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Anosmia - Marker Of Cognitive Decline In Elderly

Pandharipande M. S.[1]

Neurodegeneration is an important health problem in elderly. Significant decrements in the ability to smell are present in over 50% of the population between 65 and 80 years of age and in 75% of those 80 years of age and older. Olfactory impairment has been described in number of neurodegenerative diseases viz. Parkinson's Disease, Alzheimer's Disease, dementia with Lewy bodies (DLB), multiple system atrophy, corticobasal degeneration, and frontotemporal dementia. Olfactory impairment in Parkinson's Disease often predates the clinical diagnosis by at least 4 years. In staged cases, studies of the sequence of formation of abnormal α-synuclein aggregates and Lewy bodies suggest that the olfactory bulbs may be, along with the dorsomotor nucleus of the vagus, the first site of neural damage in Parkinson's Disease.[1] In post mortem studies of patients with very mild "presymptomatic" signs of Alzheimer's Disease, poorer smell function has been associated with higher levels of AD-related pathology.

Worldwide, about half of the older persons in need of care (two-thirds of the dependent population age 90 and above) suffer from dementia or cognitive impairment. One estimate (World Alzheimer's Report 2010) projected that the 36 million people with dementia worldwide in 2010 would increase to 115 million by 2050. The largest increases would occur in low and middle income countries where about two-thirds already live.

Brain atrophy occurs with aging after the age of 60 years and is associated with cognitive decline. Atrophy proceeds at varying rates indifferent parts of the brain. In mild cognitive impairment, atrophy has been found mostly in the prefrontal cortex and hippocampus. In the early stages of typical amnestic AD, the memory loss may go unrecognized or be ascribed to benign forgetfulness of aging. Once the memory loss becomes noticeable to the patient and spouse and falls 1.5 standard deviations below normal on standardized memory tests, the term mild cognitive impairment (MCI) is applied. This construct provides useful prognostic information, because approximately 50% of patients with MCI (roughly 12% per year) will progress to AD over 4 years. Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MOCA), and Cognistat can be used to capture dementia and follow progression Increasingly, the MCI construct is being replaced by the notion of early symptomatic AD[2].

Because of the suggestion that olfactory impairment may be an early indicator for cognitive impairment, there has been interest in the possibility of using olfactory testing to assist in diagnosis of AD or predict who will develop AD or cognitive impairment. However there has been limited research on the association of olfaction and cognition in a general population of older adults not at high risk for AD or cognitive impairment. Some studies have reported that olfaction impairment appears to precede clinical signs of cognitive impairment or AD and have hypothesized that it may be an early indicator of brain changes.[3] Olfactory impairment has been reported in both preclinical and clinical phases of AD. Autopsy studies have found neurofibrillary tangles, pathology thought to be associated with AD, appear first in the entorhinal cortex and olfactory bulb areas of the brain both in people with AD and / or dementia as well younger people with no clinical signs of dementia.[4] A recent study found the density of tangles present in the central olfactory system was inversely related to odor identification ability.[5] Neuropathological studies have revealed that brain regions and subsystems involved in odor information processing, including the olfactory bulb, piriform

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and orbital prefrontal cortices, have direct projections to perirhinal and entorinal cortices. These, in turn, have extensive projections to the hippocampus,[6] known as the primary brain region involved in initial memory formation, and also one of the first regions affected in AD neurodegeneration. In addition, the anterior olfactory nucleus and olfactory bulb are the two primary brain regions commonly affected in AD. Indeed, change in olfactory identification has been strongly associated with pathological changes in the medial temporal lobe structures.[7,8] These studies strongly imply a primary role for olfactory dysfunction as an indicator of pathological cognitive decline and dementia.

Observational and clinical studies have found a significant association between olfactory impairment and subsequent cognitive decline. For example, a large-scale study (N=1920) on the relationship between olfactory identification ability and general cognitive functioning (as measured by Mini Mental State Examination (MMSE)) indicated that olfactory dysfunction at baseline was significantly predictive of future cognitive impairment after 5 years (odds ratio (OR) = 6.62; confidence interval (CI) = 4.3610.04) Schubert *et al*[9] have also reported low sensitivity of 55.1% but high specificity (84.4%) for olfactory assessment in predicting cognitive decline.

A number of standardized olfactory and taste tests are commercially available. Most evaluate the ability of patients to detect and identify odors or tastes. For example, the most widely used of these tests, the 40 item University of Pennsylvania Smell Identification Test (UPSIT. The Indian Smell Identification Test (INSIT) uses the essence of 10 commonly used items as odorants (cardamom, kewra, khus, lemon, mango, orange, pineapple, rose, thinner, vanilla) which represent familiarity in day to day life. A score of ≤ 4 indicate anosmia .

Wilson *et al* has reported that impairment in olfactory identification at baseline was significantly associated with the incidence of mild cognitive impairment.

Olfactory abilities are primarily assessed by measuring threshold (lowest detectable concentration of odors), discrimination (ability to differentiate between odors) and identification (ability to identify odors). H. R. Sohrabi *et al*[10] studied association f cognitive decline and olfactory dysfunction in community dwellingsubjects. The major novel finding of the study was that olfactory discrimination rather than odour identification (as measured by Sniffin' Sticks D) was a significant predictor of future cognitive decline over a 3-year period. However, concluded that, the predictive value of olfactory assessment in screening those at a higher risk for AD needs further research to improve its sensitivity and specificity.

In the current issue of this journal Gaurav *et al*[11] in his hospital based observational study, reported cognitive impairment in 50% of elderly subjects and anosmia to be prevalent in 64% of cases and also documented association of anosmia and cognitive impairment ($p < 0.0001$) in elderly. Anosmia was detected bu INSIT test which is easy to perform, cheap and is suitable for Indian patients because the agents used are familiar. The test has been standardised by George *et al* and has already been used in some studies.

However, local causes and other conditions causing anosmia needs to be ruled out anddtetailed neurological assessment and neuroimaging studies or PET scan may throw additional light on the association of anosmia with cognitive impairment and other neurodegenerative disorders. Large sample sized prospective studies are essential to find out the steps in preventing the progress of disease and improve quality of life in elderly.

References :

1. Richard L. Doty, Steven M. Bromley Disorders of Smell and Taste : Harrison's principles of Internal Medicine 19th edition Vol 1, chapter 42; p 211-217.
2. William W. Seeley, Bruce L. Miller Alzheimer's Disease and Other dementias Harrison's principles of Internal Medicine 19th edition Vol 2 chapter 448 p 2598 -2608.

3. Carla R. Schubert, Lakeesha L. Carmichael, Claire Murphy, Olfaction and The 5-Year Incidence of Cognitive Impairment in an Epidemiologic Study of Older Adults : JAm Geriatr Soc. 2008 Aug; 56 (8) : 1517-1521.
4. Kovacs T, Cairns NJ, Lantos PL. Olfactory centres in Alzheimer's disease : olfactory bulb is involved in early Braak's stages. Neuro Report. 2001; 12 (2) : 285-288. [PubMed].
5. Wilson RS, Arnold SE, Schneider JA, *et al.* The relationship between cerebral Alzheimer's disease pathology and odour identification in old age. J Neurol Neurosurg Psychiatry. 2007; 78 : 30-35. [PubMed].
6. Eichenbaum H. Using olfaction to study memory. Ann N Y Acad Sci. 1998; 855 : 657-669. [PubMed].
7. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Biol. 2011; 3 : a006189. [PMC free article] [PubMed].
8. Lojkowska W, Sawicka B, Gugala M, Sienkiewicz-Jarosz H, Bochynska A, Scinska A, *et al*. Follow-up study of olfactory deficits, cognitive function, and volume loss of medial temporal lobe structures in patients with mild cognitive impairment. Curr Alzheimer Res. 2011; 8 : 689-698. [PubMed].
9. Schubert CR, Carmichael LL, Murphy C, Klein BE, Klein R, Cruickshanks KJ. Olfaction and the 5-year incidence of cognitive impairment in an epidemiological study of older adults. J Am Geriatrics Soc. 2008; 56 : 1517-1521. [PMC free article] [PubMed].
10. HR Sohrabi, KA Bates, MG Weinborn, Olfactory discrimination predicts cognitive decline among community-dwelling older adults : Transl Psychiatry. 2012 May; 2 (5) : e118.
11. GK Yadav, MS Pandharipande, RW Joshi : Anosmia marker of cognitive decline in elderly : Vidarbha Journal of Internal Medicine. July 2016;Vol. 21; 6-11.

Original Article

Anosmia Marker of Cognitive Impairment in Elderly

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Motlag M D[3], Nagpure K[3], Pandharipande A S[4], Joshi P P[5]

ABSTRACT

Background : The prevalence of olfactory impairment and cognitive impairment increase with age. Olfactory impairment has been associated with neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease. Studies have reported that olfaction impairment appears to precede clinical signs of cognitive impairment or AD and have hypothesized that it may be an early indicator of brain changes

Aims and objectives :

1) To find out the prevalence of anosmia in the elderly, 2) To find out the prevalence of cognitive impairment in the elderly and, 3) To find out the association of anosmia and cognitive impairment in the elderly.

Methods : Present study is a hospital based, observational, case-control study, in which 100 elderly subjects age > 65 years attending the geriatric OPD, were included as cases and 100 subjects < 65 years, as controls. Anosmia was assessed by Indian Smell Identification Test (INSIT), in which 10 essences were used & 1 point was awarded for correct & 0 for incorrect identification. A score of ≤ 4 indicates anosmia. Cognitive impairment was diagnosed by 30 point mini-mental state examination (MMSE) where scores ≤ 23 indicates cognitive impairment.

Results : Mean age in cases was 68.4 ± 3.7 years and in controls is 39.4 ± 7.9 years. Anosmia was detected in 64% of cases as compared to controls 4% ($p<0.01$). Mean INSIT score was significantly lower (4.02 + 1.88) in cases as compared to controis 7.36 + 1.35, $p<0.01$ Cognitive impairment was present in 50% of the cases and 1% control, ($p<0.001$) Mean MMSE score was also significantly lower in cases (20.99 + 5.1) than controls (27.47 + 1.79, $p<0.001$. Anosmia is found to be significantly associated with cognitive impairment in cases, ($p<0.001$). Univariate analysis revealed significant association of anosmia and cognitive inpairment in elderly subjects however, present study did not demonstrate independent association of anosmia with hypertension, Diabetes mellitus and dyslipidemia. There were no significant gender differences in prevalence of anosmia and cognitive impairment in elderly subjects.

Conclusions : Anosmia is prevalent in elderly. In elderly subjects, anosmia is associated with cognitive impairment.

Key Words : Anosmia, Cognitive impairement, Dementia, INSIT Score, MMSE.

Introduction :

The prevalence of olfactory impairment and cognitive impairment increase with age.[1-3] Olfactory impairment has also been associated with neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease.[4-6]

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Some studies have reported that olfaction impairment appears to precede clinical signs of cognitive impairment or AD and have hypothesized that it may be an early indicator of brain changes. Autopsy studies have found neurofibrillary tangles, pathology thought to be associated with AD, appear first in the entorhinal cortex and olfactory bulb areas of the brain both in people with AD and/or dementia as well younger people with no clinical signs of dementia.[7-9] A recent study found the density of tangles present in the central olfactory system was inversely related to odor identification ability.[10]

Because of the suggestion that olfactory impairment may be an early indicator for cognitive impairment, there has been interest in the possibility of using olfactory testing to assist in diagnosis of AD or

predict who will develop AD or cognitive impairment. However there has been limited research on the association of olfaction and cognition in a general population of older adults not at high risk for AD or cognitive impairment. The purpose of this study is to determine if odour identification ability is associated with cognitive impairment in the elderly subjects.

Aims and objectives :

1) To find out the prevalence of anosmia in the elderly
2) To find out the prevalence of cognitive impairment in the elderly and
3) To find out the association between anosmia and cognitive impairment in the elderly.

Methods :

Present study is a hospital based, cross sectional, observational study carried out on 100 elderly subjects with age > 65 years attending geriatric out patient clinic at a tertiary care hospital, 100 subjects with age < 65 years were included as controls. Cases with history of head injury, cranial surgery, sub arachnoid haemorrhage, metabolic abnormalities (thiamine deficiency, adrenal and thyroid deficiency, cirrhosis, renal failure, wegener's granulomatosis, compressive and infiltrative lesions viz. Craniopharyngioma, meningioma, aneurysm, meningoencephalocoele, vit B12 deficiency, hyperthyroidism, alcohol consumption > 80 gm/day, known psychiatric disorders schizophrenia, depression, acute medical conditions, temporal lobe epilepsy, chronic rhinitis and smokers were excluded as cases as well as controls. Permission from institutional ethics committee was obtained. All cases were evaluated for anosmia by Indian smell identification test. The sensitivity of INSIT test is 79.2% and specificity is 78% at the cut off value of 4. The Indian Smell Identification Test uses the essence of 10 commonly used items as odorants (cardamom, kewra, khus, lemon, mango, orange, pineapple, rose, thinner, vanilla) which represent familiarity in day to day life. The odorants were kept in 20 ml air tight commercially available bottles. Cotton buds dipped in the essence were placed 1 cm in front of each nostril with the other nostril closed and the procedure repeated with the other nostril. The subjects were asked to sniff and identify smell from the answer card containing 4 choices ror each odorant. First response was considered as the answer and score of 1 was awarded for correct and 0 for wrong answer, A score of < 4 indicate anosmia. INSIT was performed by the person blinded for the study. All subjects underwent ENT examination and evaluation to rule out local causes of anosmia.[11]

Cognitive impairment was assessed by Mini Mental State Examination (MMSE) Score < 23 is considered as presence of cognitive impairment. MMSE assessment was performed by the person blinded for the study. All subject underwent clinical examination. Comorbidities viz. Diabetes mellitus, hypertension, Coronary artery disease, dyslipidemia were noted. Complete blood counts and biochemical tests viz fasting and post prandial blood sugar, serum lipids, urea, creatinine were performed and thyroid functions, ECG and other investigations were performed in relevant cases.

Results :

In the present study, 100 (M 64, F 36 ratio 1.7:1) elderly subjects (age > 65 years) were compared against 100 controls (< 65 years) to find out prevalence of anosmia and cognitive impairment. Mean age in cases was 68.4 ± 3.7 years and in controls was 39.4 ± 7.9 years. M 64, F 36, M:F 1.7:1 in cases, M:F 1.1:1 in Controls. Anosmia was detected in 64% of cases as compared to controls 4% ($p<0.01$) ***(Fig. 1).*** Mean INSIT score was significantly lower (4.02 + 1.88) in cases as compared to controls (7.36 + 1.35, $p<0.01$) ***(Table 1).***

Cognitive impairment was prevalent in 50% of cases as compared to controls 1%, $p<0.001$ ***(Fig. 2).*** Mean MMSE score was also significantly lower in cases (20.99 + 5.13) than controls (27.47 + 1.79, $p<0.001$) ***(Table 2).***

Present study demonstrated association of anosmia with cognitive impairment in elderly subjects. However there was no gender differences in prevalence of anosmia in cases. ***(Table 3 & 4).***

Diabetes mellitus was documented in 11% of cases as compared to controls (zero%, p<0.001) hypertension was noted in 42% of cases and 16% (p<0.001) of controls. Ischaemic heart disease was present in 20% cases and 11% of controls p<0.07, NS Dyslipidemia was reported in 72% of cases as compared to controls (33%, p<0.001) Fasting and post prandial blood sugar, triglycerides, and LDL, systolic and diastolic blood pressure and were significantly higher in cases as compared to controls ***(Table 5).***

Univariate analysis revealed significant association of anosmia and cognitive inpairment in elderly subjects however, present study did not demonstrate independent association of anosmia with hypertension, Diabetes mellitus and dyslipidemia ***(Table 6).***

Discussion :

Present study demonstrated anosmia to be prevalent (64%) in elderly. Doty *et al*[12] reported that decreased olfactory function is very common in elderly population, being present in > 50% in subjects between the age group of 65 to 80 years and 75% in those above 80 years. Murphy *et al*[13] found prevalence of impaired olfaction in the US to be 62.5, 5 of people aged above 80 years. Wilson *et al*[14] reported that a negative correlation exists between age and olfaction scores on UPSIT.

Our study reported cognitive impairment to be prevalent in 50% in elderly. Mary *et al*[15] reported prevalence of mild cognitive impairment in the community dwelling subjects over 65 years to be 19.4%. Higher prevalence in our study could be because present study is a hospital based study and has a relatively small sample size.

Present study demonstrated significant association of anosmia and cognitive impairment in elderly. Peters *et al*[16] studied olfactory function in mild cognitive impairment and Alzheimer's disease and found anosmia in 12 out of 14 (85.7%) subjects of alzheimer's disease and 7 out of 8 cases (87.5%) cases of mild cognitive impairment Wilson *et al*[17] in his prospective study on olfactory function assessment and cognitive impairment reported that risk of developing mild cognitive impairment increased by 50% in subjects with below average scores on UPSIT. Mary *et al*[18] also reported the association of anosmia and cognitive impairment and mentioned that UPSIT scores were significantly related to ACE (for cognitive impairment) total scores (r=0.37, p, 0.005).

Anosmia has been documented by INSIT test in the present study, which has been standardised and validated by George *et al* for use in Indian patients[19]. UPSIT (University of Pennsylvania Smell Identification Test) is used in various studies worldwide was not chosen because it is costly and many Indian patients are not familiar with the ingredients used in the test.[20] In the present study, odour identification has been assessed. However, odour threshold has not been tested. Odour threshold, discrimination and quantification assessment can give further insights into the role of olfactory function in neuro degeneration. Association with neuroimaging abnormalities has also not been analysed in the present study. Present study is a hospital based, cross sectional study.

INSIT test is a simple, bedside clinical screening tool, easy to perform and is non expensive hence can be routinely performed for detection of anosmia in elderly subjects. As it is associated with cognitive impairment, it can be predicted as a marker of cognitive impairment and subjects with anosmia can be further examined and investigated for assessment of neurodegenerative diseases. Even though these diseases cannot be completely cured, interventions to prevent progression of diseases and controlling symptoms and optimising can be helpful to improve quality of life in these cases. However, large sample sized, community based, prospective and standardised studies are essential

Conflicts of interest : none reported by authors.

References :

1. Murphy C, Schubert CR, Cruickshanks KJ, *et al.* Prevalence of olfactory impairment in older adults. JAMA. 2002;288(18):2307-2312. [PubMed].
2. Doty RL, Shaman P, Applebaum SL, *et al.* Smell identification ability : changes with age. Science. 1984;226:1441-1443. [PubMed].

3. Kukull WA, Higdon R, Bowen JD, *et al.* Dementia and Alzheimer disease incidence : A prospective cohort study. Arch Neurol. 2002;59:1737-1746. [PubMed].
4. Serby M, Larson P, Kalkstein D. The nature and course of olfactory deficits in Alzheimer's disease. Am J Psychiatry. 1991;148(3):357-360. [PubMed].
5. Mesholam RI, Moberg PJ, Mahr RN, *et al.* Olfaction in neurodegenerative disease. A meta-analysis of olfactory functioning in Alzheimer's and Parkinson's Diseases. Arch Neurol. 1998;55:84-90. [PubMed].
6. Murphy C. Loss of olfactory function in dementing disease. Physiol Behav. 1999;66(2):177-182. [PubMed].
7. Braak H, Braak E. Diagnostic criteria for neuropathologic assessment of Alzheimer's disease. Neurobiol Aging. 1997;18(S4):S85-S88. [PubMed].
8. Kovacs T, Cairns NJ, Lantos PL. Olfactory centres in Alzheimer's disease : olfactory bulb is involved in early Braak's stages. Neuro Report. 2001;12(2):285-288. [PubMed].
9. Price JL, Davis PB, Morris JC, *et al.* The distribution of tangles, plaques, and related immunohistochemical markers in healthy aging and Alzheimer's disease. Neurobiol Aging. 1991;12:295-312. [PubMed].
10. Wilson RS, Arnold SE, Schneider JA, et al. The relationship between cerebral Alzheimer's disease pathology and odour identification in old age. J Neurol Neurosurg Psychiatry. 2007;78:30-35. [PubMed].
11 George J, Jose T, Behari M. Use of Indian smell identification test for evaluating olfaction in idiopathic Parkinson's disease patients in India. Neurol India 2013;61:365-70.
12 Doty RL, Kamath V, The Influences of age on olfaction : a review. Front Psychol. 2014 Feb. 7; 5:20. doi:10.3389/fpsyg.2014.00020.eCollection2014.
13 Murphy C[1], Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. JAMA. 2002 Nov.13:288 (18):2307-12.
14 Robert S. Wilson; Julie A. Schneider; Steven E. Arnold; Yuxiao Tang; Patricia A. Boyle; David A. Bennett. Olfactory Identification and Incidence of Mild Cognitive Impairment in Older Age Arch Gen Psychiatry. 2007;64(7):802-808. doi:10.1001/archpsyc.64.7.802.
15 Mary Ann F Kirkpatrick,[1] Wendell Combest,[1] Marian Newton,[1] Yvonne Teske,[1] John Cavendish,[2] Rhonda McGee,[2] and Danielle Przychodzin[2]. Combining olfaction and cognition measures to screen for mild cognitive impairment. Neuropsychiatric Disease and Treatment Vol.2006:2(4):565-570.
16 Peters JM, Hummel T, Kratzsch T, *et al.* Olfactory function in mild cognitive impairment and alzheimer's disease : an investigation using psychophysical and electrophysiological techniques. Am J Psychiatry. 2003;160:1995-2002.
17 Robert S. Wilson; Julie A. Schneider; Steven E. Arnold; Yuxiao Tang; Patricia A. Boyle; David A. Bennett. Olfactory Identification and Incidence of Mild Cognitive Impairment in Older Age Arch Gen Psychiatry. 2007;64(7):802-808. doi:10.1001/archpsyc.64.7.802.
18 Mary Ann F Kirkpatrick,[1] Wendell Combest,[1] Marian Newton,[1] Yvonne Teske,[1] John Cavendish,[2] Rhonda McGee,[2] and Danielle Przychodzin[2]. Combining olfaction and cognition measures to screen for mild cognitive impairment. Neuropsychiatric Disease and Treatment Vol. 2006:2(4):565-570.
19 George J, Jose T, Behari M. Use of Indian smell identification test for evaluating olfaction in idiopathic Parkinson's disease patients in India. Neurol India 2013;61:365-70.
20 Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test : a standardized microencapsulated test of olfactory function. PhysiolBehav. 1984 Mar;32(3);489-502.

Fig. 1 : **Prevalence of anosmia in cases and controls**

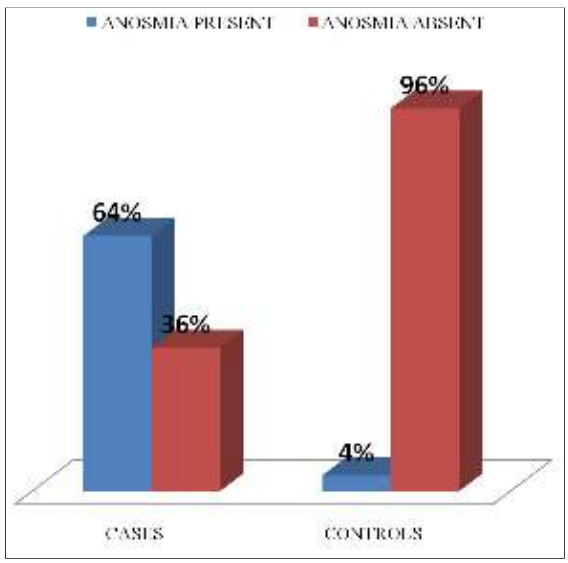

Fig. 2 : **Prevalence of cognitive impairment in cases and controls**

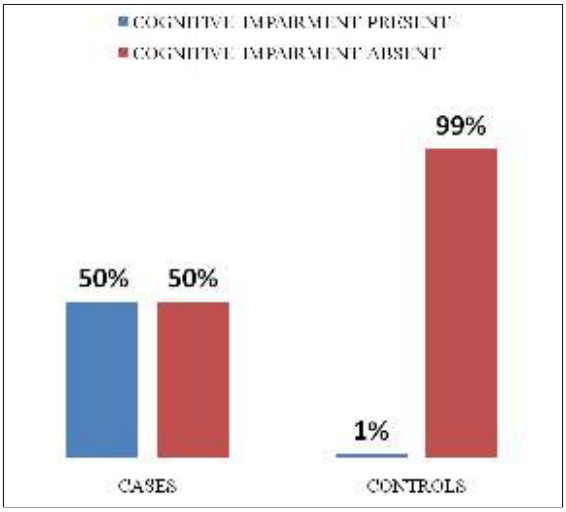

Table 1 : **INSIT Score in Cases and Controls**

Mean Insit Score	Cases N = 100	Controls N = 100	P Value
	4.02 ± 1.88	7.36 ± 1.35	<0.001

Table 2 : MMSE Scores in Cases and Controls

Mean MMSE Score	Cases N= 100	Controls N = 100	P Value
	20.99 ± 5.13	27.47 ± 1.79	< 0.001

Table 4 : **Anosmia and Cognitive Impairment - Gender Differentiation in Cases**

	Males N = 64	Females N = 36	
With Anosmia	44 (68.75%)	20 (55.55%)	chi sq.= 0.17, P value = 0.67 NS
Without Anosmia	20 (31.25%)	16 (44.44%)	
With Cognitive Impairment	31 (48.43%)	19 (52.77%)	chi sq. = 0.17, P value = 0.67NS
Without Cognitive Impairment	33 (51.56%)	17 (47.22%)	

S = Statistically significant.
NS = Statistically not significant

Table 3 : **Association of Cognitive Impairment with Anosmia in Cases**

	Cases with Anosmia N = 64	Cases without Anosmia N = 36	P Value
Cases With Cognitive Impairment N = 50	50 (78.12%)	0 (0%)	Chi sq.=56.25 P value = 6.38 x 10-14
Cases Without Cognitive Impairment N= 50	14 (21.87%)	36 (100%)	

Table 5 : **Biochemical Parameters in Cases and Controls**

Parameters	**Cases**	**Controls**	**P Value**	
FBS	96.54 ± 21.67	90 ± 6.96	0.002	S
PPBS	129.55 ± 30.23	120.94 ± 7.55	0.003	S
Cholesterol	150.68 ± 36.13	146.02 ± 25.33	0.14	NS
Triglycerides	114.67 ± 40.77	102.23 ± 31.26	0.008	S
VLDL	23.45 ± 8.24	21.1 ± 6.03	0.011	S
HDL	39.25 ± 9.17	43.05 ± 6.92	0.0005	S
LDL	89.23 ± 36.48	78.94 ± 23.90	0.009	S
T3	1.08 ± 0.23	1.036 ± 0.22	0.06	NS
T4	6.51 ± 0.60	6.61 ± 0.44	0.09	NS
TSH	1.40 ± 0.44	1.34 ± 0.30	0.12	NS
Haemoglobin	12.47 ± 0.96	12.95 ± 0.91	0.0001	S
Blood Urea	16.4 ± 3.86	15.29 ± 3.20	0.01	S
Creatinine	0.82 ± 0.22	0.778 ± 0.18	0.04	S

S = Statistically significant. NS = Statistically not significant

Table 6 : **Univariate Analysis of Cases**

		Anosmia Present (N=64)	**Anosmia Absent (N=36)**	**P Value**
Cognitive Impairment	+	50 (78.12%)	0 (0%)	Chi Sq. = 56.25
	-	14 (21.87%)	36 (100%)	P Value < 0.001
				S
Diabetes Mellitus	+	9 (14.06%)	2 (5.55%)	Chi Sq.= 1.70
	-	55 (85.94%)	34 (94.44%)	P Value = 0.19
				NS
Dyslipidemia	+	50 (78.12%)	22 (61.11%)	CHI SQ. = 3.30
	-	14 (21.87%)	14(38.88%)	P Value = 0.068
				NS
Hypertension	+	31 (48.44%)	11 (30.55%)	Chi Sq.= 3.02
	-	33 (51.56%)	25 (69.44%)	P Value = 0.08
				NS

S = Statistically significant. NS = Statistically not significant

Original Article

Hypomagnesemia in Critically Ill Patients

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ABSTRACT

Background : Magnesium (Mg) is essential for normal cellular functions and is the second most abundant intracellular cation after potassium. In general, Mg deficiency has been associated with a number of clinical manifestations. However there is a paucity of data evaluating serum magnesium at admission as a predictor of morbidity or mortality especially in Indian context. Hence the present study was undertaken to determine the usefulness of admission serum magnesium levels with regards to patient outcome.

Aims and Objectives : To study serum magnesium level in critically ill patients and to correlate it with Length of stay in MICU, Need for ventilatory support, Duration of ventilatory support, APACHE II score and mortality.

Results : In the present study 44% of patients were hypomagnesemic as compared to 56% of patients who were normomagnesemic. The patient with hypomagnesemia had longer duration of hospital stay (3.52 ± 1.60 vs 2.51 ± 0.87) more frequent need for ventilatory support (60.46% vs 39.53%) had higher mortality (60% vs 40%) higher APACHEII score and higher frequency of sepsis (62.96% vs 37.03%) compared to patients with normal magnesium. Serum hypokalemia was present in 55.17% of patients with hypomagnesemia and hypocalcemia was present in all the patients with hypomagnesemia. Hypertension (60% vs 40%), Diabetes mellitus (64.51% vs 58.06%) was significantly higher in hypomagnesemic than normomagnesemics.

Conclusion : Patients with hypomagnesemia on admission are significantly at high risk of mortality, requirement of ventilation, prolonged ventilatory support and longer duration of hospital stay and higher APACHE II score. So it is recommended to do serum magnesium level on admission in patient admitted in intensive care units.

Key words : Hypomagnecemia, Critically ill patients, APACHE II score.

Introduction :

Magnesium (Mg) is essential for normal cellular functions and is the second most abundant intracellular cation after potassium. It serves as a co-factor for several enzymes required for electrolyte homeostasis and is also necessary for membrane stability, cell division and generation of action potentials.[1] Magnesium is pivotal in the transfer, storage, and utilization of energy as it regulates and catalyzes > 300 enzyme systems.[2] In general, Mg deficiency has been associated with a number of clinical manifestations such as atrial and ventricular arrhythmias, cardiac insufficiency, coronary spasm, sudden death, skeletal and respiratory muscle weakness, bronchospasm, tetany, seizures and other neuromuscular abnormalities and a number of electrolyte abnormalities, including hypokalemia, hypocalcemia, hyponatremia and hypophosphatemia.[3-5] Magnesium deficiency is common in critical illnesses[6], and correlates with higher mortality rate and worse clinical outcome in the intensive care unit patients.[6] Hypomagnesemia is often overlooked, although it carries prognostic significance. The Prevalence of hypomagnesemia (measuring total serum magnesium) has a wide range (11% to 61%) and considerable controversy exists regarding its effects on morbidity and mortality.[1] Hence the present study was undertaken to determine the usefulness of admission serum magnesium levels with regards to patient outcome considering mortality, need and duration of ventilatory support, length of stay in ICU and APACHE II Score.

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Methodology :

A Prospective observational study was conducted for a period of three year at tertiary care hospital

after clearance from Institutional Ethics Committee. The patients with APACHE II score more than 20 admitted in ICU were enrolled after taking written informed consent. Demographic data such as age and sex were recorded. Patients were assessed for presenting complaints, history of other diseases and habits through an interview with the patients or care giver. Further, these patients underwent a thorough clinical examination for vitals (pulse rate, blood pressure and respiratory rate) and other clinical signs including Glasgow coma score (GCS) followed by systemic examination. These findings were recorded on a predesigned and pretested proforma. A blood sample was collected for estimation of serum total magnesium level by CALMAGITE METHODE on admission. Other haematological biochemical and radiological investigation were performed as indicated in every patient. Patients were followed up for the outcomes such as mortality, need of ventilator support, duration of ICU stay and APACHE II Score.

Statistical Analysis :

The data obtained was coded and entered into Microsoft Excel Worksheet. The categorical data like sex, presenting complaint and ventilatory support was expressed as actual numbers and percentage and comparison was done using Pearson's chi-square test. The continuous data like age, temperature, pulse rate was expressed as mean ± standard deviation (SD) and comparison was done by unpaired student 't' test. A probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

Statistical software STATA version 13.1 was used for statistical analysis.

Results :

Total 100 patients included in the study were analysed in two groups based on serum magnesium level that is, serum magnesium < 1.5 mg/dl were considered hypomagnesemic and serum magnesium = 1.5 mg/dl were considered normomagnesemic.

In the present study 44% of patients were hypomagnesemic as compared to 56% of patients who were normomagnesemic Mean age of the cases inhypomagnesemic gr was 50.40 + 16.35 vs 42.39 + 13.89 in normomagnesemic group. Among patients with hypomagnesemia 72.22% of patients were aged more than 60 years as compare to 27.77% in patients with normomagnesemia. This difference was statistically significant (p=0.0008). ***(Table 1)***

The mean duration of hospital stay in patients with hypomagnesemia was significantly high (3.52 ± 1.60 days) compared to normomagnesemic patients (2.51 ± 0.87) (p=0.0001). ***(Table 1)***

Significantly higher number of patients with hypomagnesemia required ventilation (60.46%) compared to patient with normomagnesemia (39.53%) (p<0.004). Mean days of ventilation among patients with hypomagnesemia was also significantly high (3.12 ± 1.42) compared to normomagnesemic patients (2.16 ± 0.70) (p=0.004). ***(Table 1)***

All the patients with APACHE II score of > 30 were having serum hypomagnesemia as compared with none of the patient with normomagnesemia had APACHE II score > 30. This difference was statistically significant (p=0.0001). ***(Table 1)***

Mortality was 60% in patients with hypomagnesium levels as compared to 40% of patients with normomagnesemia. This difference was statistically significant (p=0.001). ***(Table 1)***

Pre-existing risk factors like hypertension & Diabetes Mellitus were significantly more hypomagnesemia group as compared to Normomagnesemia group (Hypertension 60% vs 40% & DM 64.51% vs 58.06%) (p=0.035 & p=0.001).

At time of admission 55.5% of patients with Glasgow coma score between 5-10 had low serum magnesium as compared to 44.4% of patients with normal serum magnesium. This difference was statistically significant (p=0.024). ***(Table 1)***

ARDS was observed significantly more (87.5%) in patients with hypomagnesium compared to 12.5% in patients with normal serum magnesium level. Next common complication observed was sepsis ie in 62.96% of patients with low serum magnesium compared with 37.03% patients with normal serum

magnesium. ***(Table1)***

Similarly multiorgan dysfunction was seen in 66.66% patients with hypomagnesemia compared with 33.33% of patients with normal serum magnesium .

When electrolytes were estimated, hypokalemia was seen predominantly in 55.17% of patients with hypomagnesemia and next common was Hypocalcemia which was seen in all the cases with hypomagnesemia compared with 54.16% with normal serum magnesium. ***(Table 1)***

Reported incidence of hypomagnesemia in critically ill patients in previous studies[10,11] is 56% and 52%, While in the present study it was 44% which is slightly less than others.

Mean age of the patients with hypomagnesemia, 60.27+0.82 vs 58.84+0.86 of normomagnesemia is reported in one of the studies[1]. In the present study mean age of the patients with hypomagnesemia was 50.40+16.35 vs 42.39+13.89 yrs. innormomagnesemic group which was statistically significant.

Table 1 : **Results of present study. In Two different groups**

Parameters	Serum Magnesium		p-value
	<1.5	**= 1.5**	
Age in years	50.40 ± 16.35	42.39 ± 13.89	S
Mortality rate	30/44 (60%)	20/56 (40%)	S
Prevalence	44/100 (44%)	56/100 (56%)	
GCS	10.38 ± 1.50	11.10 ± 1.50	S
APACHE-II	25.02 ± 3.28	22.25 ± 1.66	S
Serum sodium	134.63 ± 10.3	135.17 ± 9.34	NS
Hypokalemia	3.66 ± 1.11	4.16 ± 0.93	S
Sr. Calcium	6.65 ± 1.05	7.26 ± 0.89	S
Duration of ICU(days)	3.52 ± 1.60	2.51 ± 0.87	S
Duration of ventilatory support (days)	3.12 ± 1.42	2.16 ± 0.70	S
Need for ventilation	26/44(60.4%)	17/56(39.5%)	S

S = Statistically significant. NS = Statistically not significant

Discussion :

Magnesium plays an important role in homeostasis and is a cofactor for most of ATP reactions. Hypomagnesemia is an emerging electrolyte disturbance in hospitalized patients especially in the critically ill ones. Many factors contributes to hypomagnesemia like impaired GI absorption, nasogastric suction poor intake and drugs causing increase renal loss. Most of the studies measured total serum magnesium however RBC MAGNESIUM is a better index of intracellular magnesium. Its prevalence has a wide range (11% to 61%) and considerable controversy exists regarding its effects on morbidity and mortality.[7-9]

No statistically significant difference was observed between hypomagnesemia & gender in the present study. In contrast **Safavi M** *et al.*[12] reported 51% of the patients with hypomagnesemia were males and 49% were females with male to female ratio of almost 1:1.

Hypomagnesemia is known to cause muscle weakness and respiratory failure. It is one of the factors causing difficulty in weaning the patient from the ventilator.[13] A strong association was observed between severity of Hypomagnesemia and need of mechanical ventilation for longer duration prolonged hospital stay also.[13,14]

In the present study 26 (60.46%) patients with Hypomagnesemia required ventilation as compared to 17 (39.53%) patients with normal magnesium levels. The mean duration of ventilation in patients with hypomagnesemia was also significantly high (3.12 + 1.42 days) compared to (2.16 + 0.70 days) in cases with normal magnesium & mean duration of hospital stay was also significantly more in hpomagnesemic patients. Similar kind of results are reported by **Demircan F** *et al*[14]

Hypomagnesemic patients have more severe organ dysfunction and higher APACHE II score than the other patients. This may be explained by a strong association of hypomagnesemia with sepsis and septic shock, a common cause of death in the ICU patients. Cases with hypomagnesemia may have significantly higher mortality risk based on APACHE II score at admission. In most of the previous studies higher mortality was reported in critically ill cases with hypomagnesemia with high APACHE II score.[12,14,15] The present study could find similar results.

Rubeizet *et al*.[16] reported nearly double mortality rate (46% vs 25%) in hypomagnesemic patients compared to those with normomagnesemia. In contrast, **Guerin** *et al*.[9] found no significant difference between hypomagnesemic and normomagnesemic patients in ICU mortality (18% vs 17%) but noted higher mortality in hypermagnesemic patients.

The disparity in rates of mortality among the hypomagnesemics could be attributed to the various other factors such as age, history and clinical presentation at admission.

Hypomagnesemia has been known to be associated with diabetes mellitus, insulin resistance and hypertension. Hypomagnesemia is due to increase renal loss of magnesium that accompanies glycosuria. Magnesium supplementation is associated with decreased insulin requirements and better control of blood sugar[17-18] Amomgst pre-existing risk factors Hypertension and DM did not show any significant association with Hypomagnesemia.

Magnesium plays an important role in sepsis. Hypomagnesemia is associated with increase release of endothel in and proinflammatory cytokines. In the present study sepsis was observed in 62.96% of cases with Hypomagnesemia while multiorgan dysfunction in 66.66% cases suggesting that ARDS with sepsis and multiorgan failure are commonly associated with serum hypomagnesemia. Similar kind of results are reported by various authors in their studies previously.[14,19]

Zafar, Mir Sadaqat Hassan *et al.*[19] found that Hypomagnesemic patients mostly comprised of multiorgan dysfunction (41.17%), respiratory failure (17.64%) and septicemia (11.76%) where asnormomagnesemic patients had mostly septicemia (20%), post-operative course (16%), respiratory failure (14%), renal failure (10%) and acute myocardial infarction (10%).

Hypomagnesemia is commonly associated with other electrolyte abnormalities. Like Hypokalemia & hypophosphatemia, hypocalcemia and hyponatremia. **Whang** *et al.*[20] in his study on critically ill cases with hypomagnesemia reported hypokalemia in 42%, hypophosphatemia 29%, hyponatremia 27% cases and 22% patients hadhypocalcemia. In the study by **Limaye** *et al.*[10], half of the patients (48%) with hypokalemia had low serum magnesium levels. **Zafar, Mir Sadaqat Hassan** *et al.*[19] found that associated electrolyte abnormalities in hypomagnesemic patients were hypokalemia (58.82%), hyponatremia (47.05%), hypocalcemia (70.58%) and hypophosphatemia (29.41%).

In our study, hypokalemia was seen in 55.17% of patients with hypomagnesemia and Hypocalcemia was seen in all the cases with hypomagnesemia compared with 54.16% with normal serum magnesium. This incidence was slightly more as compared to others.

Hypokalemia, hypocalcemia, hypophosphatemia are said to be the predictors of hypomagnesemia. Hypokalemia seen in hypomagnesemic patients is relatively refractory to potassium supplementation until magnesium deficiency is corrected.[20-21] This is

due to defective membrane ATPase activity and also because the renal potassium loss is increased in presence of hypomagnesemia..

Overall, hypomagnesemia is a common electrolyte imbalance in the critically ill patients and is associated with higher mortality rate, more frequent and prolongedventilatory support. Therefore, early diagnosis and treatment of hypomagnesaemia is necessary.

Conclusion :

Hypomagnesemia is a common electrolyte imbalance in critically ill patients. Patients with hypomagnesemia on admission are significantly at high risk of mortality, requirement of ventilation, prolonged ventilatory support and longer duration of hospital stay. It may be the result of underlying disease, diuretics or sepsis.

Implication of the study :

Additional studies are required to address the current approach to magnesium imbalance in critically ill patients, as well as the association of hypomagnesemia with morbidity and mortality, and the effect of the correction of this electrolyte disorder. It seemed that correction of hypomagnesemia decreases hypomagnesemia associated morbidity, therefore early diagnosis and treatment of hypomagnesemia is necessary. Monitoring of serum magnesium level may have prognostic, and perhaps, therapeutic implications and we physicians should be alert to the high incidence of magnesium deficiency in critically ill patients

Conflicts of Interest : None reported by authors.

References :

1. Mousavi SAJ, Salimi S, Rezai M. Serum Magnesium Level Impact on the Outcome of Patients Admitted to the Intensive Care Unit Tanaffos 2010;9(4):28-33.
2. González EP, Santos F, Coto E. Magnesium homeostasis. Etiopathogeny clinical diagnosis and treatment of hypomagnesaemia. A case study. Nefrologia 2009;29(6):518-24.
3. Al-Ghamdi SM, Cameron EC, Sutton RA. Magnesium deficiency Pathophysiologic and clinical overview. Am J Kidney Dis 1994;24: 737-52.
4. Sanders GT, Huijgen HJ, Sanders R. Magnesium in disease: A review with special emphasis on the serum ionized magnesium. Clinical Chemistry Laboratory Medicine. 1999;37(11-12):1011-1033.
5. Speich M, Bousquet B, Nicolas G. Reference values for ionized, complexed, and protein bound plasma magnesium in man and women. ClinChem 1981;27:246-8.
6. Tong GM, Rude RK. Magnesium deficiency in critical illness. J Intensive Care Med 2005;20(1):3-17
7. Reinhart RA, Desbiens NA. Hypomagnesemia in patients entering the ICU. Crit Care Med 1985;13:506-7.
8. Chernow B, Bamberger S, Stoiko M, Vadnais M et al. Hypomagnesemiain patients in postoperative intensive care. Chest 1989;95:391-7.
9. Guerin C, Cousin C, Mignot F et al. Serum and erythrocyte magnesium in critically ill patients. Intensive Care Med 1996; 22:724-7.
10. Limaye CS, Londhey VA, Nadkart MY et al. Hypomagnesemia in critically ill medical patients. J Assoc Physicians India 2011;59:19-22.
11. Huijgen HJ, Soesan M, Sanders R et al. Magnesium levels in critically ill patients : what should we measure? Am J ClinPathol. 2000;114:688- 695.
12. Safavi M, Honarmand A. Admission hypomagnesemia--impact on mortality or morbidity in critically ill patients. Middle East J Anesthesiol. 2007;19(3):645-60.
13. Zaloga G, Roberts P. Calcium, magnesium and phosphorus disorders. Textbook of critical care, 4th ed, Shoemaker, Ayres (ed), Philadelphia W.B. Saunders; 2000. p. 862-75.
14. Demircan F, Altun Y, KýlýncF. Hypomagnesemia In Internal Care Unit.IJBCS 2013;1(1):180-9.
15. Soliman HM, MercanD, Lobo SS *et al.* Development of ionized hypomagnesemia is associated with higher mortality rates. Crit Care Med 2003;31(4):1082-7.
16. Rubeiz GJ, Thill-Baharozian M, Hardie D et al. Association of hypomagnesemia and mortality in acutely ill medical patients. Crit Care Med 1993;21(2):203-9.
17. Paolisso G, Barbagallo M. Hypertension, diabetes mellitus, and insulin resistance: The role of intracellular magnesium. Am J Hypertens 1997;10:346-55.
18. Kawano Y, Matsuoka H, Takishita *et al.* Effects of magnesium supplementation in hypertensive patients

: Assessment by office, home, and ambulatory blood pressures. Hypertension 1998;32:260-5.

19. Zafar, Mir Sadaqat Hassan, et al. "Significance of serum magnesium levels in critically ill-patients." International Journal of Applied and Basic Medical Research 4.1 (2014) : 34.
20. Whang R, Flink EB, Dyckner T. Magnesium depletion as a cause of refractory potassium repletion. Arch Intern Med 1985;145:1686-1689.
21. Webb S, Schade DS. Hypomagnesemia as a cause of persistanthypokalemia. JAMA 1975; 233:23-24.

Zika Virus : A Review for Clinicians

Kharkar S[1]

ABSTRACT

Zika virus is a flavivirus related to Dengue virus, yellow fever virus and West Nile virus. It is Considered an emerging arbovirus transmitted by mosquitoes of the genus Aedes. Clinical picture is Characterised as a "dengue-like" syndrome, with abrupt onset of fever and an early onset skin rash, pruritic often.

Nevertheless, until now deaths and complications Caused by the disease are not reported. The rapid spread of the virus and its epidemic potential are especially problematic in countries where there are the circulation of other arboviruses which imposes difficulties in the differential diagnosis and healthcare burden. Control measures are the same recommended for dengue and chikungunya which are based in health education and vector control.

Key Words : Zika Aedes; arboviruses; flavivirus; Flaviviridae Infections.

Introduction :

Zika virus is a flavivirus related to Dengue virus, yellow fever virus and West Nile virus. It is Considered an emerging arbovirus transmitted by mosquitoes of the genus Aedes. It first identified in 1947 in the Zika Forest in Uganda, isolated on rhesus monkey used for the study the yellow fever virus. Sporadic cases have Been Detected in African countries and at the end of the 70's in Indonesia. In 2007 epidemics were described in Micronesia and other islands in the Pacific Ocean and more recently in Brazil. Clinical picture is characterised as a dengue-like syndrome, with abrupt onset of fever and an early onset skin rash, pruritic Often. Occasionally the disease Has Been associated with Guillain-Barré syndrome. Nevertheless, until now deaths and complications Caused by the disease are not reported. The diagnosis can be Performed by PCR or by IgG and IgM antibodies detection. The rapid spread of the virus and its epidemic potential are especially problematic in countries where there are the circulation of other arboviruses which imposes difficulties in the differential diagnosis and healthcare burden. Control measures are the same recommended for dengue and chikungunya which are based in health education and vector control.[1]

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Etiology

The Zika virus (ZIKV) belongs to Flaviviridae family and the genus flavivirus is therefore related from an evolutionary point of view with other arbovirus transmitted by mosquitoes, as are the dengue virus, yellow fever (YFV) and viruses West Nile. It is a virus with a genome of ribonucleic acid (RNA) of simple positive polarity chain. Although not known to virion structure, compared to other known flavivirus, this must be limited by a co lipid envelope derived from the endoplasmic reticulum of cells in which these viruses replicate, restricting this housing externally with a capsid structure and symmetry, consisting of the C protein and the viral genome.[2]

Zika virus, has a positive-sense, single-stranded RNA genome approximately 11 kilobases in length. The genome contains 5' and 3' untranslated regions flanking a single open reading frame (ORF) that encodes a polyprotein that is cleaved into three structural proteins : the capsid (C), premembrane / membrane (prM), and envelope (E), and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, 2K, NS4B, and NS5). A previous genetic study using nucleotide sequences derived from the NS5 gene indicated three ZIKV lineages : East African (one strain examined), West African (three strains examined), and Asian (one strain examined).

The viral envelope contains the two surface proteins (designated M and E) and, additionally, the viral genome encodes number of other proteins, non-structural di-tas that either have enzymatic activity (NS3 : RNA helicase and protease and NS5 : RNA polymerase, RNA-dependent) or perform regulatory functions (control replication, transcription, translation and immune response) during the replication intracellular.[2]

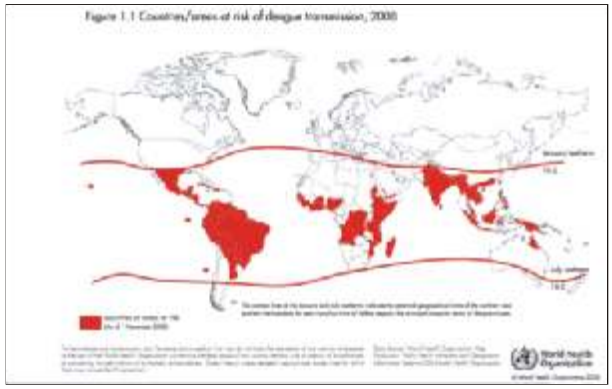
Disease distribution

After isolation of the virus in 1940s, it was detected the first cases of infection ZIKV in humans in 1952 in Uganda.[3] 1953 were also detected cases in Nigeriaand 1956 mosquitoes Aedesaegypti species were infected laboratory resulting in successful transmission of the virus in mice by 60% of cases. in the 1960s, individuals with positive serology for ZIKV continued to be identified in serological surveys conducted in Nigeria and also in patients with fever for FMD epidemic in 1970. Between the years 1975 to 1977 were found serological and virological evidence of infection ZIKV in Sierra Leone, Nigeria, Senegal, Gabon, Costa Mar me in African Central.[3,4]

The first evidence of virus circulation outside the African continent took place between the years 1977 and 1978, when cases of acute febrile illness were admitted to a hospital in Indonesia, and found antibodies in serum ZIKV 30[5,6]. In February 2014, for the first time in the Americas, cases were reported in Easter Island (Chilean territory in the Paci Ocean Co), probably related to the outbreak in Micronesia and PF. In 2015 was confirmed virus circulation in northeastern Brazil from viral isolation in suspected cases of dengue.[7,8,9]

Recently, the Ministry of Health of Brazil published a note that cases of the disease had been confirmed in eight states of the country, including the North, Northeast and sudpste

Fig. 1 : **shows the countries where it already became clear the presence of infection in zero epidemiological surveys and indigenous transmission of the disease.**



Clinical manifestations of infection caused by ZIKV, the information is limited to descriptions of isolated cases or series of cases in epidemic situations. The incubation period ranges from three to 12 days after the mosquito bite infected similarly to that described for other arboviroses[10] Clinical manifestations of the disease can vary depending on location, and often a syndrome 'type-dengue'. asymptomatic infections are also described from survey results serological.[11-12]

McNamara 7 described the first three human cases of infection ZIKV in 1954 in Nigeria, associated with jaundice. However the location was endemic for malaria and FA and therefore it was not possible to differentiate between the manifestations of the disease ZIKV other diseases. Later, Bearcroft[35] induced infection in healthy volunteer through exposure to Ae. aegypti infected; the patient presented with a fever especially and self-limited without rash, three days after the inoculation. In fact, this seems not experimentally infected individuals have developed viremia sufficiently intense to allow transmission of the ZIKV Ae. Aegypti that about him fed.

Fig. 2 : **rash caused by infection Zika virus and conjunctivitis**

Descriptions of cases of the disease in Africa in the following years featured the disease ZIKV as a febrile episode of acute onset, accompanied by mild headache, emergence of maculo-papular rash pruritic, on the second day, involving the face, trunk, limbs, palms and soles.

The diagnosis was confirmed by clinical and epidemiological criteria and negative serology for dengue virus. Fever gives a day or two after the onset of the rash, which may persist for two to 14 days (average duration of six days).[13,14]

Usually the disease is low, but in some cases reported in Brazil was high, reaching 39 C. 5 are reported myalgia, joint pain and mild backache, but unlike the cases of chikungunya, the pain is less intense and more affect hands , knees and ankles. Usually their disappearance occurs about a week, with an average duration of three to five days.[12] Conjunctivitis has been commonly reported and, characteristically, has no pus. There may be other manifestations as anorexia, nausea, vomiting, dizziness and back-pain orbital[15,16]

It can be assumed that the infection by ZIKV is benign, but as the epidemic that occurred in the PA, in Brazil there have been many cases of Guillain-Barré syndrome (GBS), which came a few days after the development of clinical the infection. The triggering mechanism of this condition is not yet known, a likelihood that autoimmune phenomenon as observed in other infections. So far there has been no death registration in patients who developed GBS, although some cases have required treatment in intensive care units. Nevertheless, the association between infection and ZIKV GBS still lacks verification through analytical studies[16]

Information about the hematological and biochemical changes in the disease ZIKV are scarce in the literature. In some case reports are described increased lactate dehydrogenase and C-reactive protein. There may be leukopenia and thrombocytopenia.[15]

The diagnosis was confirmed by clinical and epidemiological criteria and logical negative serology for dengue virus.[13]

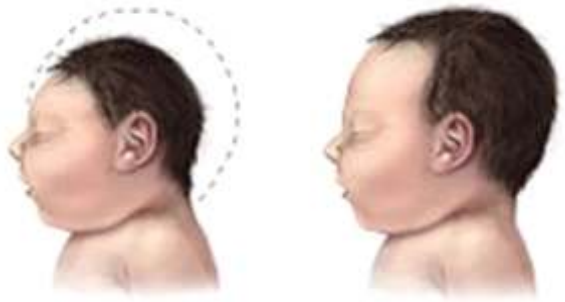
The differential diagnosis is made primarily with dengue and chikungunya. The rash illness caused by virusesT like Human parvovirus B19 infection by the Epstein-Barr virus, measles and rubella among others should also be investigated for their high transmission capacity in community . The infection ZIKV should also be considered in cases of post-travel fever in individuals returning from climates tropical.

There are no known cases of reinfections by ZIKV if thinking that an infection gives permanent immunity

Symptom	Dengue	Chikungunya	Zika
fever	+++	++	+
mayalgia	+++	++	+
exanthema	+	++	+++
arthralgia	+/-	+++	+
conjunctivitis	-	++	+++
shock	+++	+/-	-
neutropenia	++	+	SI
headache	++	+	+/-
dyscrasias	++	+/-	-
thrombocytopenia	+++	+/-	+/-
Lymphopenia	++	+++	SI

Table 1 : most common clinical manifestations fever caused by dengue virus, chikungunya and Zika virus

Pregnancy



Microcephaly

It is believed that the disease may be spread from mother-to-child in the womb and cause microcephaly. This is not yet confirmed, but there are a very few well documented reports.

In November 2015, reports from the Brazilian Health Ministry found two cases in Northeastern Brazil of severely affected babies in whom amniocentesis confirmed the presence of the Zika virus in the amniotic fluid. The ultrasound findings showed that both babies had a small head circumference (microcephaly) due to the destruction of different parts of the brain. One of the fetuses was also found to have calcifications in their eye and microphthalmia. Another study in an autopsy of a microcephalicfetus found Zika virus DNA as well as pathological damage in only the brain and not other organs, suggesting that the virus is neurotropic.

Investigators have also found evidence of eye abnormalities such as chorioretinal scarring in newborns with Zika-associated microcephaly. These lesions could lead to significant vision loss. It is still unclear whether this can happen in Zika exposed newborns that do not have microcephaly.

Laboratory diagnosis

Due to the absence, so far, commercial tests for serological diagnosis of infections ZIKV, the diagnosis of acute infection with this virus may be performed by RT-PCR (amplification by reacting polymerase chain, preceded by reverse transcription) directly from RNA extracted from patient serum, preferably harvested until the sixth day of disease. However, in the case of Yap island epidemic virus was identified (via the viral genome cation amp) at the 11th day after onset of symptoms.[17,18] The virus may also be detected by molecular techniques applied in other body fluids such as saliva and urine.

IgM antibodies can be found on the third day of illness and IgG antibodies should be investigated in acute and convalescent serum.[17] A problem in relation to the serology is the possibility of cross-reactivity as a result of previous infection by other flavivírus.[17,18] Nevertheless, several studies that have been reported or qualitative ratings or quantitative, the presence of anti-ZIKV antibodies in biological samples, and some of the techniques employed are not standardised techniques being used in laboratory specific contexts (technical in- house).

Despite the existence of diagnostic tests, its use is still very limited because there is no commercial kits available in the market. Therefore, the diagnosis is limited to government institutions involved in health surveillance, or teaching and research institutions. The detection of viral genomes by RT-PCR is the most sensitive method and specific to allow a diagnosis of infections to ZIKV, however these methods are not, as yet, fail-safe. Contrary to what happens to other viruses, the restricted circulation of the virus has limited knowledge about their actual genetic diversity, so there is a different probability of zero that the primers used in amp ZIKV genome cationscan not allow the amp cations required (false negative amp cation). This case should be evaluated hereinafter.

Treatment

There are no vaccines in India Bharat Biotech International, Hyderabad has developed vaccine) or antiviral drugs specific, and symptomatic treatment. The utilization analgesics and antipyretics should be careful to avoid induction of adverse effects such as hepatopathy, nephropathy and allergies. The use of aspirin (salicylates) should be discouraged to prevent the induction of bleeding events in patients diagnosed with dengue erroneously as infections by ZIKV under clinical diagnosis not be conclusive and even serological test present possibility of failure.

The intense itching that accompanies the rash has been reported by patients as a serious discomfort. The therapeutic approach to relieve symptoms can start-up with the guidance of avoiding hot baths, excessive use of soap and proper hydration of the skin. If there is no satisfactory answer are recommended cold baths and the use of cooling lotions containing calamine or menthol. The pathogenesis of cutaneous manifestations is still unclear, so the use of older antihistamines can be helpful in the patient more for that cause sedation than for his performance in the cause of pruritus Corticosteroids should not be used for is unknown its effectiveness and the regression of this symptom.

GBS must be addressed in a conventional manner. The diagnosis is made by progressive weakness of finding two or more members, exiaarre and evolution in a maximum of four weeks. The CSF analysis may show increased protein and low cellularity (albumin-cytological dissociation). Suspected patients should be monitored in intensive care units at risk of progression to paralysis of the respiratory muscles. Therapeuticoptions for GBS include plasmapheresis or intravenous hyperimmune immunoglobulin both are expensive, but decrease the time.

Control measures

The Aedesaegypti is a highly synanthropic mosquito, which takes advantage of peri domestic environments and even can make your blood meals inside human habitations. Considering that is one of the vectors ZIKV and given that vector control measures based on the use of insecticides can be complicated by (i) financial constraints, (ii) logistical issues, (iii) regulation fastened to the use of insecticides and/or (iv) spreading resistance in the vector population, the removal of larvae breeding plays an important role in the control of this vector. Personal protective measures should be encouraged as well as use of repellent and installing screens on windows and doors. The health surveillance should prioritise the detection and investigation of suspected cases in order to interrupt transmission in problem areas. Individuals with active disease or recently should not donate blood.

References :

1. Haddow AD, AJ Schuh, Yasuda CY, Kasper MR, Heang V, Huy R, *et al.* Genetic characterization of Zika virus strains : geographic expansion of the Asian lineage. Trop Dis. 2012; 6: e1477.
2. The Faye, Freire DC, Iamarino A, Faye O, de Oliveira JV, Diallo M, et al. Molecular evolution of Zika virus During its emergence in the 20th century. Trop Dis. 2014; 8: e2636.
3. Zanluca C, Melo VC, Mosimann AL, GI Santos, Santos CN, Light K. First report of autochthonous transmission of Zika virus in Brazil. Mem Inst Oswaldo Cruz. 2015; 110: 569-72.
4. Dick GW. Epidemiological notes on some viruses isolated in Uganda; Yellow fever, Rift Valley fever, Bwamba fever, West Nile, Mengo, Semliki forest, Bunyamwera, Ntaya, Uganda S and Zika viruses. Trans R Soc Trop Med Hyg.1953; 47:13-48.
5. Monath TP, DC Wilson, J. Casals The 1970 yellow fever epidemic in Okwoga District, Benue Plateau State, Nigeria. 3. Serological responses in persons with and without pre-existing heterologous group B immunity. Bull World Health Organ. 1973;49:235-44.
6. Saluzzo JF, Gonzalez JP, JP Hervé Georges AJ. Serological survey for the prevalence of Certain arboviruses in the human population of the south-east area of Central African Republic. Bull Soc Pathol Exotfiliales. 1981;74:490-9.
7. RS Lanciotti, Kosoy OL, JJ Laven, Velez OJ, Lambert AJ, AJ Johnson, et al. Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. Emerg Infect Dis.2008;14:1232- 9.
8. Musso D, Nilles EJ, Cao-Lormeau VM. Rapid spread of emerging Zika virus in the Paci c area. ClinMicrobiolInfect. 2014;20:O595-6.
9. Promed email [homepage of the internet]. Zika virus - Brazil (11) (various states), cases con rmados. [Accessed 2015 Jul 20]. Available in : http://www.promedmail.org/direct.php?id=20150612.3431199.
10. AJ Haddow, Williams MC, Woodall JP, Simpson DI, LK Goma. Twelve isolations of zika virus from aedes (Stegomyia) africanus (theobald) taken in and above the Uganda forest. Bull World Health Organ. 1964;31:57-69.
11. Musso D, C Roche, Robin And Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zikavirus.Emerg Infect Dis. 2015;21:359-61.

12. The Gezer, Henderson BE, Christensen S. multipurpose serological survey in Kenya. 2. Results of arbovirus serological tests. Bull World Health Organ. 1970;43:539-52.
13. Fagbami AH. Zika virus infections in Nigeria : virological and seroepidemiological investigations in Oyo State. J Hyg.1979;83:213-9.
14. Bearcroft WG. Zika virus infection Experimentally induced in the human volunteer. Trans R Soc Trop Med Hyg.1956;50:442-8.
15. Simpson DI. Zika virus infection in man. Trans R Soc Trop Med Hyg.1964;58:335-8.
16. Oehler and Watrin L Larre P-LeparcGoffart I Lastere S Valour F, etal. Zika virus infection complicated by Guillain-Barre syndrome - case report, French Polynesia, December 2013. Euro Surveill.2014;19.
17. Zammarchi L, Stella G Mantella A, Bartolozzi D, D Tappe, Günther S, et al. Zika virus infections imported to Italy : clinical, immunological and virologicalndings, and public health implications. Clin Virol.2015;63:32-5.
18. Zammarchi L, Tappe D, C Fortuna, Remoli ME, Günther S, G Venturi,et al. Zika virus infection in a traveler returning to Europe from Brazil, March 2015. Euro Surveill.2015; 20.

Approach to Tropical Infections in India

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ABSTRACT

Tropical fevers are defined as infections that are prevalent in, or are unique to tropical and subtropical regions. These infections are always in consideration whenever a pyrexial episode occurs however one must remember that many common infections, such as influenza and tuberculosis, also occur in the tropics and may have atypical presentations confusing the clinician. In a vast country like India a knowledge of areas with recent outbreaks can be very helpful in recognizing the clinical entity. This article is to focus on most common infections during monsoon on the basis of available epidemiologic data from India. These included dengue hemorrhagic fever, rickettsial infections/scrub typhus, malaria (usually falciparum), typhoid, and leptospira bacterial sepsis and common viral infections like influenza.

Key words : tropical fever, India

Tropical fevers are defined as infections that are prevalent in, or are unique to tropical and subtropical regions. Some of these occur throughout the year and some especially in rainy and post-rainy season. Major Concern about them is, high prevalence and morbidity and mortality caused by these infections, and overlapping clinical presentations, difficulties in arriving at specific diagnosis and need for early empiric treatment.

Pyrexial illness is a presentation of many diseases particularly associated with tropical environments, but one should remember that many common infections, such as influenza and tuberculosis, also occur in the tropics or may be acquired en route to and from exotic locales. Febrile patients may also have chronic or recurrent medical problems that are unrelated to their tropical exposure, including non-infectious disease e.g. autoimmune or malignant conditions.

This article is to focus on most common infections during monsoon on the basis of available epidemiologic data from India with emphasis on appropriate diagnosis and apt management. These included dengue hemorrhagic fever, rickettsial infections / scrub typhus, malaria (usually falciparum), typhoid, and leptospira bacterial sepsis and common viral infections like influenza.

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'Syndromic approach' to diagnosis and treatment of tropical infections can help in narrowing down the possibilities and simplifying the treatment. Commonly seen syndromes are undifferentiated fever, fever with rash / thrombocytopenia, fever with acute respiratory distress syndrome (ARDS), fever with encephalopathy and fever with multi organ dysfunction syndrome.

The tropical infections may be approached in the under the following syndromes[1].

1) Acute undifferentiated fever : patients with acute onset fever without any localizing signs
   a. malaria, dengue, leptospirosis, scrub typhus, typhoid, other common viral infections)
2) Fever with rash / thrombocytopenia : Acute onset fever with a transient skin rash or exanthema, with or without thrombocytopenia (platelet count < 100,000)
   a. Dengue, rickettsial infections, meningococcal infections, malaria (falciparum), leptospirosis, measles, rubella, other viral exanthems
3) Fever with ARDS : Acute onset fever with respiratory distress in the form of SpO2 <90% at

room air or frank ARDS with PaO2/FiO2 ratio <200.

a. Scrub typhus, falciparum malaria, influenza (including H1N1), hantavirus infection, meliodosis, severe community acquired pneumonia,

b. diffuses alveolar hemorrhage secondary to tropical infections

4) Acute Febrile encephalopathy / Acute encephalitic syndrome

a. encephalitis HSV, Japanese B, enterovirus

b. meningitis - S. pneumoniae, N. meningitides, H. Influenza

c. scrub typhus, cerebral malaria, typhoid encephalopathy

5) Fever with multiorgan dysfunction

a. bacterial sepsis, malaria, scrub typhus, leptospirosis

b. Dengue Hepatitis A or E with fulminant hepatic failure, Hantavirus infection,

c. macrophage activation syndrome

These infections should be suspectedin all febrile patients as delay in the institution of specific therapy may lead to increased morbidity andmortality. Since the symptoms of many infections mayoverlap with one another and with severe bacterialsepsis, it may be very difficult to identify theseinfections at the time of presentation.

Localizing clinical symptoms and signs are important clues like headache; myalgia and arthralgia; photophobia, conjunctivitis; skin rashes and localizeddermal lesions(eschar); lymphadenopathy, hepatomegaly, and splenomegaly; jaundice, and anemia[2].

While evaluating these patients review of history (travel, occupation) will be really helpful in deciding differentials diagnosis or ruling out the etiology. The geographic and travel history, both within and outside the country, both recent and past is of vital importance. The other important tool is incubation period of the disease, few of them have very short incubation period while for others it varies up to 3-4 weeks. Based on this data differential can be narrowed down to more specific ones.

Since there is significant overlap between clinical presentation and epidemiological aspect, good clinical judgment and appropriate laboratory investigations are crucial. The turnaround time for laboratory investigations tends to vary and could delay the definite treatment, a conscious decision to empirically treat life threatening infections should be taken while awaiting the lab results. Things to be kept in mind while ordering labs

1. Time to positivity (NS1 - 2-5 days, blood culture for enteric-max in first week, IGM Elisa-might be negative in early infections due to low antibody levels (false negative).
2. Sensitivity of test and its specificity-sensitivity and specificity for IGM Elisa Scrub typhus □ 90%. While for weilfelix it drops down to 40%[3].
3. False positives and false negatives - It must also be borne in mind that the serological tests have a tendency to cross-react and these interactions should be borne in mind while interpreting the

Incubation period of common tropical infections-

Short : = 10 days	Intermediate : 7 28 Days	Long : > 4 weeks	Variable : Weeks to years
Arbovirus infections Avian influenza Crimean-Congo Hemorrhagic Fever Chikungunya Dengue Marburg / Ebola Hemorrhagic fever	Hemorrhagic fever with renal syndrome Leptospirosis, Malaria (falciparum, ovale, vivax) Typhoid and paratyphoid fever Typhus	Leishmaniasis Malaria (malariae)	Melioidosis

results, a single serological test could be suggestive but to make a definitive diagnosis, a fourfold rise in paired / convalescent sera needs to be demonstrated. This may not have great clinical significance but is important from epidemiological purpose.

Blood culture remains gold standard for enteric fever. Despite being on prior antibiotics blood culture positivity rates can be as high as 40% if performed by BACTEC method[4].

Yet, most of the time, empiric therapy needs to be initiated at the outset. There can be no uniform guideline for empiric therapy but trends of tropical infections should guide the treating physician. In a sick patient, the idea is to hit wide and hit early with the intention to deescalate once the definitive diagnosis is established. Single patient with two different etiologies at same time is also possible owing to mode of spread and epidemiological aspect of the disease and should be kept in mind while analyzing non resolving fever.

The first aim in the emergency is to stabilize the patient by taking care of the vitals, establishing a patent airway, maintaining oxygenation and a mean arterial pressure to have adequate tissue perfusion.

Paracetamol in the therapeutic dose of 3 to 4 gram is safe but higher doses should be avoided so as to prevent an added drug induced liver insult.

Dengue fever -

Common misconceptions about dengue management include blood transfusions and platelet transfusion.

There is no role of prophylactic platelet transfusion in uncomplicated dengue fever[5]. High dose dexamethasone regimen is not effective in achieving a higher rise in the platelet count in the acute stage of dengue fever or dengue shock syndrome[6].

Cases of Dengue fever / Dengue Haemorrhagic Fever (DF/DHF) should be observed every hour. Serial platelet and haematocrit determinations, drop in platelets and rise in hematocrits are essential for early diagnosis of DHF.

Pregnancy and dengue -

Dengue in pregnancy must be carefully differentiated from preeclampsia. An overlap of signs and symptoms, including thrombocytopenia, capillary leak, impaired liver function, ascites, and decreased urine output may make this clinically challenging. If the mother acquires infection in the peripartum period, newborns should be evaluated for dengue with serial platelet counts and serological studies.

Malarial fever -

With the availability of antigen based rapid diagnostic kits, ruling out malaria is easy. Malaria is ruled out if two RDTs are negative. The role of empiric chloroquine / quinine / artesunate in era of rapid diagnostics should be limited as indiscriminate use may potentiate drug resistance.

Anti-malarial drug resistance is a major public health problem which hinders the control of malaria. In India resistance of ***Plasmodium falciparum*** to chloroquine, the cheapest and the most used drug was first reported in the year 1973 from Diphu of Karbi-Anglong district in Assam state. Resistance to artemisinin compounds has been reported from Myanmar Cambodia border. Hence ACT combination therapy has become the need of hour[7].

ACT recommended by WHO for uncomplicated malaria in children and adult include -

1. artemetherlumefantrine
2. Artesunate - Mefloquine
3. Artesunate - Amodiaquine
4. Artesunate - SP
5. Dihydroartemisinin Piperaquine

In recent phase 4 trial, (AMPQPArterolane Maleate Piperaquine Phosphate) showed comparable efficacy and safety to AL in the treatment of uncomplicated P. falciparum malaria in adolescent and adult patients. AMPQP demonstrated high clinical and parasitological response rates as well as rapid parasite clearance. The drug has been available in India for the last few years[8].

Malaria and pregnancy -

Maternal mortality is approximately 50% in severe malaria, which is higher than non-pregnant adult. fetal death and premature labor are also common. The risks of infant growth restriction and infant malaria infection is maximal when maternal malaria occurs in the 12 weeks prior to delivery. Recurrent malaria is also associated with acute respiratory and diarrhea during infancy.

Artemisinin based treatments are now first line therapy for malaria in pregnancy and are superior to and less toxic than quinine. To prevent malaria in pregnant women and newborn infants, WHO recommends intermittent preventive treatment of malaria in pregnancy (IPTp) with a treatment dose of sulfadoxine-pyrimethamine to be offered at each scheduled antenatal care (ANC) visit (maximum monthly) after the first trimester

However, PREGACT Study Groupand Kakuru *et al*, present new findings to support the use of artemisinin-based combination therapy in both the prevention and the treatment of uncomplicated P. falciparum malaria in pregnancy. Artemether + lumefantrine is associated with the fewest adverse effects and with acceptable cure rates but provides the shortest post-treatment prophylaxis, whereas dihydro artemisinin piperaquine has the best efficacy and an acceptable safety profile[9,10].

Enteric fever -

There is increasing resistance for fluoroquinolonesowing to rampant use across the country. Mic (minimal inhibitory concentrations)for fluoroquinolones are also changing, and should be kept in mind while interpreting culture report. Ciprofloxacin cut-off for susceptibility using disk diffusion was raised from 21 to 31 mm and the MIC value lowered from 1 to 0.06 ìg/mLin CLSI 2012 update[11].

However, on the contrary, MDR s-typhi (resistant to chloramphenicol, amoxicillin and co-trimoxazole) prevalence is low[12]. Until now, extended-spectrum â-lactamase (ESBL) producing S. enterica ser. Typhi strains have been uncommon and have been described only in a few patients of Asian origin and in travelers returning from that region.

Ceftriaxone is an effective drug for treating typhoid, safe to use in children and antimicrobial resistance remains rare. The requirement for parenteral administration is a disadvantage, but the long half-life allows the convenience of once daily administration. Although ceftriaxone is able to penetrate intracellularly, it is slowly bactericidal in vitro against Salmonella Typhi and lacks a post-antibiotic effect (unpublished data). Symptom resolution with ceftriaxone is often slow and the optimum duration of therapy unclear. Short courses of £7 days can lead to unacceptable levels of relapse and regimens of between 10 and 14 days are often recommended.

Azithromycin is another alternative for treating mild-to-moderate enteric fever. It can be given orally, has excellent intracellular penetration and a long half-life allowing once-daily administration. Doses have varied between 10 and 20 mg/kg/day for between 5 and 7 days, and the optimum dose and duration are yet to be determined[13]. It is now widely used for treating typhoid, but there are no validated guidelines for the interpretation of in vitro antimicrobial susceptibility testing[14].

Rickettsial infections -

There is paucity of evidence based on randomized controlled trials for the management of rickettsial diseases including scrub typhus.

Without waiting for laboratory confirmation of the Rickettsial infection, antibiotic therapy should be instituted when rickettsial disease is suspected.

Doxycycline is the drug of choice and it can be used safely even in children below 8 years of age. However, pregnant women, azithromycin or chloramphenicol can be used as alternatives. There is in vitro Antagonism between Cefotaxime and Anti-Rickettsial Antibiotics against Orientiatsutsugamushi, needs further evaluation in vivo studies[15]

Levofloxacin is effective in patients with scrub typhus, but has a longer time to defervescence compared with tetracycline antibiotics. When levofloxacin is used for severe scrub typhus, higher mortality may be attributed to the longer time to defervescence.

Doxycycline and / or Chloramphenicol resistant strains have been seen in South-East Asia. These strains are sensitive to Azithromycin.

Prevention :

Dengue fever - The World Health Organization's Strategic Advisory Group of Experts on Immunization (SAGE) has recommended the use of dengue vaccine to control spread of disease. The WHO has set objectives to reduce dengue morbidity by 25 percent and mortality by 50 percent by 2020. The vaccine has been approved in four countries already, including Mexico and Brazil, which have regulatory authorities recognized by the WHO.

Enteric fever - Two typhoid vaccines are available for use : 1) a Vi capsular polysaccharide vaccine for parenteral use and 2) an oral live-attenuated vaccine. The two currently available vaccines have moderate efficacy in populations where typhoid is endemic. In a systematic review and meta-analysis, the estimated 2.53.0-year cumulative efficacy was 55% (95% confidence interval [CI] = 30%70%) for the parenteral Vi polysaccharide vaccine and 48% (CI = 34%58%) for the oral Ty21a vaccine, each based on a single trial.

Malaria - More than 30 P. falciparum malaria vaccine candidates are at either advanced preclinical or clinical stages of evaluation. 14 Approaches that use recombinant protein antigens and target different stages of the parasite lifecycle are being developed, but only the RTS, S/AS01 vaccine has completed Phase 3 evaluation and received a positive regulatory assessment.

References :

1. Abrahamsen SK, Haugen CN, Rupali P, Mathai D, Langeland N, Eide GE, et al. Fever in the tropics: Aetiology and case - fatality - A prospective observational study in a tertiary care hospital in South India. BMC Infect Dis 2013;13:355.
2. Blumberg L, Frean J. Dermatological manifestations of tropical diseases. SA Dermatology. Review (2004); 4 (2): 5-14.
3. Koh GC, Maude RJ, Paris DH, Newton PN, Blacksell SD. Diagnosis of scrub typhus. Am J Trop Med Hyg 2010; 82:368-70.
4. Jog S, Soman R, Singhal T, Rodrigues C, Mehta A, Dastur FD. Enteric fever in Mumbai - clinical profile, sensitivity patterns and response to antimicrobials. J Assoc Physicians India 2008; 56:237-40.
5. Shashidhara KC, Sudharshan KA, Basavana H, Bhograj A. Effect of high dose of steroid on platelet count in acute stage of dengue fever with thrombocytopenia. J ClinDiagn Res. 2013; 7(7):1397-1400.
6. Tassniyom S, Vasanawathana S, Chirawatkul A, Rojanasuphot S. Failure of high-dose methylprednisolone in established dengue shock syndrome: a placebo-controlled, double-blind study. Pediatrics. 1993;92(1):111-115.
7. Guidelines for the treatment of malaria. Third edition, April 2015.
8. AMPQP Study Team, A Phase 3, Double-Blind, Randomized Study of Arterolane Maleate Piperaquine Phosphate vs Artemether Lumefantrine for Falciparum Malaria in Adolescent and Adult Patients in Asia and Africa Clin Infect Dis. (2016) 62 (8): 964-971.
9. The PREGACT Study Group. Four artemisinin-based treatments in African pregnant women with malaria. N Engl J Med2016; 374:913-927.
10. Kakuru A, Jagannathan P, Muhindo MK, et al. Dihydroartemisininpiperaquine for the prevention of malaria in pregnancy. N Engl J Med2016; 374:928-939.
11. Antimicrobial susceptibility of Salmonella enterica serovars in a tertiary care hospital in southern India. Ashwini Choudhary, Ram Gopalakrishnan, Nambi P. Senthur, V. Ramasubramanian, K. Abdul Ghafur, M.A. Thirunarayan, Indian J Med Res. 2013 April; 137(4): 800-802.
12. Garg A, Verma S, Kanga A, Singh D, Singh B. Antimicrobial resistance pattern and in vivo activity of azithromycin in Salmonella isolates. Indian J Med Microbiol 2013; 31:287-9.
13. Trivedi NA, Shah PC. A meta-analysis comparing the safety and efficacy of azithromycin over the alternate drugs used for treatment of uncomplicated enteric fever. J Postgrad Med 2012; 58:112-8.
14. Bhutta ZA. Current concepts in the diagnosis and treatment of typhoid fever. Br. Med. J. 333, 78-82 (2006).
15. Lee OH, Baek JH, Lee J-S, Chung M-H, Lee SM, Kang J-S. In vitro Antagonism between Cefotaxime and Anti-Rickettsial Antibiotics against Orientiatsutsugamushi. Infection & Chemotherapy. 2014;46(3):189-193.

Drug Update

Pramlintide

Pitale S U[1], Sahasrabuddhe A V[2]

ABSTRACT

Amylin is a second beta-cell hormone that is co-secreted with insulin, in response to nutrient stimuli. Diabetes represents a state of bihormonal beta cell deficiency and that lack of amylin action may contribute to abnormal glucose homeostasis. Amylin has glucose-lowering effects in both animals and humans.The effects of Pramlintide (amylin analogue)can be summarized as follows : (1) suppression of endogenous glucagon production, especially in the postprandial state; (2) consequent reduction of postprandial hepatic glucose production; (3) reduction in gastric emptying time; (4) centrally mediated induction of satiety; and (5) reduction in postprandial glucose levels. Pramlintide has been approved as an adjunct to insulin in both type 1 and type 2 DM. Though it has not yet found place in any of the standard guidelines.

History of Amylin :

In year 1900, Opie had identified a hyaline material in islets of Langerhans, which was later found out to be amyloid[1]. In 1987, a sequence of a 37 amino acid peptide was extracted from amyloid containing pancreatic material in patients with Type 2 diabetes mellitus. This was initially called IAP or "islet amyloid polypeptide, DAP" or "diabetes associated peptide". This was changed in 1988 to amylin to indicate the origin of the peptide and the fact that its presence was not restricted to individuals with type 2 diabetes mellitus[2,3,4,5]. Following the discovery of amylin, a second beta-cell hormone that is co-secreted with insulin in response to nutrient stimuli, it was realized that diabetes represents a state of bihormonal beta cell deficiency and that lack of amylin action may contribute to abnormal glucose homeostasis. Experimental studies show that amylin acts as a neuroendocrine hormone that complements the effects of insulin in postprandial glucose regulation through several centrally mediated effects[6]. The analog of human amylin was given the name pramlintide and proprietary name Symlin[2].

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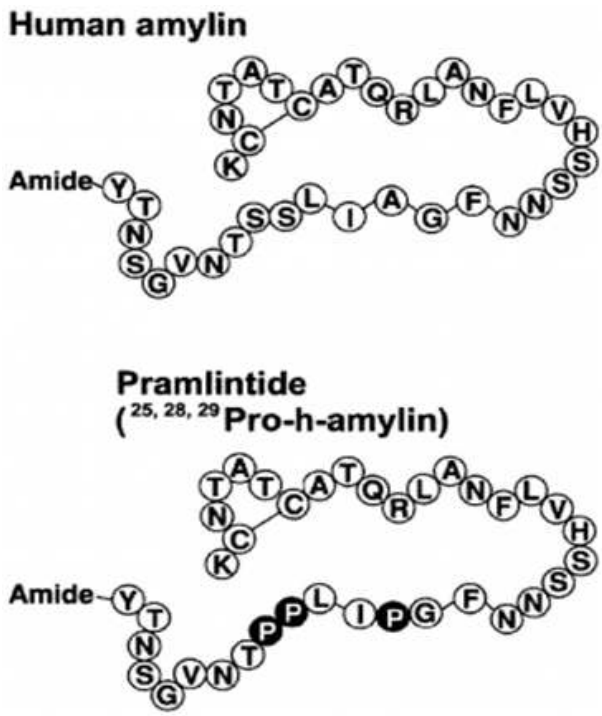
Chemical Structure :



Human amylin and Pramlitide[7]

Pramlintide is a water-soluble salt with a pH of 4.0. This leads to an issue with combination with other injectible anti-hyperglycemic agents[7]. Native amylin was characterized as "glue like," somewhat unstable as a compound in solution, modifying amylin to a compound with more manageable physical properties resulted in the development of pramlintide. Pramlintide has similar physiologic effects as native amylin, but could be produced as

the stable inject able product now available for clinical use as Symlin™[8]

Mechanism of Action -

An amylin analog, pramlintide, is used to treat insulin-requiring diabetes. Its anorexigenic actions give it potential as an obesity treatment. There are 3 amylin receptors (AMY1, AMY2, AMY3), comprising the calcitonin receptor and receptor activity-modifying proteins 1, 2 and 3, respectively[9].

SYMLIN does not extensively bind to red blood cells or albumin (approximately 40% of the drug is unbound in plasma).

Metabolism and Elimination

Absorption

The absolute bioavailability of pramlintide following a single subcutaneous dose of SYMLIN is approximately 30% to 40%. In healthy individuals, the half-life of pramlintide is approximately 48 minutes. The primary metabolite, Des-lys1 pramlintide (2-37 pramlintide), is biologically active in vitro. Overall exposure (AUC) to pramlintide is relatively constant with repeat dosing of SYMLIN, indicating no bioaccumulation[6].

Renal Impairment

No studies have been conducted in patients with end-stage renal disease. In a single-dose pharmacokinetic study in patients with type 1 diabetes, 60 mcg of SYMLIN was administered to 4 patients with normal renal function (ClCr > 90 mL/min), 9 patients with mild renal impairment (ClCr 60-89 mL/min), 5 patients with moderate renal impairment (ClCr 30-59 mL/min) and 3 patients with severe renal impairment (ClCr 15-29 mL/min). No statistically significant differences were noted in total (AUC0-8) and peak (Cmax) exposure of pramlintide for mild, moderate, and severe renal impairment categories in comparison to patients with normal renal function; although, inter-patient variability in pharmacokinetic parameters was high[6].

Hepatic Impairment

Pharmacokinetic studies have not been conducted in patients with hepatic impairment[6].

Geriatric

Pharmacokinetic studies have not been conducted in the geriatric population[6].

Pediatric

The efficacy and safety of SYMLIN have not been established in the pediatric population. The use of SYMLIN is not recommended in pediatric patients due to the risk of severe hypoglycemia[6]

Gender

No study has been conducted to evaluate the effect of gender on pramlintide pharmacokinetics[6].

Race/Ethnicity

No study has been conducted to evaluate the effect of ethnicity on pramlintide pharmacokinetics[6].

Drug Interactions

Effect of Pre-Mixing SYMLIN with Insulin

Pharmacokinetic profiles of pramlintide and insulins after coadministration of 30 mcg SYMLIN with different insulins (regular, NPH, and 70/30 premixed formulations of recombinant human insulin) as one subcutaneous injection, premixed in one syringe, were compared to those observed after the co-administration of SYMLIN and different insulins given as separate subcutaneous injections. The effects of premixing on pramlintide pharmacokinetics varied across the different insulin products with a maximum decrease of 40% in pramlintideCmax and a maximum increase of 36% in pramlintide AUC0-8. Similarly, effects of premixing on insulin pharmacokinetics varied across different insulin products with a maximum increase of 15% in insulin Cmax and up to a 20% increase in insulin AUC0-600min. Always administer SYMLIN and insulin as separate injections and never mix.

Acetaminophen : SYMLIN did not affect acetaminophen AUC regardless of the time of acetaminophen administration in relation to SYMLIN injection.

Oral Contraceptives : When a single dose of a combination oral contraceptive product, containing 30 mcg ethinyl estradiol and 300 mcg norgestrel, was administered 15 minutes after SYMLIN

injection (90 mcg dose) in healthy female subjects, there was no statistically significant change in the Cmax and AUC of ethinyl estradiol. However, the norgestrel Cmax was reduced by about 30% and Tmax was delayed by 45 minutes; there was no effect on norgestrel AUC. The clinical relevance of this change is unknown.

Ampicillin : The Tmax for ampicillin was delayed by approximately 60 minutes[6].

Actions of Pramlintide / Amylin :

Amylin has glucose-lowering effects in both animals and humans[10]. The effects of Pramlintide and amylin can be summarized as follows : (1) suppression of endogenous glucagon production, especially in the postprandial state; (2) consequent reduction of postprandial hepatic glucose production; (3) reduction in gastric emptying time; (4) centrally mediated induction of satiety; and (5) reduction in postprandial glucose levels.

Pramlintide and Type-1 Diabetes :

In a multicenter study of 480 patients with type 1 DM, White house and colleagues showed that treatment with pramlintide led to a mean reduction in HbA1c of 0.67% from baseline to week 13 that was significantly ($p<0.0001$) greater than the placebo reduction (0.16%); a significant placebo-corrected treatment difference was sustained through week 52 ($p=0.007$). This was not accompanied by an increased overall event rate of severe hypoglycemia. Ratner and colleagues showed that the addition of pramlintide 60 ìg 3 times daily (tid) or 4 times daily (qid) to insulin led to significant reductions in HbA1c of 0.29% ($p<0.011$) and 0.34% ($p<0.001$) respectively, compared with a 0.04% reduction in placebo group, over 52 weeks. In this study, the proportion of pramlintidevs placebo-treated patients who achieved an HbA1c of <7% was 3-fold higher. This was achieved without an increase in concomitant insulin use in the pramlintide-treated group. In a subset of these patients combined with patients from other studies in whom HbA1c values were <8.0% at entry, favorable effects on glycemic control were also demonstrated[10,11,12,13]

Pramlintide and Type 2 Diabetes :

In type 2 DM pramlintide has been approved for use as an adjunct to preprandial insulin with or without concurrent metformin or sulfonylurea therapy in patients with sub-optimal glucose control. This approval was based on the ability of pramlintide to improve glucose control when added to insulin therapy and has been supported by both short and long term studies[14,15].

Pramlintide and Food Intake :

Pramlintide administration led to sustained weight loss when given for up to one year to type 1 and type 2 diabetic patients at doses resulting in plasma concentrations close to those in non-diabetic humans[16,17,18]. The weight change in type 1 was 0.5 kg for the 30/60 µg pramlintide four-times daily and in type 2, -1.5kg for the 150 µg pramlintide three-times daily, as compared with+1.0 kg for the placebo group. Meal termination, satiety and anorexia induced by amylin and its analogue pralamintideis supposed to be muli-factoral. The various mechanisms leading to this effect are : 1). Via gastrointestinal hormones. 2). Direct action on area post-rema outside blood brain barrier by amylin 3). Amylin may induce anorexia through its effect on brain serotonin by increasing the transport of the precursor tryptophan into the brain to inhibit feeding by serotonin action in the paraventricular nucleus. 4). Inhibition of stimulation of feeding by the potent hypothalamic neuropeptide Y (NPY)[19].

Pramlintide and Gastric Emptying :

A subcutaneous injection of amylin produced a dose-related slowing of gastric emptying in both diabetic and control rats, in greater magnitude than other gut peptides. The major brain sites regulating gastric motility are the dorsal vagal complex of the brainstem, composed of the nucleus tractussolitarius, dorsal motor nucleus of the vagus, and area postrema. Amylin receptors are identified in these locations and also in stomach fundus[19].

Pramlintide and CAD :

Pramlintide use has also been associated with a significant reduction in postprandial markers of

oxidative stress including significantly reduced postprandial excursions of glucose, nitrotyrosine, and oxidized LDL8. Pramlintide has no significant effect on blood pressure.

Dose, Administration and Side Effects :

Pramlintide is presently available only in a pen system. There are 2 different pens available: 60 mcg pen generally utilized for Type 1 DM individuals and 120 mcg pen utilized for Type 2 DM individuals. Both pens have various increments with the 60 mcg pen allowing for an initial starting dose of 15 mcg and increasing in 15 mcg increments to 60 mcg. The 120 mcg pen allows for 60 mcg and 120 mcg doses.

It is generally administered in divided doses prior to each meal subcutaneously. It is approved in the US to be used with individuals, both Type 1 and Type 2 DM who are utilizing insulin therapy. It is not approved at the present time to be utilized with other agents such as GLP-1 agonists and other oral agents.

The most common side effect of pramlintidehas been nausea, vomiting, anorexia or decrease in appetite. Hypoglycemia can be an issue also, particularly if intake is diminished[16]. Weight loss was noted in individuals and several studies indicated that nausea was not responsible[17].

References :

1. Opie, E.L. The relation of diabetes mellitus to lesions of the Hyaline degeneration of the islands of Langerhans; Journal of Experimental M397; 1900.
2. Schorr, Alan. Pramlintide/Symlin (Islet Cell amyloid polypeptide analogues or amylin analogue) [internet]. 2014 Aug 13; Diapedia 8105127829 rev. no.18.
3. Cooper, GJS, Willis, AC, Clark, A, Turner, RC, Sim, RB and Reid, KB; Purification and characterization of a peptide from amyloid-rich pancreases of type 2 diabetic patients; Proceedings National Academy Science, USA 1987; 84:8628.
4. Cooper, GJS, Leighton, B, Dimitriadis, GD, Parry-Billings, M, Kowalchuk, JM, Howland, K, Rothbard, JB, Willis, AC and Reid, KB; Amylin found in amyloid deposits in hyman type 2 diabetes mellitus may be a hormone that regulates glycogen metabolism in skeletal muscle; Proceedings National Academy Science USA 1988; 85: 7763.
5. Cooper, GJS, Day, AJ, Willis, AC, Roberts, AN, Reid, KB and Leighton, B; Amylin and the amylin Structure, function and relationship to the iselt amyloid and to diabetes mellitus; Biochim. Biophys.1989; A1014; 247.
6. Weyer, C.; Maggs, D.G. Young, A.A.; Kolterman, O.G.Amylin Replacement With Pramlintide as an Adjunct to Insulin Therapy in Type 1 and Type 2 Diabetes Mellitus : A Physiological Approach Toward Improved Metabolic Control . Current Pharmaceutical Design, Volume 7, Number 14, 1 September 2001,(21) pp. 1353-1373.
7. Gunberger, G.; Novel therapies for the management of type 2 diabetes mellitus : Part 1. Pramlitide and bromocriptine-QR Journal of Diabetes:2013 5:110.
8. Hoogwerf BJ, Doshi KB, Diabb D. Pramlintide, the synthetic analogue of amylin : physiology, pathophysiology, and effects on glycemic control, body weight, and selected biomarkers of vascular risk. Vasc Health Risk Manag. 2008 Apr; 4(2):355-362.
9. Gingell JJ1, Burns ER, Hay DL Activity of pramlintide, rat and human amylin but not Aâ1-42 at human amylin receptors. Endocrinology. 2014 Jan;155(1):21-6. doi:10.1210/en.2013-1658. Epub 2013 Dec. 20.
10. Uwaifo GI, Ratner RE. Novel pharmacologic agents for type 2 diabetes. EndocrinolMetabClin North Am. 2005;34:155-97.
11. Ratner R, Whitehouse F, Fineman MS, *et al.* Adjunctive therapy with pramlintide lowers HbA1c without concomitant weight gain and increased risk of severe hypoglycemia in patients with type 1 diabetes approaching glycemic targets. ExpClinEndocrinol Diabetes. 2005;113:199-204.
12. Ratner RE, Dickey R, Fineman M, *et al.* Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus : a 1-year, randomized controlled trial. Diabet Med. 2004;21:1204-12.
13. Whitehouse F, Kruger DF, Fineman M, *et al.* A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. Diabetes Care. 2002;25:724-30.
14. Gottlieb A, Fineman M, Bahner A. Pramlintide therapy in addition to insulin in type 2 diabetes: effect on metabolic control after 6 months. Diabetologia. 2007;42(Suppl):A232.

15. Hollander P, Maggs DG, Ruggles JA, et al. Effect of pramlintide on weight in overweight and obese insulin-treated type 2 diabetes patients. Obes Res. 2004;12:661-8.
16. Whitehouse F, Ratner R, Rosenstock J, et al. Pramlintide showed positive effects on body weight in type 1 and type 2 diabetes. Diabetes. 1998;47:A9.
17. Whitehouse F, Kruger DF, Fineman MS, et al. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. Diabetes Care. 2002;25:724-30.
18. Ratner R, Want LL, Fineman MS, et al. Adjunctive therapy with the amylin analogue pramlintide leads to a combined improvement in glycemic and weight control in insulin-treated patients with type 2 diabetes. *Diabetes TechnolTher.* 2002;4: 51-61.
19. Red TK, Geliebte A, Pi-SunyerF X. Amylin, Food Intake, and Obesity. Obesity Research Vol. 10 No. 10 October 2002.

Teneligliptin : A New DPP-4 inhibitor for Type 2 Diabetes

Kharkar S[1]

ABSTRACT

Teneligliptin, a novel DPP-4 inhibitor, characterised by five consecutive rings, which produce a potent and long-lasting effecting glycemic control. It is currently used in cases showing insufficient improvement in glycemic control even after diet control and exercise or a combination of diet control, exercise, and sulfonylurea- or thiazolidine class drugs. In adults, teneligliptin is orally administered at a dosage of 20 mg once daily, which can be increased up to 40 mg per day. Because the metabolites of this drug are eliminated via renal and hepatic excretion, no dose adjustment is necessary in patients with renal impairment. The safety profile of teneligliptin is similar to those of other available DPP-4 inhibitors. However, caution needs to be exercised when administering teneligliptin to patients who are prone to QT prolongation. Although clinical data for this new drug are limited, this drug shows promise in stabilising glycemic fluctuations throughout the day and consequently suppressing the progression of diabetic complications.

Key words : teneligliptin, DPP-4 inhibitor, diabetes

Introduction :

Dipeptidyl peptidase IV inhibitors are a class of oral anti-hyperglycemic agents for the treatment of type 2 diabetes. The anti-glycemic effect of DPP-4 inhibitors is mediated by inhibiting the degradation of the incretin hormone glucagon-like peptide-1 (GLP-1) and stimulating insulin release in response to increased blood glucose levels. Incretins are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4), and have a very short half-life as a result. DPP-4 inhibitors increase the levels of active GLP-1 and GIP by inhibiting DPP-4 enzymatic activity thus, in patients with diabetes, these inhibitors improve hyperglycemia in a glucose-dependent manner by increasing serum insulin levels and decreasing serum glucagon levels.Among all DPP-4 inhibitors, vildagliptin, saxagliptin and teneligliptin are peptide mimetic compounds, which have been discovered by replacing segments of peptide-based substrates. Whereas, sitagliptin, alogliptin and linagliptin are non-peptide mimetic compounds, which Therefore, their chemical structures are diverse, suggesting that each of their binding modes in DPP-4 would be unique.[1,2]

On the basis of binding subsites all DPP4 inhibitors are categorized into 3 classes *(Table 1 & Fig. 1)*.[1]

Class	Criteria	Molecules
I	Binding to S1 & S2 only (interactions with the core S1 and S2 subsites and a covalent bond with Ser 630 in the catalytic triad)	Saxagliptin Vildagliptin
II	Binding to S1, S2 & S'1, S'2 (interactions with the S'1 and / or S'2 subsites in addition to the S1 and S2 subsites	Linagliptin Alogliptin
III	Binding to S1, S2 & S2 extensive subsites (interactions with the S1, S2 and S2 extensive subsites)	Sitagliptin Teneligliptin

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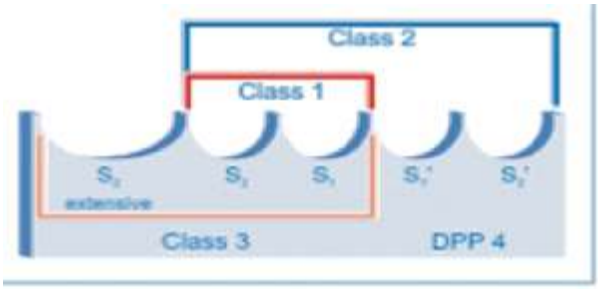

Fig. 1 : **The concept of 3 classes on the basis of the inhibitor's binding subsitesDPP4 inhibitor**

Teneligliptin bind to the S2 extensive subsite. Although both inhibitors appear to bind to the subsites in the same manner, teneligliptin has 5-fold higher activity. Following three potential reasons may be responsible for the difference.

Teneligliptin consists of a considerably rigid which are directly connected, the loss in entropy is small upon binding to DPP-4. [1,3]

1. The carbonyl group of teneligliptin, derived from the peptide mimetics, forms a hydrogen bond with the side chain of Asn710.
2. For teneligliptin, introduction of the "anchorlockdomain", which binds to the S2 extensive subsite, increased the activity by 1500-fold over the corresponding fragments that binds to S1 and S2 only.
3. Because of above mentioned unique features teneligliptin is one of the most potent DPP4 inhibitor ***(Table 2)***

Table 2 : **The DPP-4 inhibitory activity**

Compound	DPP-4 inhibition, IC50 (nmol/L)
Vildagliptin	29.2
Saxagliptin	6.3
Alogliptin	4.9
Linagliptin	0.6
Sitagliptin	10.3
Teneligliptin	1.9

Clinical Particulars :

Therapeutic indications[4,5,6]

Teneligliptin Tablets are indicated as a mono therapy adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). In adults, 20 mg of teneligliptin may be orally administered once daily. If this dosage is insufficient, the dosage is increased to 40 mg once daily.

Effects on insulin :

The relative insulin concentrations were higher in the teneligliptin-treated groups because of the decreased blood glucose concentrations of the patients in these groups.

Effects on glucagon :

There were no significant differences in the glucagon concentrations between the two teneligliptin-dosage groups, although glucagon secretion was lower with teneligliptin treatment at 20 mg, particularly after dinner.

Contraindications :

Teneligliptin Tablets are contraindicated in patients with Hypersensitivity to the drug or any of its components. Severe ketosis, diabetic coma or pre-coma and also for immediate remedy in type 1 diabetes. Severe trauma, before and after surgery and when the blood glucose has to be controlled with insulin injection.

Pregnancy and lactation :

Teneligliptin should be used in pregnant women or in women who may possibly be pregnant only if of this product in pregnant women has not been established. Breast-feeding must be discontinued during administration of this product in lactating women (transfer to milk in animal studies (rats) has been reported.).

Undesirable effects :[8]

In clinical trials conducted in Japan, 232 adverse reactions to this drug (including abnormal laboratory tests) were reported in 156 patients (9.5%) of total 1645 patients. The most frequently observed adverse reactions were hypoglycemia in 43 patients (2.6%) and constipation in 14 patients (0.9%).

a) Hypoglycemia

b) Intestinal Obstruction (0.1%)

c) Liver dysfunction (unknown frequency)

d) Interstitial pneumonia (frequency unknown)

Overdose

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

Clinical Pharmacology[6]

Mechanism of Action

The glucagon-like peptide-1 (GLP-1) is secreted from alimentary canal in response to meal that promotes insulin secretion from pancreas and regulates blood sugar post meal by controlling glucagon secretion. Teneligliptin exhibits a hypoglycemic effect by controlling the degradation of GLP-1 by inhibiting dipeptidyl peptidase-4 (DPP-4) activity and thereby increasing blood concentration of active GLP-1.

Metabolism :

The unaltered substance and the metabolites M1, M2, M3, M4, and M5 were observed in the blood plasma. Furthermore, the ratio of AUC of teneligliptin, M1, M2, M3, M4, and M5 with respect to AUC calculated from the plasma radioactive concentration up to 72 hours after administration was 71.1%, 14.7%, 1.3%, 1.3%, 0.3%, and 1.1%.

Excretion :

When a single oral dose of 20 mg and 40 mg teneligliptin was given to the healthy adults on empty stomach, about 21.0 to 22.1% of dose was excreted as unaltered substance in urine, and the renal clearance was 37 to 39 mL/hr/kg. Dosage radioactivity was excreted in urine and 46.5% was excreted in faeces up to 216 hours after administration. Furthermore, with respect to the dosage up to 120 hours after administration, the accumulated urinary excretion rate of unaltered substance, M1,M2, and M3 was 14.8%, 17.7%, 1.4%, and 1.9%, respectively and the accumulated faeces excretion rate of unaltered substance, M1, M3, M4, and M5 was 26.1%, 4.0%, 1.6%,0.3%, and 1.3%, respectively.

References :

1. Mika Nabeno, FumihikoAkahoshi, Hiroyuki Kishida, IkukoMiyaguchi, Yoshihito Tanaka, Shinichi Ishii, et al. A comparative study of the binding modes of recently launched dipeptidyl peptidase IV inhibitors in the active site.Biochemical and Biophysical Research Communications.2013; 434:191-196.
2. Eto, T., Inoue, S., Kadowaki, T. Effects of once-daily teneligliptin on 24-h blood glucose control and safety in Japanese patients with type 2 diabetes mellitus: a 4-week, randomized, double-blind, placebo- controlled trial. Diabetes ObesMetab 2012, 14(11):1040-6.
3. Peptidase-4 inhibitor, in Japanese patients with type 2 diabetes mellitus. Diabetes ObesMetab 2013;15(9): 810-8.
4. A dipeptidyl peptidase-4 inhibitor, combined with metformin in Korean patients with type 2 diabetes mellitus: a 16-week, randomized, double blind, placebo-controlled phase III trial. Diabetes, Obesity and Metabolism 2015. Dec 5. doi: 10.1111/dom.12424.
5. With type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled study with an open-label, long-term extension. Diab Obesity Metab. 2013;16:418-425.
6. Japanese patients with type 2 diabetes mellitus. J Diabetes Investig. 2013; 4:576-584.
7. Seiichi Tanaka, MD, Kunihiro Suzuki, MD, PhD, Chie Aoki, MD, PhD, Ma Niitani, MD, Kanako Kato, MD, TakanoriTomotsune, MD, *et al*. Add-On Treatment with Teneligliptin Ameliorates Glucose Fluctuations and Improves Glycemic Control Index in Japanese Patients with Type 2 Diabetes on Insulin Therapy. Diab Tech &Ther.2014; 16:1-8.
8. M. Goda, T. Kadowaki. Teneligliptin for the treatment of Type 2 Diabetes. Drugs of Today 2013, 49(10): 615-629.

Table 3 : **Precautions for co-administration of teneligliptin tablets with other drugs**[7]

Drug name	Clinical condition / Measures	Mechanism / risk factors
Drugs for diabetes Sulfonylurea fast-acting insulin secretagogueglucosidase inhibitor BiguanideThiazolidinediones GLP-1 analog preparation SGLT2 inhibitor Insulin preparation	Since hypoglycemia might occur, these drugs should be administered while carefully observing the patient's condition. Particularly, when co administered with sulfonylurea or insulin formulation, there is a possibility of higher risk of hypoglycemia.	Hypoglycemic action is increased.
Drugs increasing hypoglycemic action-blocking agents Salicylic acid Monoamine oxidase inhibitor	Since the blood sugar may further decrease, these drugs should be administered while carefully observing the patient's condition in addition to blood sugar level.	Hypoglycemic action is increased.
Drugs decreasing hypoglycemic action Adrenalin adrenocortical hormone	Since the blood sugar may increase, these drugs should be administered while carefully observing the patient's condition in addition to blood sugar level.	Hypoglycemic action is decreased.
Drugs known to cause QT Prolongation Class IA antiarrhythmic drug Quinidine sulfate hydrate, procainamide hydrochloride Class III antiarrhythmic drugs amiodarone hydrochloride, sotalol hydrochloride	QT prolongation might occur.	QT prolongation is with single administration of these drugs

Table 4 : **Other adverse reactions**

Incidence/Types	0.1% ~ 1%	<0.1%
Digestive system	Constipation, abdominal swelling, abdominal discomfort, nausea, increased amylase, increased lipase, acute pancreatitis	
Liver	Increased AST (SGOT), increased ALT (SGPT), and increased -GTP	Rise in ALP
Kidney and urinary system	Albuminuria, positive ketone body in urine, increased uric acid in blood	
Skin	Eczema, Wet rash, pruritus, allergic dermatitis	
Others	Increased CK (CPK), increased serum potassium, fatigue, allergic Rhinitis, and increased serum uric acid	

Table 5 : **Pharmacokinetic parameters at the time of single dose oral drug administration in healthy adults**

Strengths	Cmax (ng/mL)	AUC0-inf (ng.hr/mL)	tmax (hr)	t1/2 (hr)
20 mg	187.20 ± 44.70	2028.9 ± 459.5	1.8 (1.0-2.0)	24.2 ± 5.0
40 mg	382.40 ± 89.83	3705.0 ± 787.0	1.0 (0.5-3.0)	20.8 ± 3.2

Tattoo Granuloma

Shaikh W N[1], Rambhia K[2], Mukhi J[3], Singh R P[4]

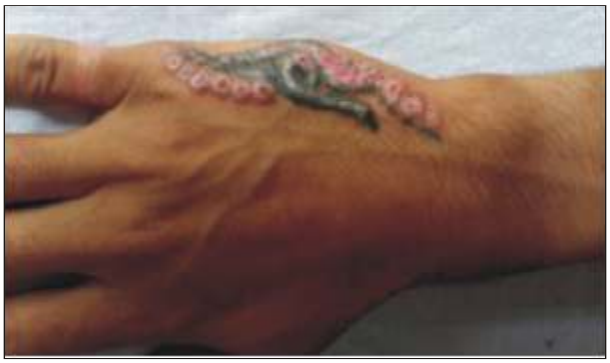

Figure 1 : **Nodules and Plaques along red ink sparing green ink**

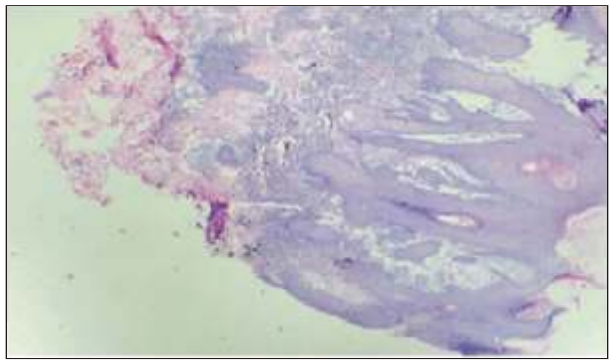

Figure 2 : **4 X, H & E view showing multiple granulomas in dermis**

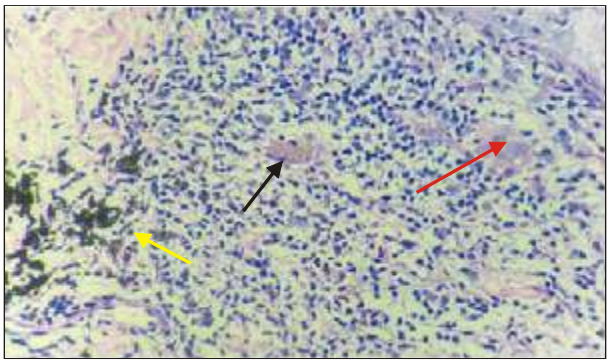

Figure 3 : **4O X, H &E view showing foreign body type giant cells *(red arrow)* pigment within giant cell *(black arrow)* and extra cellularly *(yellow arrow)***

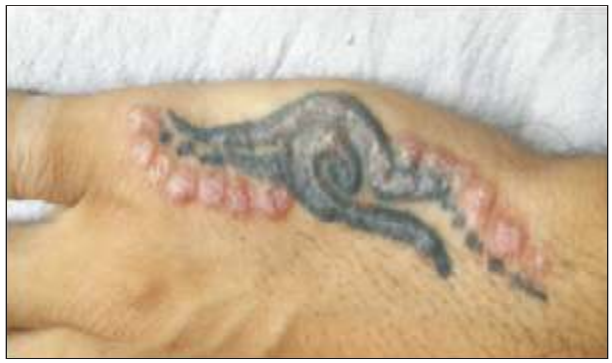

Figure 4 : **After 2 weeks of topical halobestol, reduction in size is seen**

A 20 year male student presented with itchy, painlesserythematous to skin colored plaques studded with nodules along the tattoo on ulnar side of right hand since 20 days with tattoo being done 1 month back. Nodules and plaques were seen along red ink, sparing green ink on the tattoo ***(Fig. 1).*** General and systemic examination was unremarkable.

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Biopsy was done from a nodule, revealing granulomatous inflammation ***(Fig. 2)*** with foreign and langhans type of giant cells with pigment both intracellularly within giant cells and extracelluarly ***(Fig. 3).***

Patient was started on high potent corticosteroid (Halobestol) topically twice a day under occlusion for 2 weeks. Significant improvement in itching and reduction in size of lesion was noted. ***(Fig. 4)***

Tattoing is becoming popular nowadays in all age groups, increasing the cutaneous reactions parallerly.[1] Tattoo colors consist of inorganic pigments, organic dyes, or a combination of both. In the past, it appears that heavy metals, that were the backbone of tattooing for decades, have been

replaced by organic colorants.[2] Tattoo artists use various pigment compounds to create different colors and hues. Depending upon the compounds used and the color of the tattoo, a variety of cutaneous reactions can be expected. The composition of ink used for professional and amateur tattoo differs significantly. For amateur tattoos, carbon particles are used, while for professional tattoos, a mixture of insoluble metals with organic dyes is used.[3] With the growing interest in tattoos, there is also a need of awareness for unwanted adverse effects. Concerns are growing by official bodies and dermatologists.[4] Tattoo reactions can be divided into three main categories: inflammatory, infectious, and neoplastic. Inflammatory manifestations include focal oedema, pruritus, papules, or nodules at the tattoo site. Histologically they can be classified as lichenoid, eczematoid, foreign body granulomatous, and sarcoidal.[5] Foreign body reactions, mostly of the granulomatous type or pseudolymphomatous type, are seen commonly. Most of them resolve either spontaneously or after treatment with topical corticosteroids.[6] The most frequent tattoo reactions concern allergic contact dermatitis due to delayed hypersensitivity reaction to different pigments contained in the tattoos.[7] The main pigment causing allergic reaction is the red one, due to the presence of mercury and its sulphides. However, nowadays most reactions are not due to the traditional presence of mercury sulphides, but due to new organic pigments (e.g., Pigment Red 181 and Pigment Red 170)[1]

Steroids, laser therapy (Q Switched Nd-YAG), and excision are the backbone of treatment for allergic reactions to tattoos.[3]

Reactions to tattoos are increasingly being encountered in clinical dermatological practice. It is important for dermatologists to be aware of these reactions as their occurrence is bound to rise in future with increasing popularity of tattooing as a body art.[3]

Conflicts of interest : none reported by authors

References :

1. Andrea Bassi, Piero Campolmi, Giovanni Cannarozzo, *et al.*, "Tattoo-Associated Skin Reaction : The Importance of an Early Diagnosis and Proper Treatment," BioMed Research International, vol. 2014, Article ID 354608, 7 pages, 2014.
2. Kaur RR, Kirby W, Maibach H. Cutaneous allergic reactions to tattoo ink. J Cosmet Dermatol 2009;8:295-300.
3. Sanghavi SA, Dongre AM, Khopkar US. Tattoo reactions - An epidemic on the surge : A report of 3cases.IndianJDermatolVenereolLeprol2013;79:231-4.
4. R. Korner, C. Pfholer, T. Vogt *et al.*, "Histopathology of body art revisited-analysis and discussion of 19 cases," Journal der Deutschen Dermatologischen Gesellschaft, 2013. vol. 11, pp. 1073-1080.
5. Ortiz AE, Alster TS. Rising concern over cosmetic tattoos. DermatolSurg 2012;38:424-9.
6. Jones B, Oh C, Egan CA. Spontaneous resolution of a delayed granulomatous reaction to cosmetic tattoo. Int J Dermatol 2008;47:59-60.
7. M. M. Tang, H. Beltranimelli, and D. Perruchoud, "A tattoo complicated by allergic contact dermatitis and pannicultis," Journal of the European Academy of Dermatology and Venereology, 2014.vol. 28, no. 1, pp. 127-128.

Secondary Spontaneous Pneumothorax : Bullous Emphysema or Bullous lung Disease

Munje R[1], Atram J[2], Gaur S[3], Walke V[4]

Case 1 :

68 years old male patient, came to the OPD with complaints of increased breathlessness, cough with expectoration and chest pain on ltside. On examination patient had Pulse-100/min, RR-30 with SpO2 of 80% on room air, the breath sounds were decreased on left side with bilat polyphonic rhonchi.

X-ray chest PA view S/o Pneumothorax on left He was having h/o breathlessness since 2 years for which he was taking inhaled bronchodilator, and was chronic smoker having smoking index of 600. CT Chest done to evaluate the cause of pneumothorax and showed left sided Pneumothorax with paraseptal emphysema with B/L upper lobe multiple bullae, largest of size (5.6*3.9).Pleural aspiration with under waterseal was done i.v.o breathlessness. Approximately 800ml of air was aspirated from pleural space. Patient clinically improved .

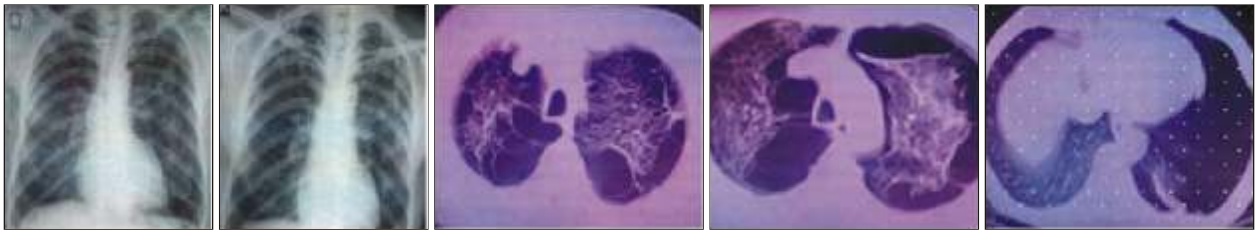

Fig. 1 & 2 **showing ltsided pneumothorax and expanded lung after Pleural aspiration.**
Fig. 3 to 5 **showing multiple bullae b/l upper lobe and lt lower lobe with paraseptal emphysema.**
Fig. 5 **showing pneumothorax on lt side.**

Case 2 :

55 years old male patient, came with complaints of increased breathlessness and chest pain on left side since 2 days before hospitalization. Patient was smoker. On examination he was tachypneic with RR-34/min., pulse 118/min. and SpO2 76%. On Systemic examination, breath sounds were absent on lt side as a whole and decreased in rtinframammary region. X-ray chest PA view revealed Lt sided Pneumothorax, and giant emphysematous Bulla in right Lower zone. ICD with under water seal was inserted on the left side in view of severe respiratory distress and low spO2. Patient clinically l improved. CT chestdone which showed Multiple bilateral Upper lobe and Lower Lobe Bullae with Lt sided Pneumothorax , emphysematous changes with Giant emphysematous Bulla in Rt Lower Lobe. Case was diagnosed as Bullous Emphysema.

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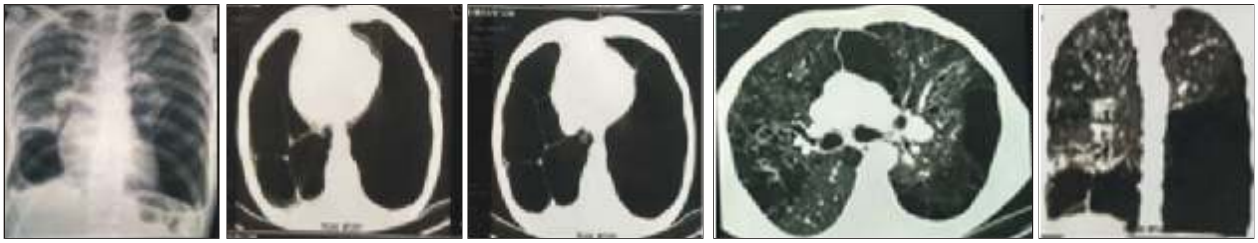

Fig. 1 **Showing Lt sided Pneumothorax with Giant bulla in rt lower zone.**
Fig. 2 to 5 **CT chest showing Paraseptal emphysema Multiple bullae b/l lower lobe with Pneumothorax on lt side.**

Bullous emphysema was described by burke as idiopathic, distinct clinical syndrome of severe progressive dyspnea caused by extensive ,predominantly asymmetric upper lobe emphysema that may lead to respiratory failure while Bullous lung disease is an entity characterized by the presence of bullae in one or both the lung fields, with normal intervening lung[1].

Bullae are air-filled, thin-walled spaces greater than 2 centimeter in diameter in the distended state and is identified as area of transradiancy that usually do not contain blood vessels and is confined by visible walls[2]. Giant bullae are those that encompass more than one-third of the lung volume. The presence of emphysema associated with large bullae is referred to as bullous emphysema. It is either congenital without general lung disease or a complication of chronic obstructive lung disease with generalized lung disease. Extensive paraseptal emphysema coalesces to form giant bullae, compressing the normal lung parenchyma and often displacing it centrally. Most patients are young male, the risk factors are smoking, alpha-1-antitrypsin deficiency, and marijuana abuse[3].

The giant bullae may remain asymptomatic for a long time, their progression may cause worsening dyspnoea. The bullae range in size from a few centimeters to giant bullae nearly filling hemithorax, mimicking a pneumothorax. A major complication of vanishing lung syndrome is pneumothorax. Infection of the bulla is also common. Computed tomography (CT) is an important tool for the diagnosis of this bullous disease[4,5].

CT scans are the most accurate means of detecting emphysema, determining its type and extent and distinguishing giant bullae from pneumothorax. High-resolution CT is an important tool for preoperative assessment, because it can identify underlying centrilobularemphysema, which is synonymous with a diagnosis of bullous emphysema. Moreover, it also allows assessment of associated diseases such as bronchiectasis, infected cysts, pleural disease, and pulmonary hypertension. Patients with giant bullous emphysema developing a secondary spontaneous pneumothorax can also be detected. PFTs can also differentiate between the bullous lung disease and with bullous emphysema. PFT values from a patient with bullous lung disease typically show a restrictive defect, whereas those from a patient with bullous emphysema show an obstructive defect.

Bullectomy, either via video thoracoscopy (VATS) or conventional thoracotomy, is the treatment of choice for giant bullous lung disease, even if asymptomatic. Bullectomy is indicated for symptomatic patients who have incapacitating dyspnea or chest pain, and who have complications related to bullous disease such as infection or pneumothorax, mainly in case of Bullous Lung Disease. Asymptomatic bullae are treated conservatively by reassurance, advise to stop smoking, avoid strenuous activities like scuba diving that can promote the rupture of the bullae. For patients of Bullous emphysema, Surgery is not much Beneficial. lung-volumereduction surgery (LVRS), which is surgical removal of 20-30% of nonbullous emphysematous lung from each side. The recently published National Emphysema Treatment Trial

showed that LVRS benefits selected subgroups of COPD patients who have upper-lobe disease and poor exercise capacity[6]. Indications for surgery with giant bullae are (1) increasing bulla size (2) Pneumothorax (3) Pulmonary insufficiency, and (4) infection within the bulla.

Aim of presenting these two case reports is that case of Pneumothorax whether it is primary or secondary should be evaluated in detail as management varies for these two different etiologies. specially in patients having high smoking index. CT chest should be done to find underlying Bullae which would be not visible on chest X-ray in a case of Pneumothorax.

Conflicts of interest : None reported by Author

References :

1. Burke R. Vanishing lungs : a case report of bullous emphysema. Radiology 1937;28:367-71.
2. CIBA Guest Symposium. Terminology, definitions, and classification of chronic pulmonary emphysema and related conditions. Thorax 1959; 14:286-99.
3. Sood N, A Rare Case of Vanishing Lung Syndrome. Case Reports in Pulmonology 2011, Article ID 957463, 2 pages doi: 10.1155/2011/957463.
4. M. D. L. Morgan and B. Strickland, "Computed tomography in the assessment of bullous lung disease," British Journal of Diseases of the Chest 1984;78:10-25.
5. Sharma N, Justaniah AM, Kanne JP, *et al.* Vanishing lung syndrome (giant bullous emphysema): CT findings in 7 patients and a literature review. J Thorac Imaging 2009;24:227-30.
6. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, RiesA,et al; National Emphysema Treatment Trial Research Group. A randomizedtrial comparing lung-volume-reduction surgery with medicaltherapy for severe emphysema. N Engl J Med 2003;348(21):2059-2073.

Ramsay Hunt Syndrome - Revisited

Shaikh W N[1], Rambhia K[2], Mukhi J[3], Singh R P[4]

Fig. 1 : **multiple vesicles and bullae seen on left side of face**

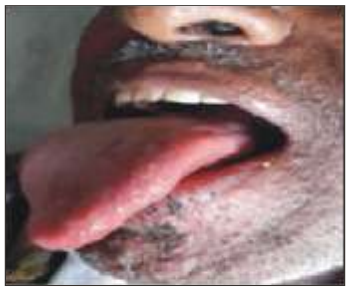

Fig. 2 : **mmultiple vesicles on left side of anterior 2/3 of tongue**

Fig. 3 : **Asymmetry of mouth is seen, patient is not able to shut left eye completely**

60 years old male farmer, presented with left sided earache, painful fluid filled lesions on left side of face, forehead, scalp, left ear and left side of tongue, associated with burning pain since 15 days. Patient has no history of hypertension, diabetes mellitus or any major medical or surgical history. Patient had no history of fever, myalgia, difficulty in opening mouth, slurred speech, taste alteration. On examination, there were multiple vesicles and bullae on an erythematous base, few were eroded with crusting on left side of forehead, cheek, chin, frontal scalp, external auditory canal, pre & post auricular area ***(Fig. 1)*** and lateral border of anterior 2/3 of tongue ***(Fig. 2).*** Left sided lower motor neuron facial paralysis was evident, patient had difficulty in puffing of mouth, asymmetry in smile, inability to shut the eye completely with upward and outward rolling of eyeball while attempting closure, blunting of nasolabial groove. ***(Fig. 3).*** ELISA HIV 1 and 2 was done which was non reactive. Tzanck smear was done revealing multinucleated giant cells other routine investigations were within normal limit.

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Based on these clinical and lab findings, we put forth a diagnosis of Ramsay Hunt Syndrome. Patient was started on acyclovir 800 mg 5 times a day for 7 days and prednisolone 40 mg once a day and was tapered. On 7 day of follow up, patient showed improvement in the symptoms of facial palsy& lesions healed up.

Ramsay hunt syndrome (RHS) also called herpes zoster oticus is a rare presentation of herpes zoster characterized by triad of ipsilateral peripheral facial paralysis (PFP), erythematous vesicles in auditory canaland otalgia[1]. VZV reactivation occurs in geniculate ganglion[2] by various immunosuppresive factors stress, fever, radiotherapy.

Closest differential diagnosis which should be considered are Bell's palsy, lyme disease, trauma, metabolic diseases and tumors[3]. RHS has worse prognosis than Bell's palsy with total recovery in about only 30% cases[3,4]. Incidence increases with age,[1]. Sometimes vesicular lesions may appear on tongue especially on anterior 2/3. In some cases PFP can precede vesicular lesions. Some do not consider vesicular eruptions as a necessary criteria for diagnosis of RHS as in RHS sine herpete.[1,3] In such cases, various presentations are seen with PFP as a constant finding. Apart from these classical triad, other symptoms are nausea, vomiting, vertigo, Sensorineural hearing loss, nystagmus, tinnitus.[1,2,5] These symptoms are related to the involvement of other cranial nerves-trigeminal, glossopharyngeal, vagus, hypoglossal. Diagnosis in mainly clinical. In

atypical cases like sine herpete, virological and serological tests are indicated[2], Early diagnosis is essential to minimize the sequelae. Combination of antiviral and corticosteroid agent is better therapy option in RHS especially within 72 hrs. of symptoms. It results in better prognosis and sequelae rate with total healing in about 75% cases.[2,3] Acyclovir is used in dose of 800 mg 5 times a day for 7-10 days.[3] In case of immunocompromised, children, serious complication, dose of 10 mg/kg/day IV is advocated every 8 hrly for 7-10 days. Corticosteroid is helpful in management of facial nerve paralysis in RHS[3,4] But caution is needed especially in periocular lesions fearing dissemination of VZV infection4In case of persistent neuralgia , surgical decompression is also an option. Despite appropriate treatment, complication / sequelae rate is about 24-90%. These include Post herpetic neuralgia, synkinesis, opthalmopathies, segmental myelitis, encephalitis.[1] Most common and important sequelae is facial nerve paralysis which is maximal at first week.

References :

1. Boemo RL, Navarrete ML, García-Arumí AM, Copa SL, Graterol D, Scherdel EP. [Ramsay Hunt syndrome : our experience]. ActaOtorrinolaringol Esp. 2010 Nov-Dec;61(6):418-21.
2. Martínez Oviedo A, LahozZamarro MT, Urozdel Hoyo JJ. [Ramsay-Hunt syndrome]. An Med Interna. 2007 Jan;24(1):31-4. Spanish. PubMed PMID :17373867.
3. Jan AM, McGuire TP, Clokie CM, Sándor GK. Unilateral facial swelling caused by Ramsay Hunt syndrome resembles odontogenic infection. J Can Dent Assoc. 2006 Nov;72(9):829-32.
4. Sobn AJ, Tranmer PA. Ramsay Hunt syndrome in a patient with human immunodeficiency virus infection. J Am Board FamPract. 2001 Sep-Oct;14(5):392-PubMed PMID:11572547.
5. Sweeney CJ, Gilden DH. Ramsay Hunt syndrome. J NeurolNeurosurgPsychiatry.2001 Aug;71(2):149-54.

Quadricuspid Aortic Valve

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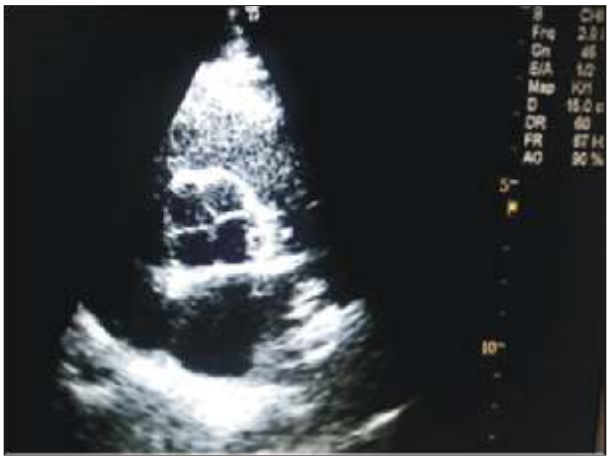

Figure 1 : **SAX View of the Aortic Valve showing four cusps in closure with central coaptation failure**

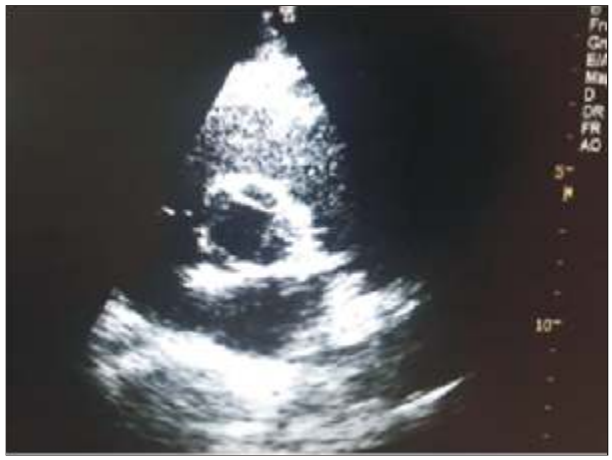

Figure 2 : **SAX View of the Aortic Valve when open showing the four cusps**

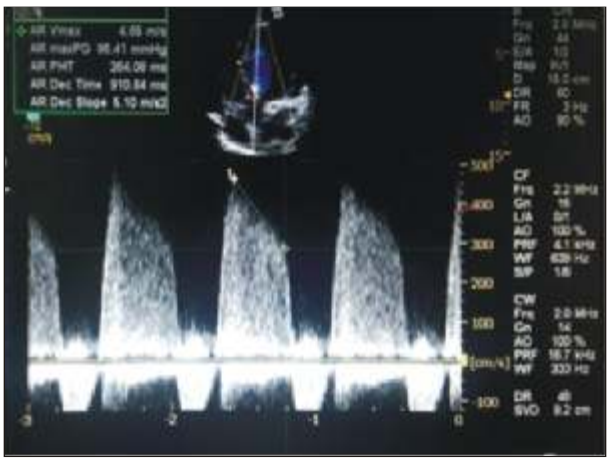

Figure 3 : **Aortic Valve Pressure Half Time showing Moderate Aortic Regurgitation.**

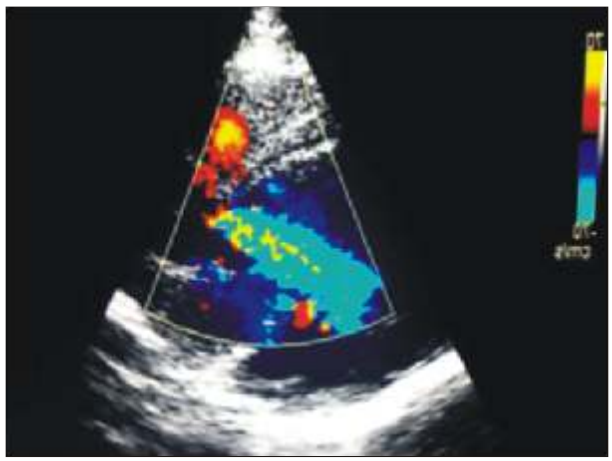

Figure 4 : **PLAX view showing moderate aortic regurgitation**

Presenting a case of 53 years old female who came with history of Class II-III exertional dyspnoea of one month duration. ECG showed non specific ST-T changes. Echo pictures showed quadricuspid aortic valve with moderate aortic regurgitation with AR PHT of 264 msec.

Quadricuspid aortic valve is a rare congenital heart defect characterised by presence of four cusps instead of usual three found normally in aortic valve[1]. Prevalence of Quadricuspid Aortic Valve has been found to be around 0.013% to 0.043% of cardiac cases.[2] and 1 in 6000 patients that undertake aortic valve surgery[3].

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The most common complication of Quadricuspid Aortic Valve is aortic regurgitation caused due to inadequate closure of four cusps during systole.[1, 2, 3]. The typical method of treatment is through surgery such as Aortic Valve Reconstruction Surgery and Aortic Valve replacement [4].

References :

1. Zhu J., Zhang J., Wu S., Zhang Y., Ding F., & Mei J. Congenital Quadricuspud Aortic Valve associated with Aortic Incompetence and Mitral Regurgitation. Journal of Cardiotjoracic Surgery, (2013). 8(1), 87.
2. Jagannath A.D., Johri A.M., Liberthson R., Larobina M., Passeri J., Tighe D., & Agnihotri A.K. Quadricuspid Aortic Valve : a report of 12 cases and a review of literature. Echocardiography, (2011). 28(9), 1035-1040.
3. Godefroid O., Colles P., Vercauteren S., Louagie Y., & Marchandise B, Quadricuspid Aortic Valve : a Rare Etiology of Aortic Regurgitation. European Journal of Echocardiography, (2006). 7(2) , 168-170.
4. Song M.G., Yang H.S., Lee D. H., Shin J.K., Chee H. K. & Kim J.S). Mid term results in patients having tricuspidaization of Quadricuspid Aortic Valve. Journal of Cardiothoracic Surgery, (2014) 9(1), 29.

Case Report

Neuroleptic Malignant Syndrome (NMS) : A Rare Occurrence in Traumatic Brain Injury

Khanzode S S[1], Giri P J[2]

ABSTRACT

Neuroleptic malignant syndrome (NMS) is a rare, but potentially lethal emergency if undiagnosed. It is usually seen in patients with psychiatry illness who are on antipsychotics medicines. NMS in traumatic brain injury is even more cryptic.

We present the case of a young male with a history of road traffic accident with diffuse axonal injury who eventually developed NMS after he received 15mg of haloperidol in divided doses over 24hours. A high index of suspicion is required to diagnose NMS in traumatic brain injury patients.

Introduction :

Neuroleptic malignant syndrome (NMS) is a rare, but potentially lethal emergency if undiagnosed. It is usually seen in patients with psychiatry illness who are on antipsychotics medicines. NMS in traumatic brain injury is even more cryptic. Fifty percent of traumatic brain injury patients have post traumatic agitation and emotional disorders. Haloperidol is most preferred drug in post-traumatic agitation. Haloperidol is incidentally the most common drug that can cause NMS. It is difficult to diagnose NMS in patients with traumatic brain injury as signs and symptoms can be overlapping with the native brain injury.

We present the case of a young male with a history of road traffic accident with diffuse axonal injury who eventually developed NMS after he received 15mg of haloperidol in divided doses over 24hours. He was successfully treated with dantrolene sodium, bromocriptine, aggressive hydration and ventilatory support. The patient responded well to treatment and was eventually discharged. A high index of suspicion is required to diagnose NMS in traumatic brain injury patients. Clinical signs like high grade fever, rigidity, deranged renal functions and elevated serum Creatinine Phosphokinase (CPK) levels are all clues to diagnosis.

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Case :

18 year old male involved in a road traffic accident was admitted to the hospital Intensive Care Unit (ICU) with history of altered sensorium, convulsions and vomiting. On examination, he was hemodynamically stable, Glasgow Coma Scale score was 8/15, pupils were bilaterally equal and reacting to light. No cervical spine injury was detected. CT scan brain was suggestive of diffuse axonal injury and mild cerebral edema. Neurosurgical opinion was sought and conservative treatment was planned. There were no long bone injuries and other systems were also within normal limits. Laboratory investigations were normal except mild leukocytosis. The patient was managed conservatively with anti-edema measures, anticonvulsants, antibiotics and supportive care. Patient was intubated as patient was drowsy due to traumatic brain injury.

On the second day of admission, patient was hemodynamically stable, but extremely irritable. In view of persistent irritability, the patient received 15mg of haloperidol over 24 hours. Haloperidol is the preferred drug in post-traumatic agitation as there is minimal effect on respiration and conscious level.[1] 24 hours later (day 3 of admission), patient developed hectic spikes of fever, became

tachycardic, tachypnoeic with labile blood pressure. Patient's GCS score dropped to 3/15 and he developed rigidity in all four limbs. There was no obvious source of infection. Laboratory` investigations revealed leukocytosis (total leukocyte count 29,200/ccm) and renal functions were deranged (blood urea-80, serum creatinine 2.3mg/dl). Arterial blood gas report revealed severe metabolic acidosis, but lactates were normal. Subsequent MRI did not reveal any increase in mass effect or hydrocephalus. Serum CPK levels were very high (CPK- 50,230U/L). ***Figure 1*** depicts the serial CPK levels in the patient. Infective work up was negative. All cultures were sterile.

Diagnosis of Neuroleptic malignant syndrome (NMS) was established. Haloperidol was promptly stopped and respiratory support in the form of mechanical ventilation was initiated. Aggressive fluid resuscitation, aggressive pharmacological and surface cooling measures were adopted. Patient was treated with dantrolene sodium 3mg/kg and bromocriptine 2.5mg thrice daily through nasogastric tube. He responded well to the treatment and his fever started settling down after 72 hours of treatment. Renal parameters improved with aggressive hydration. By fifteenth day of admission, muscle tone improved significantly, sensorium was better and the patient was weaned off successfully from the ventilator. Dantrolene sodium and bromocriptine were tapered and stopped by twenty first day. He was subsequently shifted to ward and discharged after decannulation of tracheostomy tube.

Discussion :

Neuroleptic malignant syndrome (NMS), first described nearly five decades ago, is an idiosyncratic, life-threatening complication of treatment with antipsychotic drugs that is characterized by fever, severe muscle rigidity, autonomic dysfunction and mental status changes[2]. Incidence of post traumatic agitation is quite high in patients with traumatic brain injury (TBI). Almost fifty percent of TBI patients suffer from emotional disorders and irritability[3]. Haloperidol is the preferred antipsychotic in these settings owing to minimal effect on respiration and sensorium[1]. Incidentally, haloperidol is also the most common drug causing NMS.

Dopamine is essential neurotransmitter in maintaining autonomic cardiovascular stability and regulating hypothalamic thermostat. It also plays an important role in maintaining the conscious level, and normal muscle tone. Antipsychotic-induced dopamine blockade plays a pivotal triggering role in NMS[4]. In addition, traumatic brain injury patients have diffuse axonal injury which further leads to decreased dopamine neurotransmission. This combined effect leads to hypodopaminergic state and causes signs and symptoms of NMS[5].

It is difficult to diagnose NMS in patients with traumatic brain injury as signs and symptoms can be overlapping with the native brain injury. CPK levels, leukocytosis can be associated with blunt trauma. Hence careful review of drug history, negative infective work up and exclusion of worsening brain injury are needed to diagnose NMS in head injury patients.

Clinical features of NMS are described in the table below ***(Table 1).*** The presence of all three major, or two major and four minor, manifestations indicates a high probability of the presence of neuroleptic malignant syndrome, if supported by clinical history.[6]

Treatment of NMS begins with prompt stoppage of neuroleptic agent. Aggressive hydration, temperature control and correction of electrolytes are the mainstay of treatment. In Caroff's review of sixty cases, supportive therapy was the predominant treatment modality[7]. Dantrolene sodium is a direct skeletal muscle relaxant, typical daily dose is 1 to 3 mg per kg per day intravenous and the maximum dose is 10 mg per kg per day. Its action starts within minutes of administration and causes reduction in rigidity and heat production. It is commonly given for ten days. Its dose should be tapered before stopping. Bromocriptine is a dopamine agonist, it restores the lost dopaminergic tone. To start with, it is given in the dose of 2.5 mg every six to eight hours orally or through nasogastric tube and can be titrated to a maximum dose of 40 mg per day. It should be

continued for 10 days after the control of NMS and should be tapered before stopping[8]. Other drugs like amantadine and clonidine have also been tried. Treatment of complications like renal failure might warrant renal replacement therapy. Electroconvulsive therapy (ECT) is required in NMS patients with catatonia, patients not responding to the medical therapy[8].

The main reason being difficulty in diagnosis as clinical features overlap with TBI. In a case series on NMS, nine cases of are reported with use of haloperidol in the traumatic brain injury patients[1] Younger patients are at higher risk for the development of NMS and it is twice more common in males. The reported incidence of NMS with use of haloperidol is ranging from 0.02 to 12.2%[1].

Conclusion :

Diagnosis of NMS in TBI patients is difficult as signs and symptoms may overlap with native brain injury. NMS should be suspected if there is history of use of haloperidol for post traumatic agitation, following which there is development of fever, rigidity, worsening level of consciousness and very high CPK levels. At the same time, it is important to rule out sepsis and neuroimaging should be done to rule out any new lesions or worsening of initial brain injury. NMS is a potentially life threatening emergency. Early recognition and aggressive supportive treatment along with specific medications leads to better outcome and decreased mortality. As haloperidol is the most widely used medication for post traumatic agitation, neurosurgeons and intensivists should be aware of NMS.

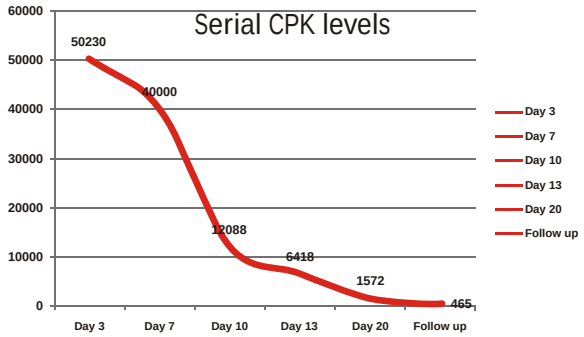
References :

1. Bellamy CJ, Kane- Gill, Sandra L, Falcione BA, Seybert AL. Neuroleptic malignant syndrome in traumatic head patients treated with haloperidol. J Trauma. 2009;66:954-8.
2. Neuroleptic Malignant Syndrome. Jeffrey R. Strawn, M.D.; Paul E. Keck, Jr., M.D.; Stanley N. Caroff, M.D. Am J Psychiatry 2007;164:870-876. doi:10.1176/appi.ajp.164.6.870.
3. Mysiw WJ, Sandel MI. The agitated brain injury patients, Part II. Pathophysiology and treatment. Arch phys Med Rehabil.1997;78:213-20.
4. Mann SC, Caroff SN, Fricchione G, Campbell EC: Central dopamine hypoactivity and the pathogenesis of the neuroleptic malignant syndrome. Psychiatr Ann 2000; 30:363-374.
5. Kadyan V, Colachis SC, Depalma MJ, Sanderson JD, Mysiw WJ. Early recognization neuroleptic malignant syndrome during truamtic brain injury rehabiltation. Brain Inj. 2003;17:631-7.
6. Levenson JL. Neuroleptic malignant syndrome. Am J Psychiatr 1985; 142: 1137-45.
7. Caroff SN. The neuroleptic malignant syndrome. J ClinPsychiatr 1980; 41: 79-83.
8. Ghanem, Al-Sulaiti,Abdel Nasser, Muhammad Ataur Rahman Neuroleptic malignant syndrome and closed head injury : A case report and review. Asian J Neurosurg. 2011 Jul-Dec; 6(2):101-105.

Table 1

Category	Manifestations
Major	Fever, rigidity, elevated creatine phosphokinase concentration
Minor	Tachycardia, abnormal arterial pressure, tachypnoea, altered consciousness, diaphoresis, leucocytosis

Figure 1 : **Changes in serial CPK levels**



Case Report

Priapism - A Rare Presentation in Chronic Myeloid Leukemia

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ABSTRACT

A young boy had stopped therapy for CML and developed priapism, which was not relieved by aspiration and decompression. Hyperleukocytosis was controlled after treatment with Imatinib with gradual improvement of priapism. Regular treatment of the underlying disorder needs to be emphasised to patients that are prone for this manifestation we here report a case of Priapism a rare presentation in chronic myeloid Leukemia .

Key-words : Priapism, Chronic Myeloid Leukemia.

Introduction :

Priapism is a rare complication of haematological disorders like Sickle cell disease and Chronic Myeloid Leukemia accounting for 20% cases[1]. The incidence of priapism in adult leukemic patients is about 1-5%, most of these are painful and due to hyperleucocytosis.[2]

We here report a case of Priapism a rare presentation in chronic myeloid Leukemia .

Case History :

A 22-year-old male with chronic myeloid leukaemiahad painful penile erection for 8 hours prior to hospitalisation. On examination, the patient was anaemic with hepato-splenomegaly. The penis was erect, firm, and tender with superficial venous engorgement ***(Fig.1).*** Rest of the examination was normal. Investigations revealed haemoglobin 5.4 g/dl, haematocrit 25.7%, total leucocyte count (TLC) 1.57 lakh/mm^3, blasts 6%, promyelocytes 6%, myelocytes 18%, band 15% and Platelet count 670000/µL. Penile Doppler revealed no blood flow in the corpora cavernosaand spongiosa. Other investigations were normal. USG guided cavernosaaspiration was unsuccessful. He was started on Tablet Imatinib 600 mg daily with adequate hydration and blood transfusion. Follow up after one month revealed Hb 8.3g/dl, TLC 9600/mm3, penile softening and improvement of priapism.

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Discussion :

Priapism is a painful involuntary prolonged erection unrelated to sexual activity and not relieved by ejaculation. Priapism is classified as either low-flow (ischemic) or high-flow (non-ischemic).[3,4]

Low-flow priapism is more common and results from pathologically decreased penile venous outflow with stasis and manifests as a painful, rigid erection. This can lead to irreversible cellular damage and fibrosis, if not treated within 24 to 48 hours. The causes are idiopathic, hematologic disorders, tumour infiltrate, or drugs.[1]

High-flow or arterial priapism results from increased arterial inflow into the cavernosal sinusoids, which overwhelms venous outflow and is painless. This type of priapism is usually due to penis or perineal trauma that results in injury to the internal pudendal artery causing fistula between the cavernosal artery and the corpus cavernosum with unregulated inflow.

Differentiating between low-flow and high-flow priapism can be achieved with a detailed history, physical examination, gas analysis of the blood within the corpora cavernosa, and penile Doppler ultrasound study.[4,5]

Priapism may be relieved by immediate aspiration with an additional injection of á-adrenergic agents

such as phenylephrine or epinephrine. If the erection persists for 24-48 hours, the patient should have a surgical shunt. One study cited 35% and 60% impotence rates for patients priapistic for 5 days and 10 days, respectively.[5] So decompression of the penis should be done within the first 24 hours.[5]

Conclusion :

Priapism is an uncommon presentation in CML and all physiciansshould be aware of this disorder and the need for early intervention and management.

Conflicts of interest : Nil

References :

1. Meng-Wei Chang *et al*-Priapism - A Rare Presentation in Chronic Myeloid Leukemia : Chang Gung Med J 2003;26:288-92.
2. Tahir J, Khalid M. Priapism An unusual presentation in chronic myeloidLeukaemia: case report and review of the literature. Biomedica 2009; 25:197-199.
3. Michael J N et al. Priapism as an Initial Presentation of Chronic Myelogenous Leukemia. Hospital Physician 1999; 48-52.
4. Burnett, A.L. Therapy insight : Priapism associated with hematologic dyscrasias. Nature Clinical Practice urology.2005; 2: 449-456.
5. Liguori G *et al.* Priapism : pathophysiology and management. Journal of Andrological Sciences 2009;16:13-20.

Legend for Fig. 1 : Priapism on hospitalisation

Case Report

Large Acute Spinal Posterior Subdural Hematoma Complicating Thrombolysis with Streptokinase in Acute Myocardial Infarction

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ABSTRACT

Thrombolysis therapy is the cornerstone of treatment of ST elevation myocardial infarction. It is associated with multiple complications. One of the complications is intracranial bleeding. But intraspinal hemorrhage causing cord compression is rare. Still rarer issubdural posterior spinal hematomaresulting in quadriplegia. We here present a case of subdural posterior spinal hematoma following Thrombolytictherapy in Acute MI

Key words : Spinal subdural hematoma, Streptokinase, Thrombolysis

Introduction :

Thrombolysis therapy is the cornerstone of treatment of ST elevation myocardial infarction. It is associated with multiple complications. One of the complications is intracranial bleeding. But intraspinalhemorrhage causing cord compression is rare. Still rarer issubdural posterior spinal hematomaresulting in quadriplegia. We here report a case of subdural posterior spinal hematoma resulting in quadriplegia following thrombolytic therapy in acute myocardial infarction.

Case Report :

35 year old male patient came to the hospital with chief complaints of Retrosternal chest pain & sweating of 2 hours duration prior to hospitalization without any other significant presentsymptoms. He was non diabetic, non hypertensive without any relevant past history.

Hisphysical examination revealed pulse of 56/min regular, BP 90/60 mmhg & no evidence of congestive heart failure Systemic examination did not reveal any abnormality. Oninvestigation ECG showed -2 mm ST elevation in II, III and aVF leads,- ST depression with T wave inversion in I and aVL, V2, - Right sided lead showed ST elevation in V4R.Suggestive of Inferior wall myocardial imfarction with RV infarct. ***(Fig. 1)*** CPKMB was raised.

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The patient was given fluid challenge with 200 mL Normal Saline and thombolysed with 1.5 MU STK . Following the thrombolysis, the chest pain decreased, heart rate increased to 78/min, regular.

Blood pressure increased to 120/80 mmHg. ECG after thrombolysis showed decrease in ST elevation.

Patient tolerated thrombolysis well without any arrhythmias or other immediate complications.

Routine investigations were normal as follows :

Sr. No.	Investigation	Result
1	Hemoglobin	10 g%,
2	Total leukocyte count	10,000/mm^3
3	Serum creatinine	1.2 mg/dl
4	Blood urea level	27 mg/dl
5	INR	1.3

Apart from Thrombolysis he was reared with antiplatelets, statins, ACE inhibitor & beta blocker after BP improved. Patient was stable for 36 hrs.

36 hours after thrombolysis the patient complained of sudden onset severe back pain in upper thoracic region which increased on coughing & developed weakness in both lower limbs and retention of urine. In the next 4 hours, patient developed profound weakness in all 4 limbs. Neurological examination revealed acute onset, progressive sensory motor quadriplegia with bladder involvement.

MRI cervical and thoracic spine revealed, large acute extra axial intraspinal posterior subdural hematoma from C2 to D3 level causing cord compression and intramedullary hyperintense signals seen in cord from C7 to D3 levels suggestive of cord edema. ***(Fig.2 & 3)***

Antiplatelet drugs were stopped. Coagulation profile was immediately obtained. Patient was referred to neurosurgeon for decompression. Patient was operated immediately and evacuation of hematoma was done. The patient gradually improved and had complete recovery in the next 7 days.

During follow up, patient had no angina, no features of heart failure and no neurological deficit.

Discussion :

Streptokinase therapy for acute myocardial infarction is associated with various bleeding complications. Intracranialhemorrhage, occurs in 0.460.88% of patients treated with thrombolytic agents.[1] Unlike intracranial hemorrhage, intraspinal hemorrhage usually occurs in epidural space most often in dorsal thoracic spine. Incidence of spinal subdural hematoma after thrombolysis is extremely rare.[2]

The most frequent clinical symptom of a intraspinal hematomais neck or back pain with or without radicular symptoms. Neurological deficits from spinal cord compression can appear insidiously or abruptly and progress in a wide clinical picture of complete paraplegia/quadriplegia to Brown Séquard's syndrome.[3]

MRI scan is the investigation of choice for suspected intraspinal hematoma. It provides multiplanar accurate information on both the location and extent of hematoma, as well as the intensity of spinal cord compression by the lesion and is useful in differentiating accompanying intraspinal masses and to follow-up the resolution of the hematoma.[4]

Emergency surgery is the treatment preferred for intraspinal hemorrages but patient-specific factors should be carefully evaluated prior to surgery. Anticoagulants and thrombolytics should be immediately discontinued and correction of coagulopathy should be undertaken prior to surgery.[5]

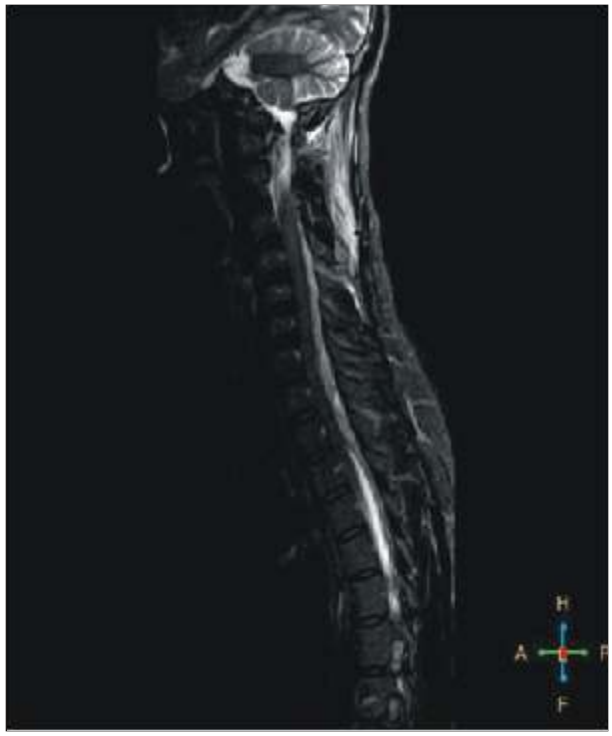

Fig. 2 : **Sagital section of spinal cord showing posterior subdural spinal hematoma**

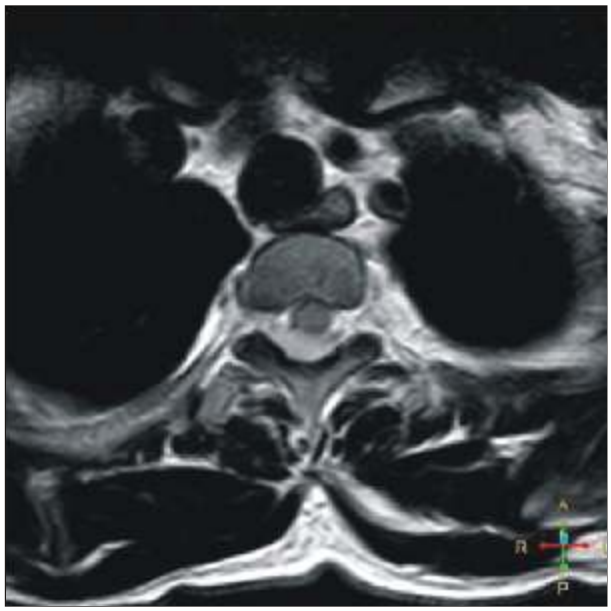

Fig. 3 : **Transverse section of spinal cord showing posterior subdural spinal hematoma**

Conservative treatment is still an important option of treatment in some selective patients with mild and rapidly spontaneous recovery symptoms or high surgical risk patients with bleeding tendency associated with severe systemic disease, advanced cardiovascular disease or advanced and irreversible spinal cord injury. Patients can be managed conservatively with reversal of coagulant effects, close observation of neurologic deficits and in occasional cases, methylprednisolone administration may achieve good results without surgery.[6]

Conclusion :

Thrombolytic therapy has significant role in reperfusion for patients of acute myocardial infarction

Presenting within 12 hours. The physician should be careful in monitoring the patients, as it may result in bleeding complications. Intraspinal hemorrhage is rare complication, early recognition & management is crucial in preventing neurodeficit.

Conflicts of interest : none reported by authors

References :

1. Ozgosmen S, Yoldas T, Kocakoc E *et al.* Spinal epidural hematoma associated with streptokinase treatment for myocardial infarction. Spinal cord 2004; 42; 374-377.
2. Dahlin PA, George J : Intraspinal hematoma as a complication of anticoagulant therapy; Clin Pharm. 1984 Nov-Dec ;3(6):656-61.
3. Kreppel D, Antoniadis G, Seeling W. Spinal hematoma : a literature survey with a meta-analysis of 613 patients. Neurosurg Rev 2003; 26: 149.
4. vanHeesewijk JPM, Caparie JWBM. Acute spontaneous spinal epidural hematoma in a child. EurRadiol 2000; 10:1874-1876.
5. Connoly SE, Winfree CJ, McCormick PC. Management of spinal epidural hematoma after tissue plasminogen activator. A case report. Spine 1996; 21: 1694-1698.
6. Hentschel SJ, Woolfenden AR, Fairholm DJ. Resolution of spontaneous spinal epidural hematoma without surgery. Spine 2001; 26:E525-E527.

Case Report

Iron overload and Liver cirrhosis in Sickle cell disease

Khot R S[1], Bhise A[2], Joshi R[3], Wankhede N[3], Joshi P P[4]

ABSTRACT

Sickle cell disease is a common entity in our region and patients of sickle cell disease receive multiple blood transfusions since early part of their lives. These transfusions lead to the excess burden of iron and can lead to haemosiderosis / hemochromatosis and multiple organ dysfunction. We report a 38 year old male who developed liver cirrhosis due to iron overload as a result of multiple blood transfusions.

Key words : Sickle Cell Disease, Multiple Transfusions, Iron Overload, Cirrhosis of Liver

Introduction :

Sickle cell disease (SCD) encompasses a group of hemoglobinopathies characterized by a single amino acid substitution in the ß-globin chain. The liver can be affected by a number of complications due to the disease itself and its treatment. In addition to the vascular complications from the sickling process, patients with SCD have often received multiple transfusions, placing them at risk for viral hepatitis, iron overload, and (combined with the effects of chronic hemolysis) the development of pigment gallstones, all of which may contribute to the development of liver disease. The clinicopathological features of Liver disease are aggravated by liver iron overload that results from cumulative red cell transfusions. Nontransferrin bound iron induces reactive oxygen species, which not only directly causes cellular damage but also depletes nitric oxide levels leading to endothelial dysfunction. Iron overload ultimately results in Cirrhosis of Liver[1].

Our patient of SCD developed Cirrhosis of liver due to chronic iron overload from repeated blood transfusions. He improved after oral iron chelation therapy.

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Case Report :

A 38 year old male patient, XYZ, cable technician by occupation came with chief complaints of yellowish discolouration of eyes since 2 months, yellowish discolouration of body since 15 days, passing highcoloured urine since 15 days, and swelling overfeet since 4 days. He also had loss of appetite, severe weakness and nausea this time. Patient was diagnosed to have sickle cell disease (SCD) 'SS' pattern in childhood. He had episodes of mild jaundice off and on. He also had repeated hospitalizations for vasoocclusive crisis. Patient had received 30 blood transfusions in last 5 years. He was a non-alcoholic.

On examination patients vitals were stable. He had pallor, deep icterus, haemolyticfacies, edema feet and blackish pigmentation of skin especially over face and extremities and nails ***(Figure 1).*** On abdominal examination his liver was palpable; 3 cm, nodular, firm and tender. Spleen was not palpable. Free fluid was present in the abdomen.

His lab investigations on admission are shown in ***Table 1.***

Ultrasound examination of abdomen revealed liver parenchymal disease with ascites with bilateral pleural effusion and cholelithiasis. Chest radiograph also revealed bilateral pleural effusion. Ascitic fluid was transudate. Magnetic resonance imaging (MRI) of abdomen was done which showed nodular cirrhosis of Liver, dilated Gall bladder and a large calculus of 2.5 cm in the neck of gall bladder which was nonobstructing with mild ascites and bilateral pleural effusion ***(Figure 2).***

Patient was started on Injectable Methylcobalamin, Oral Folic acid, Oral Spironolactone, proton pump inhibitors (PPI), multivitamins and nutritionl support. He was also given 1 unit of blood transfusion as he had severe anaemia and weakness.

However his general condition did not improve and he had persistent icterus and malaise. Patient's iron profile was done in view of hyperpigmented skin and nodular liver cirrhosisand history of multiple blood transfusions . Results are shown in ***Table 2.***

Liver biopsy was not done due to severe hyperbilirubinaemia.

His Serum Ferritin levels were more than 2000 mg/dl. Considering the chronic iron overload due to multiple blood transfusions it was possible that Cirrhosis of liver was due to haemochromatosis.

Patient was then started on Tab Desferasirox and gradually his liver functions started to improve. His Serum Bilirubin decreased to 11 mg/dl. His pleural effusion and ascitis has disappeared. His general health also improved. Patient is under follow up in our Sickle cell clinic.

Discussion :

Sickle cell disease is a commonly encountered disease in our region. Patients of sickle cell disease have repeated admissions for vaso-occlusive crises and severe anaemia and receive multiple blood transfusions. These multiple blood transfusions along with the ongoing haemolysis leads to RBC breakdown and lead to release of excessive iron which gets deposited in the body.

In sickle cell disease transfusions improve blood flow by reducing the proportion of red cells capable of forming sickle hemoglobin polymer. This limits hemolysis and the endothelial damage that result from high proportions of sickle polymer-containing red cells. Additionally, transfusions are used to increase blood oxygen carrying capacity in sickle cell patients with severe chronic anemia or with severe anemic episodes. Transfusion is well-defined as prophylaxis (stroke) and as therapy (acute chest syndrome and stroke) for major complications of sickle cell disease and has been instituted, based on less conclusive data, for a range of additional complications, such as priapism, vaso-occlusive crises, leg ulcers, pulmonary hypertension, and during complicated pregnancies. The major and unavoidable complication of transfusions in sickle cell disease is iron overload[2].

Like patients of thalassemia major, patients with sickle cell disease receive repeated blood transfusions but screening for iron overload is not commonly done as compared to thalassemia major patients. This case indicates the importance of searching and treating for iron overload in SCD patients with history of repeated blood transfusions.

Transfusion of packed red blood cells (RBCs) provides 1 □ mg per mL transfused of additional elemental iron. Long-term transfusion therapy of, for instance, 20-units RBCs/year is associated with significant iron overload (20 units x 220 □ mL per unit, 1 □ mg per mL = 4400 □ mgm exogenous iron/year). With repeated transfusions, serum transferrin becomes saturated and the excess circulating iron is transported as NTBI (non transferrin bound iron). NTBI enters cells in a dysregulated fashion; a subset of NTBI, called Labile Plasma Iron (LPI), may cause end organ damage secondary to its high redox potential[3].

Both thalassemia and SCD patients suffer from of severe hemosiderosis due to multiple blood transfusions. SCD patients tend to have higher serum ferritin levels than thalaessemia patients. However, cardiac disease and endocrine dysfunction are significantly more frequent in thalassemia patients than in SCD patients[4].

Liver and biliary tract dysfunction are common complications of sickle cell anemia and its variants. Early reports described jaundice, hepatic infarcts, acute and chronic viral hepatitis, choledocholithiasis, and cirrhosis. The pathophysiology of hepatic dysfunction was attributed to the classic histologic features of Kupffer cell erythrophagocytosis and engorgement of sinusoids by aggregates of sickled cells. More recent reports have emphasized the importance of hepatic disease as a consequence of conditions not necessarily related to hemoglobinopathy.

Table1 : **Baseline investigations of the patient**

Investigation	Patient's value
Haemoglobin %	3.5 gm/dl
Complete blood count	25,800/cumm
Platelet count	1 lakh
RBC count	0.95 million
MCV	101 fl/red cell
Serum Creatinine	2.6 mg%
Blood Urea Nitrogen	62 mg%
Serum Bilirubin	33.2 mg/dl
Direct	11.2 mg/dl
Indirect	22 mg/dl
AST	110 IU/L
ALT	22 IU/L
Alkaline phosphatase	76 IU/L
Serum Proteins	7.9 gms/dl
Serum Albumin	2.5 gms/dl
INR (International Normalized ratio)	2.1
Ascitic Fluid Analysis	Transudate
Hbs Ag	Negative
Anti HCV	Negative
HIV I & II	Negative

Table No.2 : **Showing Iron studies**

Serum Iron	205.6 microgm/dl
Serum Ferritin	>2000 ng/ml
TIBC (Total Iron Binding Capacity)	225 microgram/dl
Transferrin	153.1 microgram/dl
Transferrin saturation %	91.4%

Because liver dysfunction in SCD is difficult to define, its prevalence too is difficult to document, with previous reports of; 10%. Using liver function tests to assess liver damage in SCD is confounded by abnormal liver enzymes reflecting not only intrinsic liver disease but also hemolysis. Abnormal liver enzymes should prompt a more comprehensive liver workup including laboratory and radiologic assessments, aimed at identifying true liver dysfunction and determining severity and etiology[5].

One of the rare but important cause for cirrhosis in sickle cell disease is Iron overload due to multiple transfusions as well as looking for causes of liver dysfunction unrelated to SCD, an assessment of iron

Figure 1 : **Showing Hyperpigmentation of hands, feet and nails**

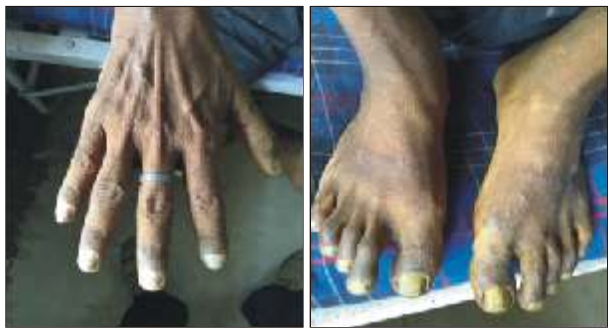
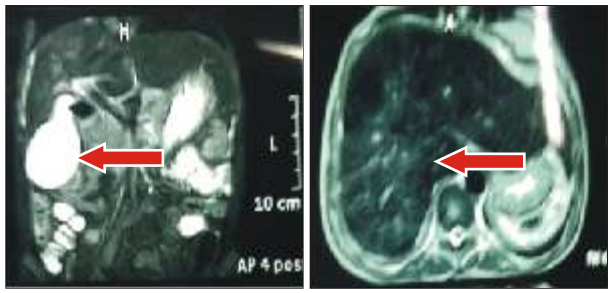


Figure 2 : **MRI Abdomen showing dilated gall bladder and cirrhotic liver**



overload must also be made, especially in view of the increasing use of blood transfusion in SCD. The risk of hepatic siderosis is further likely to escalate with the increasing life span in SCD patients and cumulative exposure to transfused red cells[6].

In a patient suspected to have iron overload, the recommended investigations are Serum ferritin levels, T2 weighted MRI and Liver Biopsy which is the gold standard. We could not do liver biopsy in our patient as he had severly compromised liver function. Serum ferritin may be relatively unreliable in SCD. The cut-off point for serum ferritin levels from which one can consider that tissue damage has already occurred is still to be determined: certainly, in cases where the values are > 1000 mg/dl, the damages to organs and tissues have already occurred and some authors defend that the utilization of chelating agents be started at levels < 500 mg/dl[7]. Our patient had Serum Ferretin levels of >2000mg/dl.

A noinvasive technique SQUID - The Superconducting Quantum Interference Device quantitatively determines Hepatic Iron

concentration (HIC) by magnetic measurement, which is a reliable predictorof HIC, but expensive and available in few institutions worldwide, mostlyfor research purposes.T2*MRI is a well-validated predictor of HIC and cardiac complications from iron overload[7].

Iron chelation for iron overload is recommended. Quantitatively, chelation is considered appropriate when liver iron concentration exceeds 7 mg Fe/g dry weight, roughly equivalent to transfusion of more than 20 units of red cells. It is also indicated if serum ferritin levels are high and patient has end organ damage. In SCD or thalassemia, phlebotomy is not done due to presence of anaemia. Deferoxamine is an oral chelating agent which chelates 10-20 mg iron/day.

This case emphasizes the importance of searching and treating for iron overload in sickle cell anaemia patients with history of repeated blood transfusions. Chronic iron overload can lead to end organ damage, as in our patient who developed Cirrhosis of Liver.

Conflicts of interest : None reported by author

References :

1. John Porter and Maciej Garbowski. Consequences and management of iron overload in sickle cell disease. Hematology 2013:447-456; doi 10.118/asheducation-2013.1.447.
2. Radha Raghupathy, Deepa Manwani, and Jane A. Little, "Iron Overload in Sickle Cell Disease," Advances in Hematology, vol. 2010, Article ID 272940, 9 pages, 2010. Doi:10.1155/2010/272940.
3. B. P. Esposito, W. Breuer, P. Sirankapracha, P. Pootrakul, C. Hershko, and Z. I. Cabantchik, "Labile plasma iron in iron overload: redox activity and susceptibility to chelation," Blood, 2003; vol. 102, no. 7: pp. 2670-2677.
4. Vichinsky, Elliott, et al. "Comparison of organ dysfunction in transfused patients with SCD or â thalassemia." American journal of hematology 2005; 80.1: 70-74.
5. Cage Johnson MD. Gall Bladder and Liver Disorders in Sickle Cell Disease : a Critical Review. Downloaded from http://sickle.bwh.harvard.edu/liver.html
6. Kate Gardner,1,2 Abid Suddle,3 Pauline Kane *et al.* How we treat sickle hepatopathy and liver transplantation in adults Blood. 2014; 123(15):2302-2307.
7. Drasar E, Igbineweka N, Vasavda N, *et al.* Blood transfusion usage among adults with sickle cell disease - a single institution experience over ten years. Br J Haematol. 2011;152(6):766-770.

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