biopsy?

Q5

What is the diagnosis?

(Answers on page 42-43)

Guidelines to authors

Sri Lanka Journal of Neurology, 2015, **4**, 39-41

The *Sri Lanka Journal of Neurology* is published half yearly (June and December) by the Association of Sri Lankan Neurologists. Material received for publication in the *SLJN* must not be submitted for publication elsewhere without the editors' permission (see below under Previous Publication and under Cover Letter).

Contents

The *SLJN* publishes original papers and commentaries which have relevance to Neurology and allied sciences.

Papers

Original work concerning the causes, mechanisms, diagnosis, management and prevention of disease belong in this category. So do articles on health systems research, health economics and management, and medical ethics. They should have less than 2000 words, 5 tables and illustrations, and 20 references.

Case reports/Brief reports

This category includes case reports of drug adverse effects, of a single event that could lead to a new piece of knowledge, preliminary reports of drug trials, new patient management methods, and reports of new techniques and devices. They should not exceed 1000 words, and contain more than 3 tables or illustrations, and more than 10 references.

Leading articles and reviews

Leading articles are solicited by the editors, and are expert opinions on current topics or commentaries on other papers published in the *SLJN*. They do not usually exceed 1500 words or have more than 20 references. Tables and illustrations are usually not included in leading articles.

Perspectives and points of view

The *SLJN* also welcomes essays expressing opinions, presenting hypotheses, broaching controversial issues, clarifying recent advances in the basic sciences, and essays pertaining to medical education, history of medicine, biographical sketches, health politics and patients' rights in relation to neurosciences. They should not have more than 2000 words, 5 tables and illustrations, or 20 references.

Miscellany

The *SLJN* will also consider for publication letters (less than 400 words of text, 3 authors, and 5 references), obituaries (less than 400 words), and contributions to the picture-story series (not more than 250 words of text, 3 authors, 3 references and 2 clear black and white or colour photographs).

Submitting Manuscripts

Cover letter

Manuscripts should be submitted with a letter stating (1) that the contents have not been published elsewhere; (2) that the paper is not being submitted elsewhere (or provide information on previous publication); and (3) that the authors agree to transfer copyright to the *SLJN* if the article is selected for publication. The letter should acknowledge any potential conflict of interest (see Ethical Responsibilities below) and call the editors' attention to any possible overlap with prior publications. The name, full mailing address, and telephone number of the author responsible for correspondence about the paper should also be included. E-mail addresses are mandatory.

Submit an original copy and 3 copies (photocopies are acceptable) of all parts of the manuscript, 3 original glossy prints of all figures. All submissions must be accom-panied by an electronic copy of the manuscript and illustrations emailed to the editor.

The manuscript should be mailed, with adequate protection for figures, to Prof Saman Gunatilake, the Editor, *SLJN*, Department of Medicine, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda. SRI LANKA. Email: saman.gunatilake@hotmail.com

Ethical responsibilities

Criteria for authorship

Only persons who contributed to the intellectual content of the paper should be listed as authors. Authors should meet all of the following criteria, and be able to take public responsibility for the content of the paper.

1. Conceived and planned the work that led to the paper, or interpreted the evidence it presents, or both.
2. Wrote the paper or reviewed successive versions, and took part in revising them.
3. Approved the final version.
4. Each author should have contributed sufficiently to the work to take public responsibility for the content.

Collecting and assembling data reported in a paper and performing routine investigations are not, by themselves, criteria for authorship.

Conflict of interest

Financial support for the work, including equipment and drugs, should be listed on the title page. Authors should describe in the cover letter any financial interests, direct or indirect, that might affect the conduct or reporting of the work they have submitted. Information about potential conflict of interest may be made available to referees and will be published with the manuscript, at the discretion of the editors.

Previous publication

In the cover letter give full details on any possible previous publication of any content of the paper. eg.

1. Reworked data already reported.

2. Patients in a study already described and published.
3. Content already published or to be published in another format.

Previous publication of some content of a paper does not necessarily preclude it being published in the *SLJN*, but the editors need this information when deciding how to make efficient use of space in the Journal, and regard failure of a full disclosure by authors of possible prior publication as a breach of scientific ethics.

Informed consent

The authors must ensure that informed consent forms have been obtained. Authors should state in the methods section, when appropriate, the ethical guidelines followed. If patients are recognisable in illustrations, signed consent by the patients (or guardians) must be submitted with the paper.

Selection for publication

All articles received will be acknowledged to the corresponding author. Each manuscript will be read by the members of the editorial board to decide whether it should be further reviewed. Those selected for review may be sent anonymously to referees.

Peer review

Referees are asked to treat papers as confidential communications and not to share their content with anyone except colleagues they have asked to assist them in reviewing, or not to use content for their own purposes. They are asked to declare any conflict of interest (such as personal ties to authors), and not to copy manuscripts.

Editorial board

All articles are submitted anonymously to the Editorial Board which meets regularly. Members of the board assess articles on the basis of importance of the research problem, scientific strength, clarity of presentation and appropriateness for readers of the *SLJN*.

Editors reserve the right to modify style, shorten articles, make editorial corrections where necessary, and to determine priority and time of publication.

Preparation of manuscript

The *SLJN* will consider all manuscripts prepared in accordance with the uniform requirements for manuscripts submitted to biomedical journals developed by the International Committee of Medical Journal Editors [1]. A summary of these and the requirements of the *SLJN* are given below.

Manuscript typing

All parts of manuscript, including tables and figure legends, must be typed with double-spacing. References must also be double spaced. Manuscripts should be typed in capital and lower case letters, on white paper, 216 × 279 mm (8 × 11 in), or A4 (212 × 297 mm). Arrange components in the following order: title page, abstract, text, references, tables in numerical sequence, and figure legends. Begin each component on a separate page. Number all pages consecutively, starting with the title page.

Title page

The title page should contain the following:

1. Main title, subtitle (if any) and a maximum of 5 index words (or phrases).
2. Authors listed in the form and order in which they are to appear in the published article.
3. Institutional affiliation for each author, in a footnote on the title page of the article. The institutions listed should reflect the affiliations of the authors at the time of the study, not their present affiliations, if they differ.
4. Financial support information. Include the grant number, if any, and the granting agency. Other financial support, such as that for equipment and drugs, should also be listed.
5. Name, address, e-mail and telephone number of author responsible for correspondence.
6. The number of words in the manuscript, exclusive of the abstract, references, tables, figures, and figure legends.

Abstract

Abstracts for articles are limited to 250 words; those for Brief Reports, to 150 words. Authors of original research articles are asked to submit a structured abstract organised into the following categories (where relevant):

Objective(s)

Design setting

Patients Intervention (if any)

Measurements

Results

Interpretation

Authors are asked to see papers in any recent issue of the *British Medical Journal or Annals of Internal Medicine* for guidance on structuring the abstract.

Headings in text

Use only three levels of headings in the text. Clearly indicate the levels of headings by using different typographic conventions (such as all capital letters or bold type) or by positioning (flush to margin, indented). Keep headings short (three or four words).

Style

The *British Medical Journal, Lancet* and *Annals of Internal Medicine* are recommended to authors as guides to style, clarity of presentation and conciseness.

Units

Use SI units throughout [2], except for systemic arterial blood pressure and haemoglobin content. Other units may be given in parentheses. Use only arabic numbers.

Name of drugs and instruments

Generic names must be used for all drugs. Include the proprietary name only if it is needed for a specific purpose. Instruments may be referred to by proprietary

name, giving the name and location of the manufacturer in the text in parentheses.

References

Number references in the order in which they are first cited in the text. Use superscripted arabic numerals in the text.. Note that the *SLJN* requires the COMPLETE name of journal (and not its abbreviation), year, volume and first and last page numbers.

The reference list should not include unpublished material. Symposium papers may be cited from published proceedings; oral presentation of a paper at a meeting does not constitute publication. References to articles or books accepted for publication but not yet published must include the title of the journal (or name of the publisher) and the year of expected publication. Unpublished work (personal communication, papers in preparation) may be cited by inserting a reference within parentheses in the text; authors must submit a letter of permission from the cited persons to cite such communications.

Sample references below are in the style required by the *SLJN*.

Journals: List all authors when 4 or fewer; when 5 or more, list only the first 3 and add et al.

1. Standard article.

   Bernstein H, Gold H. Sodium diphenylhydantoin in the treatment of recurrent arrhythmias. *Journal of the American Medical Association* 1965; **19**1: 695-9.

2. Corporate author.

   The Royal Marsden Hospital Bone Marrow Transplantation Team. Failure of syngeneic bone marrow graft without preconditioning in posthepatitis marrow aplasia. *Lancet* 1977; **2**: 242-4.

3. Special format.

   Cahal DA. Methyldopa and haemolytic anaemia (Letter). *Lancet* 1975; **1**: 201.

Books: List all authors or editors when 4 or fewer; when 5 or more, list only the first 3 and add et al.

1. Author.

   Eisen HN. Immunology: *An introduction to molecular and Cellular Principles of the Immune Response*. 5th ed. New York: Harper and Row,1974.

2. Editors.

   Dausset J. Colombani J, eds. *Histocompatibility Testing* 1972. Copenhagen: Munksgaard, 1973.

3. Chapter in a book.

   Hellstrom I, Helstrom KE. Lymphocyte-mediated cytotoxic reactions and blocking serum factors in tumor-bearing individuals. In: Brent L, Holbrow J, eds. *Progress in immunology* II. v. 5. New York: American Elsevier, 1974: 147-57.

Other citations in Reference List:

1. In press (must have journal title).

   Dienstage JL. Experimental infection in chimpanzees with hepatitis A virus. *Journal of Infectious Diseases* 1975. In press.

2. Magazine article.

   Roueche B. Annals of medicine: the Santa Claus culture. *The New Yorker* 1971. Sep 4: 66-81.

In-text citations of unpublished material (to be placed within parentheses):

1. Personal communication.
   (Strott CA, Nugent CA. Personal communication).

2. Unpublished papers.

   (Lerner RA, Dixon FJ. The induction of acute glomerulonephritis in rats. In preparation). (Smith J. New agents for cancer chemotherapy. Presented at the Third Annual Meeting of the American Cancer Society, June 13, 1983, New York).

Tables

All tables must be typed double-spaced. Tables should be numbered with arabic numerals, in the order in which they are cited in the text. A table title should describe concisely the content of the table.

Figures

Figures should be professionally drawn or prepared using a computer and high-resolution printer. Lettering should be uniform in style. Free hand or typewritten lettering is not acceptable. Number the figures in the order in which they are cited in the text. Photomicrographs should have scale markers that indicate the degree of magnification. Submit three glossy prints of each figure. Indicate on a label the name of the first author of the paper, the figure number, and the top of the figure: then paste the label on the back of the figure. Do not mount figures on backing board.

Colour figures may be submitted and will be published if essential.

Legends for figures

Reduce the length of legends by using partial sentences. Explain all abbreviations and symbols on the figure, even if they are explained in the text. Stain and magnification should be given at the end of the legend for each part of the figure. If there is no scale marker on the figure, the original magnification used during the observation should be given, not that of the photographic print.

Acknowledgements

Acknowledge only persons who have contributed to the scientific content and provided financial or technical support. Authors must submit written permission from persons acknowledged for other than financial or technical support.

References

1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *New England Journal of Medicine* 1991; **324**: 424–8.
2. Young D. Implementation of SI units for clinical laboratory data: style specifications and conversion tables. *Annals of Internal Medicine* 1987; **106**: 114–29.

Answers to picture quiz

Sri Lanka Journal of Neurology, 2015, **1**, 42-43

Answer 1

Caveolinopathy - limb girdle muscular dystrophy type 1C

Caveolin-3 is a protein that in humans is encoded by the CAV3 gene. Mutations identified in this gene lead to interference with protein oligomerization or intra-cellular routing, disrupting caveolae formation and resulting in Limb-Girdle muscular dystrophy type-1C (LGMD-1C), HyperCKemia, distal myopathy or rippling muscle disease (RMD). Other mutations in caveolin causes Long QT Syndrome or familial hypertrophic cardiomyopathy, although the role of Cav3 in Long QT syndrome has recently been disputed.

Answer 2

Emery-Dreifuss muscular dystrophy (EDMD)

EDMD is characterized by the clinical triad of (1) joint contractures that begin in early childhood; (2) slowly progressive muscle weakness and wasting initially in a humero-peroneal distribution and later extending to the scapular and pelvic girdle muscles; and (3) cardiac involvement that may include palpitations, presyncope and syncope, poor exercise tolerance, and congestive heart failure. The X-linked form is caused by mutations in EMD, the gene encoding emerin; the dominant/recessive forms are caused by mutations in LMNA, the gene encoding lamin A/C.

Answer 3

McArdle disease

Glycogen storage disease type V (GSD-V) is a metabolic disorder, more specifically a glycogen storage disease, caused by a deficiency of myophosphorylase. Its incidence is reported as 1 in 100,000 approximately the same as glycogen storage disease type I. GSD type V is also known as McArdle disease or muscle phosphorylase (myophosphorylase) deficiency. The disease was first reported in 1951 by Dr. Brian McArdle of Guy's Hospital, London.

The onset of this disease is usually noticed in childhood but often not diagnosed until the third or fourth decade of life. Symptoms include exercise intolerance with muscle pain, early fatigue, painful cramps, and myoglobin in the urine (often provoked by a bout of exercise).

Patients may exhibit a ''second wind'' phenomenon. This is characterized by the patient's better tolerance for aerobic exercise such as walking and cycling after approximately 10 minutes. This is attributed to the combination of increased blood flow and the ability of the body to find alternative sources of energy, like fatty acids and proteins. In the long term, patients may exhibit renal failure due to the myoglobinuria, and with age, patients may exhibit progressively increasing weakness and substantial muscle loss. Muscle biopsy showss subsarcolemmal cytoplasmic vacuoles (Blebs).

Answer 4

Inclusion body myositis

Inclusion body myositis (IBM) is an inflammatory muscle disease characterized by slowly progressive weakness and wasting of both distal and proximal muscles, most apparent in the muscles of the arms and legs. There are two types: sporadic inclusion body myositis (sIBM), which is more common, and hereditary inclusion body myopathy (hIBM). This is the commonest form of acquired myopathy in people over 50 years.

The muscles in the thighs – the quadriceps and the muscles in the arms that control finger flexion-making a fist-are usually affected early on. Common early symptoms include frequent tripping and falling, weakness going up stairs and trouble manipulating the fingers (including difficutly with tasks such as turning doorknobs or gripping keys). Dysphagia is present in from 40 to 85% of IBM cases.

Answer 5

Kennedy disease

Also known as spinal and bulbar muscular atrophy (SBMA), spinobulbar muscular atrophy, bulbo-spinal atrophy, X-linked bulbospinal neuropathy (XBSN), X-linked spinal muscular atrophy type 1 (SMAX1). Kennedy's disease is a debilitating neurodegenerative disorder resulting in muscle cramps and progressive weakness due to degeneration of motor neurons in the brain stem and spinal cord.

The condition is associated with mutation of the androgen receptor (AR) gene and is inherited in an X-linked recessive manner. The androgen receptor gene that is mutated in SBMA is located on the X chromosome, and the effects of the mutation may be androgen-dependent, thus only males are fully affected. Females are rarely affected; female carriers tend to have a relatively mild expression of the disease if they show symptoms at all.

Because of its endocrine manifestations related to the impairment of the AR gene, SBMA can be viewed as a variation of the disorders of the androgen insensitivity syndrome (AIS). Endocrine manifestations are gynaecomastia, impotence, erectile dysfunction, reduced fertility, low sperm count, testicular atrophy.