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# Assam Journal of Internal Medicine

OFFICIAL JOURNAL OF ASSOCIATION OF PHYSICIANS OF INDIA, ASSAM CHAPTER

A PEER REVIEWED JOURNAL

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Anomalous RCA

Rare Neurological Manifestations of Insecticide Poisoning

Ruptured hydatid cyst of lung

Stroke Mimic

PRES in childhood Takayasu's arteritis

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*A PEER REVIEWED JOURNAL*

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# ASSAM JOURNAL OF INTERNAL MEDICINE

Official Journal of Association of Physicians of India, Assam Chapter

EDITOR : PROF. SANJEEB KAKATI

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## Somatoform Disorder Current Concept and Controversies

**Dhrubajyoti Bhuyan\***

Somatoform disorders have been regarded as one of the most controversial and challenging areas of modern psychiatry<sup>1</sup> and are often thought to be residing on the “no man’s land” between the territories of medicine and psychiatry overlooking the fact that they are the essential keystone to maintain the integrity of the two discipline.<sup>2</sup>

It is well known from the time immemorial that the mind and body exert powerful effects on each other and changes in the inner world of the individual often manifest with bodily symptoms. The subtle changes in some parts of the brain can result in changes in the bodily sensation, movement and functions of internal organs.<sup>3</sup> Despite the clear reciprocal relationship between body and mind, till today, psychiatry and medicine have not been able to formulate the etiological basis of the so called medically unexplained syndrome.

These disorders are quite common in any clinical set up and are associated with significant mental distress.<sup>4</sup> It is estimated that about 50% of the patients attending primary health care set up often presents with symptoms that cannot be explained by a general medical condition.<sup>5</sup>

Lipowski viewed Somatization as the tendency of individuals to experience and communicate their psychological distress in the form of somatic symptoms and to seek medical help for them<sup>6,7</sup>. This psychological process gives rise to somatoform disorders and patients typically present themselves in nonpsychiatric settings. The symptoms are typically multiple and vague referring to single or multiple body systems or functions and

inability to explain the symptoms on the basis of existing medical model forms the basis of this diagnosis. This concept is still valid if we consider ICD-10, however DSM 5 has adopted a more practical approach to diagnosis of this group of disorders and nomenclature has been changed to Somatic Symptoms and Related Disorder. According to DSM 5 these disorders are characterized by prominence of somatic symptoms associated with significant distress and impairment rather than focusing on the criteria like absence of medical explanation for somatic symptoms, distressing somatic symptoms along with abnormal thought feeling and behaviour in response to these symptoms have been regarded as essential criteria for diagnosis.

There is even no general consensus regarding the disorders to be included under Somatoform Disorder. ICD -10 has included Somatization Disorder, Undifferentiated somatoform disorder, Hypochondriacal disorder, Somatoform autonomic Disorder, Persistent Somatoform Pain Disorder, Other somatoform disorders, Somatoform disorder unspecified. While in DSM 5 somatic symptoms and related disorders category is created by reorganizing the Somatoform Disorder group of DSM IV. DSM 5 has included following disorders into this category –

- i. Somatic symptom disorders
- ii. Illness Anxiety Disorder
- iii. Conversion Disorder (Functional Neurological symptom disorder)
- iv. Psychological Factors affecting other medical conditions,
- v. Factitious Disorder

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- vi. Other Specified Somatic symptom & related disorder
- vii. Unspecified somatic symptom disorder

In spite of the claim by mental health care professionals and primary health planners, somatoform disorder group is often neglected and least studied<sup>8</sup>. Surprisingly the studies on somatoform disorder, its prevalence and burden of disease are very few and this group of disorder is not even usually included in National Survey of mental health.<sup>9, 10</sup>

There have been various myths regarding somatoform disorder which are being refuted by recent researches, indicating the need of having a fresh look into the phenomenology.<sup>11</sup> Somatoform disorders were considered to be chronic in nature, but according to Creed F (2004) in 50% of cases it resolves over a period of 1 year which may be probably associated with reduction of associated symptoms of anxiety and depression. The traditional belief that somatoform disorders tend to occur more frequently in developing countries than developed one has also been challenged as high rates are being reported from European and South American centres in a World Health Organization study.<sup>12</sup>

Studies related to somatoform disorders in this part of the country are scanty and Kumar and Phookun in this issue of Medical Journal have reported their experience and observation in a tertiary care setting which has definitely thrown light into this gray area.

Recent qualitative research across the globe has shown that the primary care physician's attitude towards the disease and tendency to order investigations for organic diseases often reinforce the patient's somatic attributes. Under these circumstances psychiatrists often feel that with early proper interventions and timely referral could have definitely reduced chronicity and complications of the disorder. However so called proper approach will not be possible if General care physicians and other health care professionals are not made aware of these disorders and to adopt early and appropriate management of all patients who present with numerous

bodily symptoms or marked illness worry. The research paper titled Somatoform disorder : A link between psychiatry and medical symptoms with demographic profile can be viewed as a small step in this direction. Study of this kind will definitely enrich our knowledge about the disorder and will encourage the multidisciplinary research groups to include it in their research endeavour. The suffering due to somatoform disorder is immense and the cost of the treatment is also high. At the end of the day we must remember that patient does not want homeopathy or allopathy, what he wants is compassionate care and empathy. However we must remember what Tófoli LF et al said "understanding the sophisticated process encompassing mind and body through which human suffering manifests is a task that remains to be completed so that the best alternatives of care can be implemented."

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## Somatoform disorder : A link between psychiatry and medical symptoms with demographic profile

A Kumar\*, H R Phookun\*\*

### Abstract

**Background:** Somatoform disorders have always remain a grey area between Medicine and Psychiatry. This is because almost always patients present to a clinician with real physical symptoms but clinician has a hard time finding the cause of those symptoms. The frantic search of cause leads to unnecessary investigations and surgical procedures. These “unexplained symptoms” are hugely influenced by the socio-cultural-demographic background of the patient.

**Aim of the study:** To study the symptom and demographic profile of patients of somatoform disorders and to see the relationship of symptoms with demographic variables.

**Materials and methods:** 100 consecutive patients of somatoform disorders diagnosed clinically based on ICD-10 criteria were chosen after applying various inclusion and exclusion criteria. The PGI health questionnaire N-2 was used to evaluate symptoms of the patients. Data was analyzed with descriptive statistics and chi-square test.

**Result:** The patients presented with wide range of symptoms, both physical and psychological. Every patient presented with more than one symptom which were localized in many organ systems. In the sample there was predominance of males, young people, Muslims, married, low education, people who were employed, people belonging to middle and lower socio-economic status, people living in rural areas and those living in nuclear families. Age; sex; religion; marital status; education status; employment status and socio-economic status showed significant association with some of the symptoms.

**Conclusion:** The symptoms of somatoform disorders cut across many organ systems and therefore it's not surprising that such patients often consult clinicians other than psychiatrists.

**KEY WORDS :** *Somatoform, Medically Unexplained symptoms; somatic symptom disorder.*

### INTRODUCTION :

Somatoform disorders or “medically unexplained symptoms” (MUS) are a group of disorders which share three things in common between them: multiple medical symptoms; repeated help-seeking for these symptoms<sup>1</sup> and extensive investigations have ruled out any organic disease which can explain the symptoms.<sup>2</sup> The word ‘somatization’ and ‘somatoform’ is derived from the Greek word ‘soma’ meaning body. These disorders are classified into: somatization disorder, undifferentiated somatoform disorder, hypochondriacal disorder, somatoform autonomic dysfunction, persistent somatoform pain disorder, other somatoform disorder

and somatoform disorder unspecified.<sup>3</sup> Somatoform disorders are very common disorders and in primary care settings, it has been found that 15% to 20% of patients suffer from somatoform disorder.<sup>4,5,6</sup> The symptoms not only bother the patients a lot but also the physicians. Patients with unexplained symptoms make more visits to physicians, ask for unnecessary and costly investigations, undergo unnecessary procedures, and have more hospitalizations.<sup>7,8</sup> Similarly, lack of findings on repeated investigations lead to therapeutic nihilism in the clinicians.<sup>9</sup> The chronic nature of illness is a great burden not only on the functioning of the patient but also on the health-care utilization and economy.

The more interesting fact is that the term ‘somatoform disorder’ has been changed to ‘somatic symptom disorder’. The basic shift in concept is that now even if the patient has some genuine medical illness and is excessively preoccupied which causes significant emotional, cognitive or behavioural changes then the patient can be diagnosed with this disorder. This has far

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reaching consequences in that even if a genuine medical illness is present, psychological factors should not be overlooked.<sup>10</sup>

Culture has strong role in modulating subjective experiences. While in one culture expression of inner experiences may be discouraged while in others feelings tend to be somatized. Like delusions, where content is influenced by culture, subjective distress in somatoform disorders is also influenced by socio-cultural factors.<sup>11</sup>

**Aim of the study:** To study the symptom and demographic profile of patients of somatoform disorders and to see the relationship of symptoms with demographic variables.

#### **MATERIALS AND METHOD :**

**Place of Study:** This study has been conducted on patients attending Psychiatry OPD as well as patients admitted in the Department of Psychiatry of Gauhati Medical College and Hospital. Gauhati Medical College and Hospital is a tertiary care institute situated in Guwahati, Assam and receives patients both from Assam as well as neighbouring states of North-East India.

**Period of Study:** The period of study extended from November 2013 to August 2014.

**Selection of study Sample:** 100 patients diagnosed clinically (based on ICD-10 criteria), to be suffering from somatoform disorder were chosen by serial sampling subject to fulfilment of selection criteria.

**Selection criteria:** Both male and female patients were selected. Patients suffering from other psychiatric disorders such as schizophrenia, psychosis, bipolar disorder, moderate or severe depression, primary diagnosis of anxiety disorders, mental retardation as well as suffering from physical illness which could explain the symptoms of the patients were excluded. Illiterate patients were also excluded because they were unable to read the self-reported questionnaire.

**Consent & Ethical Consideration:** Written informed consent was taken both from the patient and guardian, in front of a witness. The study is approved by the Institutional Ethics Committee of Gauhati Medical College and Hospital.

#### **MATERIALS AND TOOLS USED:**

**1. Semistructured Proforma :** A Semistructured Proforma was prepared to document the socio-demographic data, diagnosis of the patients.

**2. ICD-10 :** ICD-10 is the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD), a medical classification list by the World Health Organization (WHO). Chapter F of ICD-10 defines and explains diagnostic criteria of mental and behavioral disorders. The code ranges from F00 to F99. The codes for different Somatoform disorders fall between F45.0 to F45.9.

**3. Modified Kuppuswamy's scale for estimating Socio-Economic status:**<sup>12</sup> Kuppuswamy's scale is widely used to determine the socio-economic status of Indian families. The scale consists of three items namely: Education of the Head of the family, Occupation of the Head of the family, and Total Family income (in Rs.) per month.

#### **4. PGI Health Questionnaire N-2:**<sup>13</sup>

The questionnaire is developed by Dr. N.N. Wig and Dr. S.K. Verma of Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India in Hindi and English. The scale consists of 60 questions to be responded by patients themselves. First 50 questions are about Physical and Mental health status of the patient. Next 10 questions are Lie questions and check answers of social desirability. If a patient score 5 or more on lie scale then he fails for other questions also. Although the scale was developed to check Neuroticism in patients, its questions related to different physical and mental health components can be used to study the symptomatology of our patients in this study. The symptom clusters fall into: Eye symptoms; Gastro-Intestinal symptoms; Disturbance of sleep; Weakness and Fatigue; Pain in Body; complaints in Head; Hot Sensation in the Body; Urinary symptoms; Disturbance of Attention; Memory complaints; Anxiety(somatic); Anxiety(Psychological); Fear/Phobia; Obsessive thoughts; depressive symptoms; Hypochondriacal ideas and Somatic preoccupation. Some questions related to ENT complaints and Neurological complaints were additionally included to make the questionnaire more comprehensive. The questionnaire was translated in Assamese to meet the local needs of the patients.

**Study design & Statistical analysis:** This is a Cross-sectional Observational study. It is an exploratory study and no hypothesis is put forward. The socio-demographic

data are shown using descriptive statistical methods. Comparison of the variables are done using chi square test to find out two-tailed probability of chance (p-value) as per the requirement of the study.

**Results:** The results are shown in tables 1 to 7.

Table 1: Descriptive analysis of Socio-demographic data of the sample

Socio-demographic profile	N=100	%
<b>Age-group (yrs)</b>		
18-39	50	50
40-59	43	43
60-79	7	7
<b>Sex</b>		
Male	52	52
Female	48	48
<b>Religion</b>		
Hindu	51	51
Muslim	49	49
<b>Marital status</b>		
Married	75	75
Unmarried	16	16
Widow/ separated	9	9
<b>Education</b>		
Upto primary	50	50
Middle school and Matriculation	30	30
Higher secondary and above	20	20
<b>Occupation</b>		
Unemployed	46	46
Employed	54	54
<b>Socio-economic status</b>		
Upper-middle	15	15
Lower-middle	36	36
Lower	49	49
<b>Locality</b>		
Rural	78	78
Urban	22	22
<b>Type of family</b>		
Nuclear	56	56
Joint	44	44

Table 2: Descriptive analysis of symptom-profile of the sample

Symptom/symptom cluster	% (N=100)	Symptom/symptom cluster	% (N=100)
Eye Symptoms	46	Disturbance of Attention	31
ENT symptoms	21	Memory Complaints	44
Gastro-Intestinal symptoms	83	Anxiety(Somatic)	66
Disturbed sleep	70	Anxiety(Psychological)	87
Weakness & Fatigue	86	Phobia/Fear	27
Neurological symptoms	43	Obsessive thoughts	58
Pain in body	54	Depressive symptoms	62
Complaints in Head	84	Hypochondriacal ideas	25
Hot sensation	63	Somatic preoccupation	66
Urinary symptoms	35		

Table 3: Type of somatoform disorders in the sample

Type of somatoform disorderq	N=100	%
Undifferentiated somatoform disorder (UD)	42	42
Somatization disorder (SD)	43	43
Hypochondriacal disorder (HD)	7	7
Somatoform autonomic dysfunction(SAD)	6	6
Persistent somatoform pain disorder (PSPD)	2	2

## DISCUSSION :

### Socio-demographic data

In this study, 50% (n=50) of patients are in the age group 18-39 years, 43% (n=43) are in the age group 40-59 years, and 7% (n=7) patients are in the age-group 60-79 years. The minimum age in the sample is 20 years while maximum age is 75 years. Mean age is 39.36 years. The mean age of the sample found in different other studies are as follows: 35.7 years; 37.6

Table 4: Relationship of symptoms with Age and Gender

Symptom/symptom cluster	Age- groups			p-value	Gender		p-value
	18-39 (N=50)	40-59 (N=43)	60-79 (N=7)		Male (N=52)	Female (N=48)	
Eye Symptoms	25	20	1	.2059	20	26	.1154
ENT symptoms	13	6	2	.3194	8	13	.1513
Gastro-Intestinal symptoms	41	36	6	.9570	46	37	.1302
Disturbed sleep	32	31	7	.1390	34	36	.2945
Weakness & Fatigue	43	36	7	.5156	39	47	.0010
Neurological symptoms	18	19	6	.0443	18	25	.0779
Pain in body	28	22	4	.8835	24	30	.1013
Complaints in Head	44	34	6	.4995	40	44	.0445
Hot sensation	33	24	6	.2599	39	24	.0097
Urinary symptoms	16	17	2	.6999	20	15	.4500
Disturbance of Attention	16	13	2	.9731	11	20	.0267
Memory Complaints	20	22	2	.3875	17	27	.0177
Anxiety(Somatic)	35	26	5	.5959	31	35	.1607
Anxiety(Psychological)	42	38	7	.4687	43	44	.1825
Phobia/Fear	17	7	3	.0981	11	16	.1705
Obsessive thoughts	28	27	3	.5638	31	27	.7334
Depressive symptoms	28	28	6	.2709	26	36	.0101
Hypochondriacal ideas	14	11	0	.2751	16	9	.1655
Somatic preoccupation	33	26	7	.1229	34	32	.8924

Table 5: Relationship of symptoms with Religion and Marital status

Symptom/symptom cluster	Religion		p-value	Marital Status			p-value
	Hindu (N=51)	Muslim (N=49)		Married (N=75)	Unmarried (N=16)	Widow/ Separated(N=9)	
Eye Symptoms	24	22	.8284	37	6	3	.5010
ENT symptoms	13	8	.2607	17	3	1	.7030
Gastro-Intestinal symptoms	40	43	.2147	60	15	8	.3660
Disturbed sleep	36	34	.8958	55	10	5	.4233
Weakness & Fatigue	40	46	.0261	65	12	9	.2121
Neurological symptoms	20	23	.4355	31	7	5	.7162
Pain in body	28	26	.8535	40	8	6	.7055
Complaints in Head	43	41	.9304	62	14	8	.8166
Hot sensation	29	34	.1947	46	10	7	.6268
Urinary symptoms	18	17	.9498	27	5	3	.9311
Disturbance of Attention	16	15	.9345	21	4	6	.0514
Memory Complaints	24	20	.5296	32	7	5	.7625
Anxiety(Somatic)	39	27	.0241	50	12	4	.2929
Anxiety(Psychological)	46	41	.3323	66	12	9	.1783
Phobia/Fear	11	16	.2120	17	7	3	.2044
Obsessive thoughts	28	30	.5219	43	11	4	.4839
Depressive symptoms	32	30	.8756	44	10	8	.2104
Hypochondriacal ideas	12	13	.7290	17	7	1	.1260
Somatic preoccupation	35	31	.5715	47	14	5	.1260

Table 6: Relationship of Symptoms with Education and Employment status

Symptom/symptom cluster	Education			p-value	Employment Status		p-value
	Upto primary school (N=50)	Middle & High School (N=30)	Higher Secondary & above (N=20)		Employed (N=54)	Unemployed (N=46)	
Eye Symptoms	23	16	7	.4440	21	25	.1788
ENT symptoms	10	10	1	.0532	9	12	.3647
Gastro-Intestinal symptoms	41	26	16	.7990	48	35	.1523
Disturbed sleep	37	22	11	.2615	36	34	.5692
Weakness & Fatigue	47	23	16	.0663	42	43	.0561
Neurological symptoms	20	12	11	.4798	19	24	.1316
Pain in body	31	14	9	.2739	29	25	.8911
Complaints in Head	45	23	16	.2494	42	42	.1175
Hot sensation	34	20	9	.1747	28	35	.0218
Urinary symptoms	17	11	7	.9711	21	14	.5009
Disturbance of Attention	19	8	4	.2808	15	16	.5906
Memory Complaints	23	14	7	.6619	18	26	.0335
Anxiety(Somatic)	31	25	10	.0359	35	31	.9527
Anxiety(Psychological)	44	28	15	.1608	46	41	.7747
Phobia/Fear	13	8	6	.9425	11	16	.1639
Obsessive thoughts	25	18	15	.1545	31	27	.9417
Depressive symptoms	34	17	11	.4625	29	33	.0999
Hypochondriacal ideas	10	7	8	.2111	16	9	.3541
Somatic preoccupation	33	19	14	.8880	34	32	.6292

years; 36.8 years.<sup>14,15,16</sup>

52% of patients in the study are males while 48% are females. Male: Female ratio is 1.08. Gender is one of the strongest demographic influences on somatic symptom as reported in various studies and most of the studies have found a female predominance of the

Table 7: Relationship of Symptoms with Socioeconomic status, Locality and Type of family

Symptom/symptom cluster	Socio-economic status			p-value	Locality		p-value	Type of Family		p-value
	Upper middle	Lower middle	Lower (N=49)		Rural (N=78)	Urban (N=22)		Joint (N=44)	Nuclear (N=56)	
Eye Symptoms	4	16	26	.1944	34	12	.3625	17	29	.1903
ENT symptoms	2	6	13	.3981	15	6	.6020	10	11	.7070
Gastro-Intestinal symptoms	13	29	41	.8559	66	17	.6253	38	45	.4273
Disturbed sleep	9	23	38	.2612	53	17	.5623	30	40	.7251
Weakness & Fatigue	12	29	45	.2565	68	18	.8625	39	47	.5006
Neurological symptoms	8	16	19	.5943	33	10	.9844	19	24	.9740
Pain in body	7	21	26	.7356	43	11	.8540	24	30	.9227
Complaints in Head	11	31	42	.4732	65	19	.9895	38	46	.5677
Hot sensation	7	19	37	.0365	51	12	.4965	32	31	.0741
Urinary symptoms	4	17	14	.1563	27	8	.9194	15	20	.8658
Disturbance of Attention	1	11	19	.0626	24	7	.8673	16	15	.3040
Memory Complaints	4	13	27	.0747	33	11	.6901	18	26	.5810
Anxiety(Somatic)	10	24	32	.9897	48	18	.1289	29	37	.9864
Anxiety(Psychological)	13	29	45	.3108	66	21	.3290	36	51	.1720
Phobia/Fear	2	9	16	.3184	21	6	.8109	13	14	.6113
Obsessive thoughts	10	19	29	.6396	49	9	.1108	28	30	.3114
Depressive symptoms	8	18	36	.0667	46	16	.3549	25	37	.3440
Hypochondriacal ideas	5	10	10	.5340	20	5	1.000	9	16	.3521
Somatic preoccupation	9	21	36	.3009	49	17	.3130	30	36	.6831

patients.<sup>17,18</sup> The cause of opposite finding in this study is unclear and may be related to chance factor. Also, most of the studies are conducted in other countries and their finding may not be applicable to the Indian population.

Almost equal percentage of patients belonged to both Hinduism and Islam (51% vs 49%). There were no patients belonging to other religion. An Indian study from Chandigarh found that 73.33% of patients of somatoform disorders were Hindus.<sup>19</sup>

Maximum numbers of patients in the study are married (75%). Next large group is unmarried patients (16%) followed by widows (8%). Only 1 patient was married but separated. A higher prevalence in married patients is also reported by many other researchers.<sup>20,21,22</sup>

In this study 50% (n=50) of patients are educated upto primary school, 30% (n=30) upto class 8<sup>th</sup> or 10<sup>th</sup>, 20% (n=20) have studied till higher secondary or beyond. Two Indian studies as well as studies from Japan and Dhaka found low illiteracy among somatizers. The mean number of years of education in these studies was found to be around 10- 12 years.<sup>15,19,23,24</sup>

In this study 46% (n=46) of patients are unemployed (46%). Unemployed group consists of those who don't contribute to family income and includes students and housewives. Among the employed, self-employed have the highest somatoform disorders (34%). Pvt. Employees are 7% while Govt. employees constitute 13% of sample. Similar unemployment status of 47.5%; 40% is reported in previous studies.<sup>24,25,26</sup>

49% (n=49) of patients belonged to lower socio-economic class, 36% (n=36) belonged to lower-middle

class while 15% (n=15) belonged to upper-middle socio-economic class. There is no patient belonging to Upper class. An Indian study<sup>22</sup> and a study in Dhaka<sup>21</sup> reported prevalence of somatoform disorders more in the lower socio-economic group while another one found equal prevalence in both lower and middle SES.<sup>27</sup>

78% patients lived in rural areas, a finding supported by foreign studies.<sup>14,28</sup> The most interesting

fact is that 3 Indian studies found a higher prevalence of this disorder in the urban population.<sup>19,27,29</sup> This discrepancy in the finding may be due to population pattern attending Govt. hospital O.P.D in the present study. More of rural population attends Govt. hospitals in this geographical area. 56% of patients in the study lived in nuclear families but another study found an almost equal prevalence in both joint and nuclear families.<sup>30</sup>

## SYMPTOM- PROFILE

The symptoms observed in this study can be conveniently divided into physical and psychological symptoms. The physical symptoms/ symptom clusters have following frequencies: eye symptoms like heaviness, burning sensation and watering from eyes (46%); ENT symptoms (21%); gastro-intestinal (83%); weakness and fatigue(86%); neurological symptoms like tingling, numbness, pins and needle sensations, pulling sensation (43%); pain at various sites of body (54%); complaints in head like heaviness, headache, uneasy sensation (84%); hot sensation in body including hot air coming from ears & head (63%); genitourinary complaints like burning micturation, difficulty in passing urine (35%) and somatic symptoms of anxiety such as palpitation, sweating, thirst and dryness of throat (66%).

The frequencies of psychological symptoms are as follows: disturbed sleep (70%); disturbance of attention (31%); memory-related complaints (44%); psychological symptoms of anxiety (87%); phobia (27%); obsessive symptoms (58%); depressive symptoms (62%); hypochondriacal ideas (25%); and somatic preoccupation (66%).

The symptomatology reported by many earlier studies are not exhaustive, some just mentioning the symptom occurrences without their frequencies. One study reports following symptoms and their frequencies: fainting- 33.3%; menstrual problems- 33.3%; head complaints- 57.4%; body pain- 60.1%; palpitation- 25.6%; genito-urinary- 25%; abdominal complaints- 84.4%; fatigue- 18.7%; and insomnia- 17.4%. These symptoms were also accompanied by psychological distress in the form of anxiety and depressive symptoms.<sup>31</sup>

In a Sri Lankan study, the symptoms most commonly present were: low backache (54%); chest pain (including back of the chest) (40%); pain in the limbs (38%); abdominal pain (22%); headache (34%); pain in the joints (31%); numbness in various body parts (29%); fatigue (28%); bloating of the abdomen (21%); Faintish feeling (13%); loss of appetite (10%); burning sensation over various body parts (12%); sleep disturbance (7%); pain along the spine (4%).<sup>32</sup>

#### **Relation of Symptoms with Socio-demographic profile :**

Previous studies have described in their findings, the association between somatoform disorders and different demographic variables. However, after an exhaustive search of literature, it was found that none of the previous studies have studied the association of individual symptoms in relation to demographic variables.

In our study, 18 out of 19 symptom clusters studied don't show any association with age. Only neurological symptoms show a significant trend. Prevalence of this symptom is highest in the age group 60-79 years (85.7%) and lowest in the age group 18-39 years (36%). 2 studies found no association of symptoms with age<sup>33,34</sup> while 2 studies found an association of symptoms with older age.<sup>35,36</sup>

When symptoms are compared with sex, it is found that weakness and fatigue; complaints in head; disturbance of attention; memory complaints and depressive symptoms are significantly higher in females while hot sensation in the body are significantly associated with male sex. An earlier study found that headache was found mostly in females.<sup>37</sup>

Religion is found to be a contributory factor in two symptoms in this study. While weakness and fatigue is significantly complained more by Muslims,

the somatic symptoms of anxiety are found significantly higher in Hindus. There is lack of Indian studies on this demographic variable but a western study found no association of symptoms with religion.<sup>38</sup>

Marital status is seen to influence the complaints of attention. A problem in attention is found significantly higher in widows/separated group (66.7%) and lowest in unmarried group (25%). No association was also found in other studies.<sup>38,34,39</sup>

The patients with high education status have significantly lowest complaints related to somatic anxiety and ENT complaints. On the other hand these two symptoms are highest in those who are educated upto middle & high school. So it appears that both high education and low education acts as a protective factor. Probably patients with high education status have better insight and people with low education are not aware of medical issues and thus are not much concerned with the symptoms. Less education is said to be the contributory factor in other studies.<sup>33,40</sup>

Employment status is found to have significant association with 3 out of 19 symptom clusters. Weakness and fatigue; hot sensation in the body; and memory complaints are found significantly higher in the unemployed group than the employed group. This can point out to the fact that job security is a protective factor for somatoform disorder. According to previous studies, somatic symptoms are reported to be more prevalent in unemployed.<sup>33,41</sup>

In a general trend, most of the symptoms are more prevalent in lower socio-economic status but in particular, hot sensation in the body is significantly associated with low-socio-economic status. This symptom decreases as the socio-economic status improves. Thus, it can be said that financial security acts as a protective factor. Some of the previous studies didn't found any significant association<sup>38,42,43</sup> while some found positive association with low socioeconomic status.<sup>33,41,39</sup>

Locality of living doesn't have any significant influence on the symptom profile of the patients as also seen in one previous study.<sup>40</sup> Living in joint family or nuclear family doesn't influence symptoms in the present study and no prior studies are available on this variable.

## SUMMARY AND CONCLUSION :

Concluding the specific findings of this study, few of the somatic symptoms are found significantly higher in old age; females; both Muslims and Hindus; widows; people with neither too high nor too low education status; unemployed and people with low-socio-economic status. The symptoms can origin from any part of the body/organ system and can be either specific or vague at times. It is equally important to pick up the psychological distress associated with these symptoms which can be in the form of disturbance of thinking, emotions and behaviour. In the presence of these psychological symptoms, the vague physical complaints should not be simply dismissed telling the patients that they don't have any illness. The high prevalence of such somatic symptoms in the background of different psychological symptoms should always alert the clinicians about this diagnosis so that instead of unnecessary harassment of the patient, they can be timely referred to psychiatric services.

Since there is a clear link between these symptoms and the socio-demographic variables of the patients, it's equally important to acknowledge these variables because they can lead to better understanding of the factors responsible for the origin of the symptoms.

### Limitations of this study

This study has certain limitations. First, it didn't include those patients who are illiterate. It can't be denied that the percentage of such patients is quite large. Second, the questionnaire used to assess symptoms was translated only in Assamese. The catchment area of the hospital where the study is conducted, consists of many people whose first language is Bengali.

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## A Mycological Study on Otomycosis for a period of one year in a Tertiary Care Hospital of Assam

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### Abstract

**Purpose:** Otomycosis though is not a life threatening disease, but due to its complications like tympanic membrane perforation, its diagnosis and treatment is important, so the aim of this study is to find out the causative fungi. Gauhati Medical College is the premier referral hospital of the North East Region. Hence a cross-section of various groups of people can be studied here. **Materials & Methods:** Aural swabs were taken for those patients with history and clinical features suggestion of otomycosis. KOH preparation and fungal culture on SDA (with antibacterial) was done. All culture positive cases were subjected to LPCB identification technique along with other. special test for *Candida* species. **Results:** Out of 85 cases, 70 samples showed growths in SDA while there was no growth in 15 samples. Out of different fungi isolated *Aspergillus niger* headed the list 31(36%). *Aspergillus flavus* 18 (21%), *Aspergillus fumigatus* 14 in no. (16.4%) and *Candida albicans* 7 (8.24%). **Conclusion:** As per as different type of fungi were isolated. *Aspergillus niger* and *Aspergillus flavus* were predominant. The incidences were high when the climate was rainy, hot and humid.

**KEY WORDS :** *Aspergillus spp.*, *Otomycosis*, *Sabaroud Dextrose . Agar (SDA)*

### INTRODUCTION:

Otomycosis or external otitis media are acute, sub-acute or chronic infections produced by yeast and filamentous fungi that affect the squamous epithelium of the internal auditory canal. Otomycosis is found throughout the world. Its prevalence is greatest in hot, humid and dusty areas of the tropics and subtropics. It is common in India due to the high degree of humidity and heat<sup>6</sup>. Humidity in the monsoon favour the development of the fungus in the ear, specially in non-hygienic condition. The fungus is found in any decomposing matter. The air borne fungal spores are carried in droplets of water vapour, a fact that concludes with a higher incidence of otomycosis during rainy season<sup>1</sup>. The term otomycosis was suggested by Virchow in 1856. Otomycosis is predominantly caused by *Aspergillus niger* and *Aspergillus fumigates* spp.,

*Rhizopus*, *Candida* and dermatophytes also are occasional aetiologic agents. Otomycosis is found throughout the world. Its prevalence is greatest in hot, humid and dusty areas of the tropics and subtropics. The air borne fungal spores are carried on droplets of water vapour, a fact that correlates with the higher incidence of otomycosis during rainy season<sup>1</sup>. Yamashita (1963), in a review of many year of study in Japan and Formosa, listed 48 genera (including 19 species of *Aspergillus*, 6 species of *Candida* and 3 species of *Penicillium*) which he and his associates had isolated from normal ears of 2,880 persons. Therefore, simple isolation of a fungus from the ear does not constitute evidence of pathogenicity, it requires clinical co-relation<sup>3</sup>. Though otomycosis is not a life threatening disease, but due to its complication like tympanic membrane perforation, its diagnosis and treatment is important. The subtropical climate of Assam is known for its heavy rainfall during the monsoon months and high humidity during the hot summer season. These climate conditions are particularly favourable for the growth and dissemination of fungal organisms, including those causing otomycosis. These factors and the poor hygienic condition of the people in general are responsible for the

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prevalence of the disease. Gauhati Medical College is the premier referral hospital of the whole North East Region. Hence a cross section of various groups of people can be studied here. The study has been undertaken with the following aims and objectives: 1) To determine the fungal aetiological agents of otomycosis. 2) To study various predisposing factors and clinical presentations of otomycosis in relation to age and sex.

## MATERIALS AND METHODS :

The present study was carried out in Gauhati Medical College Hospital, Guwahati. The cases for the study were selected from the patients attending the E.N.T. OPD. Sample size was 85.

Inclusion criteria – Patients attending ENT, OPD of Gauhati Medical College Hospital over a period of one year. The patients included both sexes and all age groups belonging to different socio-economic status and religions. They were first diagnosed clinically on the basis of symptoms and then processed for laboratory diagnosis as follows:

**COLLECTION OF SPECIMEN :** For each ear two sterile aural swabs were taken. First swab was used for direct microscopic examination in 10% KOH preparation and second swab was used for culture.

**DIRECT MICROSCOPY :** In the study the specimen was placed on a clean, dry and grease free microscope slide and was covered with 10% KOH and a cover slip. Then it was warmed below the boiling point over a flame of a Bunsen burner<sup>3</sup>. The preparation was kept for 5 minutes<sup>4</sup>. Then the preparation was examined by light microscope for fungal elements. They were first examined under low power objective (10x) and then confirmed under high power objective (40x).

**CULTURE :** In the present study following medium was used. **Sabouraud's dextrose agar (with antibiotic):** Commercially available Sabouraud Dextrose Agar was used from Hi Media Laboratories Pvt. Ltd. 23, Vadhani Ind. Est. LBS Marg, Mumbai (M063) **Antibiotic used:** Antibiotic Chloramphenicol (0,05mg/ml) was added to prevent bacterial contamination after cooling the medium<sup>6</sup>. The inoculated culture tubes were incubated at 37°C and observed daily for fungal growth for as long as 4 weeks. Colony characters, colour, surface of the colony, edge and any pigmentation was recorded.

## LACTOPHENOL COTTON BLUE

**PREPARATION :** This test was performed to observe the characteristic appearance of conidia, hyphal arrangement and other features of the fungi. It was done by cutting a small portion of an isolated colony with a wire bent at 90° angle. Then it was placed on a slide to which a drop of lactophenol cotton blue was added. Then a coverslip was placed over it and gentle pressure with a pencil eraser was applied to disperse the growth. It was then examined microscopically under low power and then high power<sup>4</sup>.

**GRAM'S STAIN:** In case of yeast like fungus, identification was done by doing Gram's stain. Gram's stain reveals Gram positive budding yeast.

## SPECIAL TESTS FOR CANDIDA SPECIES:

**(1) GERM TUBE TEST:** In case of yeast like fungus, eg. *Candida albicans*, Germ tube test was done. *Candida albicans* produce germ tubes from their yeast cells when placed in a liquid nutrient environment and incubated at 35°C for 3 hrs. It was performed by suspending a very small inoculum of *Candida* species isolated from culture medium in 0.5ml of sheep serum. Then the tubes were incubated at 35 to 37°C for 3 hrs. After incubation, a drop of the suspension was placed on a clean, dry, grease free microscope slide and covered with a cover slip and examined under low power magnification for the presence of germ tubes. Microscopically a germ tube is seen as an appendage that is half the width and 3-4 times the length of the yeast cell from which it arises<sup>4</sup>.

**(2) CHROM AGAR:** It is a differential medium useful for the recovery, isolation of colonies and differentiation of species of *Candida*. Each species reacts with a chromogenic substrate to yield a characteristic colony colour after 48 hrs. of incubation at 37° C. CHROM agar had sensitivity and specificity near 100% for *Candida albicans*, *Candida tropicalis* and *Candida Krusei*<sup>4</sup>.

**Preparation:** The medium was prepared according to the manufacturer's guide:- 42.72 gms of the medium was suspended in 1000ml of distilled water and heated to boiling to dissolve the medium completely.

Colony Characteristics of yeast isolates grown on CHROM agar

Species	Colony characteristics
<i>Candida albicans</i>	Green
<i>Candida tropicalis</i>	Steel blue to blue grey, purple diffusion
<i>Candida krusei</i>	Pink, flat, rough, pale border
<i>Candida parapsilosis</i>	Pink- lavender, sometimes mucoid

## RESULTS:

Out of 85 cases, 70 samples showed growth in SDA while there was no growth in 15 samples. Out of different fungi isolated. *Aspergillus niger* headed the list 31(36%). *Aspergillus flavus* 18 (21%), *Aspergillus fumigatus* 14 (16.4%) and *Candida albicans* 7 (8.24%) (1) **Results of direct microscopy and Culture:** The samples obtained from 85 cases were subjected to direct microscopy in 10% KOH (Potassium hydroxide) mount, culture in SDA (Sabouraud's dextrose agar) with Chloramphenicol (0.05 mg/ml). The results, are as follows, Out of eighty five cases, seventy cases were KOH positive (82%) and also culture positive (82%). The results of KOH mount examination, culture in SDA media with Chloramphenicol are shown in the following table.

TABLE -I  
Breakup of Culture Positive, KOH Positive & KOH Negative Cases

Culture	Total	KOH+ve	KOH-ve
Culture Positive	70	70	-
Culture negative	15	0	0

**1) Predisposing factors:** Predisposing factors for the development of otomycosis were determined by historytaking and subsequent examination, 37.65% of the cases included in the study group gave history of trauma to the ears while cleaning with sticks/ feathers/ pin, 25.88% had Chronic suppurative otitis media in the affected ear, 11.76% were swimmers, 8.24% had history of topical antibiotic drops used, 2.35% used to put oil into the ears and 14.12% gave no suggestive history. Results are shown in Table below:

TABLE -II  
PREDISPOSING FACTORS

Predisposing factors	No. of Patients	Percentage (%)
Trauma	22	25.8%
CSOM	15	17.6%
Swimming	10	11.76%
Topical antibiotic	7	8.24%
Use of Oil	2	2.35%
Nothing suggestive	12	14.12%

**2) Incidence in different age group:** In this study maximum incidence was found to be in the age group 21-30 years (44.71%). This was followed by the age group 31-40 years (31.76%), age group 10-20 years (11.76%) age group 41-50 years (9.41%) and age group 51-60 years (2.35%). **Male, Female distribution in different age group:** As per sex was concerned, male suffered more than females (70.59% and 29.41% respectively), ratio being 2.4:1. Age and sex distribution is shown in table -IV.

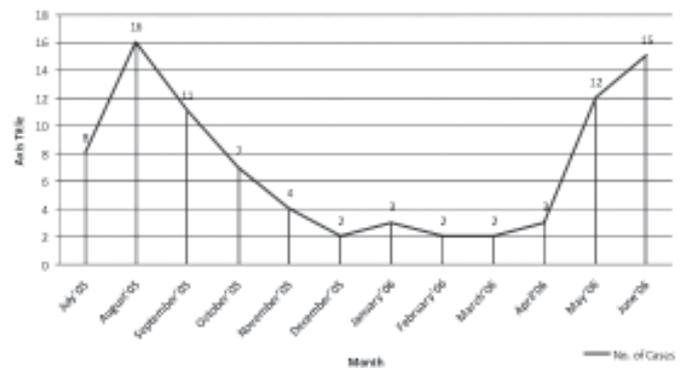
TABLE -III  
AGE AND SEX DISTRIBUTION

Age Group (year)	Male	Female	Total
10-20	8	2	10
21-30	28	10	38
31-40	15	12	27
41-50	7	1	8
51-60	2	0	2
	60(70.59%)	25(29.41%)	85(100%)

**3) Seasonal variation:** The maximum incidence of otomycosis was found in the month from May to October. At this time of the year, the temperature is hot and humid. The incidence is less in the winter months i.e. from November to April.

TABLE -IV  
INCIDENCE OF CASES OF OTOMYCOSIS IN DIFFERENT SEASONS

Month	No. of Cases	Month	No. of Cases
July'05	8	January'06	3
August'05	16	February'06	2
September'05	11	March'06	2
October'05	7	April'06	3
November'05	4	May'06	12
December'05	2	June'06	15



## 4) Clinical Presentations:

Out of the different clinical presentations of 85 (Culture negative and Culture positive) cases, most common clinical presentation in the present study were itching or pruritus (94.12%) followed by otalgia (91.76%), fullness of ear (76.47%), discharge (67.06%), impaired hearing (40%) and tinnitus (3.53%).

**5) Fungal Aetiological agents:** Out of different types of fungi isolated, *Aspergillus niger* headed the list 31(36%). *Aspergillus flavus* 18 (21%), *Aspergillus fumigatus* 14 (16.4%) and *Candida albicans* 7 (8.24%).

**6) Candida species isolation :** Out of seven (7) *Candida* species isolated, all of them were Germ tube test positive and produced green coloured colonies on CHROM agar 48 hrs. of incubation. Results are shown in Table below:-

TABLE -V  
RESULTS OF CANDIDA SPECIES ISOLATION

Candida	Germ tube test	CHROM agar
Positive	7	7
Negative	0	0

## DISCUSSION:

Otomycosis is a common fungal disease in tropical and subtropical regions of the world. From India a large number of studies have been reported in respect of different etiological species, clinical presentations, age and sex. Present study was done to find out various fungal aetiological agents causing otomycosis and their incidence in relation to age and sex, their clinical presentations and different predisposing factors. Anwarullah M., Jayakar P.A (1987)<sup>2</sup> studied 113 cases in Vishakhapatnam and found out 100 cases to be culture positive cases out of 95 cases they studied. In the present study also same type of result was found. Out of one hundred cases presenting with clinical symptoms of otomycosis, eighty five (85) had fungal aetiology diagnosed by direct microscopy and culture examination. According to the studies of Mohanty J.C. et al (1999)<sup>8</sup>, Agarwal S.R. et al (2001)<sup>1</sup>, P. Goswami (1982)<sup>15</sup> otomycosis is a disease of hot humid and rainy seasons. This is again in conformity with the result of the present study, which showed that incidence of otomycosis is high in monsoon and hot summer season. Maximum cases were found in the months from May to October. The incidence of otomycosis was found greater in males than in females by the studies of Mohanty J.C. et al. (1999, Male : Female 2.8:1)<sup>12</sup>, Agarwal S.R. et al (2001, Male: Female 1.59:1)<sup>1</sup>, Ashish Kumar (2005, Male Female 1.1:1)<sup>4</sup>. Similar incidence was found in the present study also the male : female ration being 2.4:1. But Sheikh M.S. et al (1993)<sup>18</sup> found opposite result. Mohanty J.C. et al, 1999; Agarwal S.R. et al, 2001; Sheikh M.S. et al; Ozcan M. et.al. 2003, Ashish Kumar, 2005<sup>(12,1,18,13,4)</sup> found trauma as the most common predisposing factor, which was found in the present study also. *Aspergillus niger* was followed by *Aspergillus flavus* in most of the studies. (Mohanty J.C. et. Al, 1999, 24%; Ali Zarei Mahmoudabadi, 2006, Chander J. et. Al, 1996, 33.7)<sup>(12,3,5)</sup>. In the present study also *Aspergillus flavus* was found to be the second most common fungal aetiological agent (27.06%). Studies of Mohanty J.C. et al. 1999, Gutierrez P.H. et al. 2005; Ashish Kumar, 2005, Ali Zarei Mahmoudabadi, 2006<sup>(12,8, 4,3)</sup> isolated *Candida albicans* and also *Candida non-albicans* as aetiological agents. But in the present study all candida species isolated were only *Candida*

*albicans* (8.24%). Some of the studies showed the isolation of *Mucor* and *Penicillium* from cases of otomycosis (Pahwa V.K. et al, 1983; Mohanty J.C. et al. 1999; Sheikh M.S. et al, 1993; P.Goswami, 1982)<sup>(14,12,18,15)</sup>. But in the present study, *Mucor* and *Penicillium* were not isolated from the cases of otomycosis.

## CONCLUSION:

Otomycosis is fairly common in this part of the country. Males suffer more than female. As far as clinical presentations were concerned itching and pain were common. Common predisposing factor was trauma to the ear while cleaning with stick, feather or pin. As far as different types of fungi were isolated, *Aspergillus niger* and *Aspergillus flavus* were predominant.

The incidences were high when the climate was rainy, humid and hot. This study has given us a clear insight into the mycological aspects of otomycosis. Therefore otomycosis has got scope for further study in this region for students and microbiologists as well as clinicians.

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## A Study of Thyroid Disorder During Pregnancy

P Chandrasekhara\*, M Aslam\*\*, K Kala\*\*\*, F Sultana\*\*\*\*

### Abstract

**Introduction :** Thyroid disorders are encountered frequently during pregnancy. The most common cause of maternal hypothyroidism is Hashimoto's thyroiditis which is an easily treatable condition that has been associated with increased risk of low birth weight, fetal distress, and impaired neuropsychological development of fetus. Hyperthyroidism in pregnancy is less common.

**Objectives :** To assess the thyroid status in pregnancy, pattern of disease and pregnancy outcome in these subjects.

**Methodology :** Apparently healthy pregnant women with uncomplicated single intrauterine gestations reporting to a rural tertiary care center, Obstetric department were randomly studied, clinically for any thyroid abnormalities during their ante natal checkup. They were investigated for thyroid stimulating hormone (TSH) and in cases with abnormal TSH, FT3, FT4 and TPO were done.

**Results :** A total of 409 cases were studied, 24 (5.86%) cases had laboratory features of hypothyroidism of which 20 (83.33%) were subclinical and 4 (16.77%) cases had overt hypothyroidism. 6 (25%) cases had raised anti TPO levels. 1 patient had threatened abortion. Out of 9 cases with abnormal thyroid function who were followed up, 6(66.7%) patients underwent emergency LSCS due to fetal distress and 1(11.1%) had undergone elective LSCS 1 (11.1%) had breech presentation and 1(11.1%) FTND. 7(87.5%) were low birth weight, 1 IUD due to cord prolapse and 1 child born out of preterm labour died after birth, rest of the other pregnancies had normal pregnancy outcome.

**Conclusion :** Thyroid disorders are common in pregnancy, and the most common disorder is subclinical hypothyroidism. Early detection of Thyroid dysfunction can help in starting treatment in affected pregnancies, for better outcome. Hence, Thyroid function test must be advised to all pregnant women.

**KEY WORDS:** *Thyroid disorders, Pregnancy, Hypothyroidism, Subclinical Hypothyroidism*

### INTRODUCTION :

Thyroid dysfunction during pregnancy had been an important research area in clinical endocrinology due to the fact that thyroid dysfunction has immense impact on maternal and fetal outcomes<sup>1,2</sup>. More importantly, children born to hypothyroid mothers have poor intellectual function during later part of their life<sup>3</sup>. There has been a wide geographic variation in prevalence of hypothyroidism during pregnancy. It varies from 2.5% from the West to 11% from India<sup>4,5</sup>. It seems that prevalence of hypothyroidism is more in Asian countries compared to the West<sup>6</sup>.

A normal pregnancy results in a number of important physiological and hormonal changes that alter thyroid function. Thyroid function tests change during pregnancy

due to the influence of two main hormones: human chorionic gonadotropin (hCG), the hormone that is measured in the pregnancy test and estrogen, the main female hormone. HCG can weakly turn on the thyroid and the high circulating hCG levels in the first trimester which may result in a slightly low TSH (called subclinical hyperthyroidism). When this occurs, the TSH will be slightly decreased in the first trimester and then return to normal throughout the duration of pregnancy. Estrogen increases the amount of thyroid hormone binding proteins in the serum which increases the total thyroid hormone levels in the blood since >99% of the thyroid hormones in the blood are bound to these proteins. However, measurements of "Free" hormone usually remain normal. The thyroid is functioning normally if the TSH, Free T4 and Free T3 are all normal throughout pregnancy.

Clinical or subclinical thyroid disorders are usually detected during pre-conceptional counselling or in women who have just conceived and have done tests for thyroid function. According to recent American Thyroid Association (ATA) guidelines, the recommended reference ranges for TSH are 0.1 to 2.5 mIU/L in the

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first trimester, 0.2 to 3.0 mIU/L in the second trimester, and 0.3 to 3.0 mIU/L in the third trimester<sup>7</sup>.

Maternal thyroid disorder influences the outcome of mother and fetus, both during and also after pregnancy. The most frequent thyroid disorder in pregnancy is maternal hypothyroidism. It is associated with fetal loss, placental abruptions, pre-eclampsia, preterm delivery and reduced intellectual function in the offspring. In pregnancy, overt hypothyroidism is seen in 0.2% cases and sub clinical hypothyroidism in 2.3% cases. Fetal loss, fetal growth restriction, pre-eclampsia and preterm delivery are the usual complications of overt hyperthyroidism seen in 2 of 1000 pregnancies whereas mild or sub clinical hyperthyroidism is seen in 1.7% of pregnancies and not associated with adverse outcomes. Autoimmune positive euthyroid pregnancy shows doubling of incidence of miscarriage and preterm delivery.

Overall, the most common cause of hypothyroidism is the autoimmune disorder known as Hashimoto's thyroiditis. Hypothyroidism can occur during pregnancy due to the initial presentation of Hashimoto's thyroiditis, inadequate treatment of a woman already known to have hypothyroidism from a variety of causes, or over-treatment of a hyperthyroid woman with antithyroid medications. Approximately, 2.5% of women will have a slightly elevated TSH of greater than 6 and 0.4% will have a TSH greater than 10 during pregnancy. Untreated, or inadequately treated, hypothyroidism has been associated with maternal anemia, myopathy, congestive heart failure, pre-eclampsia, placental abnormalities, low birth weight infants, and postpartum hemorrhage. Untreated severe hypothyroidism in the mother can lead to impaired brain development in the baby. This is mainly seen when the maternal hypothyroidism is due to iodine deficiency, which also affects the baby. All women with overt and subclinical hypothyroidism should be treated irrespective of thyroid peroxidase (TPO) antibody positivity with levothyroxine during pregnancy to maintain serum TSH in the trimester-specific goal range. It has been recommended to check serum TSH every four weeks during pregnancy so that appropriate dose adjustments can be made<sup>7</sup>.

Overall, the most common cause (80-85%) of maternal hyperthyroidism during pregnancy is Graves' disease and occurs in 1 in 1500 pregnant patients. In

addition to other usual causes of hyperthyroidism, very high levels of hCG, seen in severe forms of morning sickness (hyperemesis gravidarum), may cause transient hyperthyroidism. The typical ill-effects in pregnancy are repeated miscarriage, poor growth of fetus, premature delivery, pregnancy-induced hypertension, etc. Untreated mother can also develop thyrotoxic crisis. Uncontrolled maternal hyperthyroidism has been associated with fetal tachycardia, small for gestational age babies, prematurity, stillbirths and possibly congenital malformations. The preferred regimen is titration regimen; preferred medicine is propylthiouracil (PTU). Aim is to keep free T4 in the upper normal range, sometime TSH can be little lower than normal range. The dose of PTU depends on the control, sometime goes even up to 400-800 mg/day. It is to be given every 8<sup>th</sup> hourly. Liver function tests should be monitored with PTU, as there is a risk of hepatotoxicity. Methimazole is not preferred in the first trimester due to the risk of aplasia cutis and the spectrum of birth defects in pregnancy. Methimazole can be given in the second and third trimesters<sup>8</sup>.

The TSH test is usually proposed as the initial test in screening because of its ability to detect abnormalities before serum T4 and T3 levels are abnormal. When used to confirm suspected thyroid disease in patients referred to an endocrine specialty clinic, the sensitive TSH has a sensitivity above 98% and a specificity greater than 92% for the clinical and functional diagnosis<sup>9</sup>.

#### **OBJECTIVES :**

1. To assess the thyroid status & pattern of thyroid diseases in pregnancy.
2. To study the pregnancy outcome of affected pregnancies.

#### **MATERIALS AND METHODS :**

Apparently healthy pregnant women with uncomplicated single intrauterine gestation reporting to a rural tertiary care center, Obstetric department were randomly studied prospectively, by ante natal checkup and then clinically for any thyroid abnormalities during their ante natal checkup. They were investigated for thyroid stimulating hormone (TSH) and in cases with abnormal TSH, FT3, FT4 and TPO were estimated by chemiluminescent method. Basic investigations were done

in all cases. Their obstetrical and perinatal outcomes were studied.

**Inclusion Criteria:**

Pregnant women with single intra uterine gestation during various stages of pregnancy were randomly selected.

**Exclusion Criteria:**

- Pregnant women with established thyroid disorders, with or without treatment.
- Patients who have undergone thyroid surgery.
- Patients who are on drugs affecting thyroid function like Lithium, Iodine, and Amiodarone.

**RESULTS :**

A total of 409 cases were studied of which 100 were in 1<sup>st</sup> trimester, 100 in 2<sup>nd</sup> trimester and 209 in 3<sup>rd</sup> trimester.

**1. MEAN AGE & TSH**

Mean age and mean TSH of patient’s trimester wise (Table 1).

**2. PRIMIGRAVIDA**

*Table 1: Mean age and mean TSH of patient’s trimester wise*

	Total (n=409)	1 <sup>st</sup> trimester (n=100)	2 <sup>nd</sup> trimester (n=100)	3 <sup>rd</sup> trimester (n=209)
Mean Age (Years)	23 ± 3.7	23.7 ± 4.1	22.97 ± 4.42	23.33 ± 3.58
Mean TSH (mIU/L)	3.1 ± 4.7	2.78 ± 2.33	2.82 ± 1.64	3.33 ± 6.3

Of the 409 patients 175 (42.78%) patients were primigravid, of them, 56 were in 1<sup>st</sup> trimester, 45 in 2<sup>nd</sup> trimester and 74 in 3<sup>rd</sup> trimester.

Mean age and mean TSH of patient’s trimester wise in primigravid women (Table 2).

**3. MULTIGRAVIDA**

*Table 2: Mean age and mean TSH of patient’s trimester wise in primigravid women*

	Total (n=175)	1 <sup>st</sup> trimester (n=56)	2 <sup>nd</sup> trimester (n=100)	3 <sup>rd</sup> trimester (n=209)
Mean Age (Years)	21.74 ± 3.13	22.07 ± 3.62	21.62 ± 3.05	21.63 ± 2.8
Mean TSH (mIU/L)	3.34 ± 6.8	2.66 ± 2.21	3.05 ± 1.77	4.01 ± 10.11

234 (57.22%) patients were multigravida, of them, 44 were in 1<sup>st</sup> trimester, 55 in 2<sup>nd</sup> trimester and 135 in 3<sup>rd</sup> trimester.

Mean age and mean TSH of patient’s trimester wise in multigravida women (Table 3).

*Table 3: Mean age and mean TSH of patient’s trimester wise in multigravida women*

	Total (n=234)	1 <sup>st</sup> trimester (n=44)	2 <sup>nd</sup> trimester (n=100)	3 <sup>rd</sup> trimester (n=209)
Mean Age (Years)	24.53 ± 3.61	25.73 ± 3.76	24.03 ± 3.31	24.27 ± 3.63
Mean TSH (mIU/L)	2.9 ± 2.2	2.89 ± 2.49	2.65 ± 1.51	2.96 ± 2.39

There was no significant differences between thyroid functions in primigravid and multigravida women.

**4. INCIDENCE OF THYROID DISORDERS**

Incidence of thyroid disorders in different trimesters (Table 4).

*Table 4: Incidence of thyroid disorders in different trimesters*

Incidence	Hypothyroidism		Hyperthyroidism		Euthyroid
	Subclinical	Overt	Subclinical	Overt	
1 <sup>st</sup> Trimester (n=100)	10 (10%)		--	--	90 (90%)
2 <sup>nd</sup> Trimester (n=100)	8 (80%)	2 (20%)	--	--	7 (70%)
	3 (3%)		--	--	
3 <sup>rd</sup> Trimester (n=209)	11 (5.26%)		--	--	198 (94.74%)
	9 (81.8%)	2(18.2%)	--	--	

Out of 409 cases studied, 24 (5.86%) cases had laboratory features of hypothyroidism and none of the patients had clinical features of hypothyroidism. 20 (83.33%) cases had subclinical hypothyroidism and 4 (16.77%) cases had overt hypothyroidism. 6 (25%) cases had raised anti TPO levels of which 3 had subclinical hypothyroidism and 3 had overt hypothyroidism. Mean TSH was higher in patients with raised anti TPO which was 9.95 ± 3.92 mIU/L than with normal anti TPO levels 7.53 ± 2.86 mIU/L. There were no cases of Hyperthyroidism in this study.

**5. 1<sup>st</sup> TRIMESTER**

10 (41.7%) out of 24 cases belonged to 1st trimester with mean TSH of 8.03 ± 1.83 mIU/L. 8 (80%) had subclinical hypothyroidism. 1 patient with subclinical hypothyroidism underwent MTP and 1 patient with hypothyroidism was admitted with threatened abortion. 2 patients had raised anti TPO levels. These patients were started on Thyroxin and dose adjusted according to the level & response to the drug.

**6. 2<sup>nd</sup> TRIMESTER**

3 (12.5%) out of 24 cases belonged to 2nd trimester with mean TSH of 6.77 ± 1.07 mIU/L. All 3 (100%) had subclinical hypothyroidism. 1 patient had raised anti TPO levels. This patient also appropriately treated with Thyroxin tablets.

**7. 3<sup>rd</sup> TRIMESTER**

11 (45.8%) out of 24 cases belonged to 3rd trimester with mean TSH of 8.61 ± 4.49 mIU/L. 9 (81.8%) had subclinical hypothyroidism. 3 patients had raised anti TPO of which 2 had overt hypothyroidism and 1 had subclinical hypothyroidism.

Out of 11 cases, 6 (54.5%) underwent emergency LSCS due to fetal distress or various maternal causes for early induction of labour. 1 patient underwent elective LSCS. 1 patient had full term normal delivery. 1 patient

had breech presentation.

Out of 9 babies delivered, 7(87.5%) were low birth weight, 1 IUD due to cord prolapse and 1 child born out of preterm labour died after birth.

## DISCUSSION :

This study was aimed to evaluate thyroid function in pregnant women and to find the pregnancy outcome in them. There has been a wide geographic variation in prevalence of hypothyroidism during pregnancy. It varies from 2.5% from the West to 11% from India<sup>4,5</sup>. It seems that prevalence of hypothyroidism is more in Asian countries compared with the West. In the present study, 5.86% cases had hypothyroidism of which 83.33% had subclinical hypothyroidism and 16.67% had overt Hypothyroidism. 10% cases belonged to 1st trimester of which 80% had subclinical hypothyroidism. 16.77% cases had positive TPO Ab. 54.5% hypothyroid women underwent emergency LSCS. 87.5% of babies delivered to hypothyroid women were low birth weight babies. In a study by Dinesh K Dhanwal et al<sup>10</sup>, the major finding was that 14.3% women in 1<sup>st</sup> trimester attending a tertiary public hospital in Delhi have hypothyroidism and majority of these women had subclinical hypothyroidism. Majority of subjects with overt hypothyroidism and good number of subclinical hypothyroidism pregnant women had positive AbTPO suggesting autoimmunity as cause of hypothyroidism.

Rao et al<sup>11</sup>, included 163 non-pregnant women with recurrent pregnancy loss in a gestational age up to 12 weeks. Hypothyroidism was found in seven (4.12%) women with recurrent pregnancy loss. The study demonstrated that hypothyroidism had a statistically significant relationship with recurrent pregnancy loss in the first trimester.

Another study examined 500 pregnant women attending two government obstetrics and gynecology hospitals in Chennai during a period of 5 months for thyroid function. Subclinical hypothyroidism was detected in 2.8%, among them TPO antibodies positivity was seen in 57.1%<sup>12</sup>.

Sahu et al<sup>13</sup>, have done thyroid function during second trimester in high-risk pregnant women and reported that prevalence of thyroid disorders, especially overt and subclinical hypothyroidism was 6.47%.

In another study from India, Nambiar V et al<sup>14</sup> have reported prevalence of hypothyroidism and thyroid autoimmunity as 4.8% and 12.4%, respectively and were significantly associated with miscarriage.

In a study by D. Glinoe et al<sup>15</sup>, women with Autoimmune thyroid disorder had a basal TSH value significantly higher in the first trimester (1.6 vs. 0.9 mIU/L;  $P < 0.001$ ) than that in women with healthy pregnancies used as controls. Free T4 concentrations were in the range of hypothyroid values in 42% of the women. Women with asymptomatic autoimmune thyroid disorder who are euthyroid in early pregnancy carry a significant risk of developing hypothyroidism progressively during gestation, despite a marked reduction in antibody titers.

In a study by Gayathri R et al<sup>12</sup>, hypothyroidism was significantly associated with increasing gestational age ( $p = 0.014$ ). Mean TSH was higher in 3<sup>rd</sup> trimester when compared to 1<sup>st</sup> and 2<sup>nd</sup> trimester in the present study. But, the incidence of hypothyroidism was higher in 1<sup>st</sup> trimester when compared to 2<sup>nd</sup> and 3<sup>rd</sup> trimesters. This may be due to less number of cases studied in 1<sup>st</sup> trimester when compared to 3<sup>rd</sup> trimester in the present study.

Kuppens SM et al<sup>16</sup>, concluded that women with TSH levels above 2.5 mIU/L during end gestation are at risk for breech presentation, and as such for obstetric complications. In the present study out of 9 deliveries 1 patient had breech presentation.

## CONCLUSION :

This study concludes that thyroid disorders are common in pregnancy, and the most common disorder is subclinical hypothyroidism. There is a high prevalence of hypothyroidism (10%) in pregnant women during 1<sup>st</sup> trimester, majority being subclinical and have high rates of TPO antibody positivity. Screening for thyroid function and autoimmunity, and timely and appropriate treatment, will improve pregnancy outcome.

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## Emergence and Challenges of Influenza A (H1N1) Infection

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### INTRODUCTION :

Influenza A H1N1 is an Orthomyxovirus which causes an acute contagious respiratory disease affecting a large number of human population<sup>1</sup>. It causes symptoms similar to those of the *Seasonal Influenza*. The name 'Swine Flu' was initially used to describe this type of Influenza because laboratory tests showed that this strain of flu virus was made up of genes that were very similar to the one that caused influenza among pigs (swine). Influenza A H1N1 virus is made up of re-assortment of genes from several different flu viruses that normally circulate among pigs, birds, and humans<sup>2</sup>. Influenza A (H1N1) virus was the cause of human influenza (flu) pandemic in the year 2009 causing 14,286 confirmed deaths worldwide<sup>3</sup>. Outbreak of Influenza A H1N1 in the year 2010 resulted in 2728 deaths and 44,987 lab confirmed cases in India.



### EPIDEMIOLOGY :

**Agent :** Influenza epidemic is caused by H1N1 strain of Influenza A virus. Humans are the reservoir of infection and a case or a sub-clinical case is the source

of infection. Communicability period of the infection is 3-5 days from the clinical onset in adults and up to 7 days in young children. The peak viral shedding occurs on day 1 of symptoms and the incubation period is about 1-2 days.

**Host :** People of all age groups are affected, the incidence being highest in extremes of ages of both the sexes. High risk cases include young children, old age, pregnant women, health workers and those with co-morbid conditions (Lung disease, heart disease, liver disease, kidney disease, blood disorders, Diabetes, Immuno-compromised and long term steroid therapy). There is no cross immunity between the different sub-types or strains. Antibodies appear in blood 7 days after an acute attack; reach maximum in 2 weeks and drop to pre-infection level in 8 to 12 months.

**Environment :** Most outbreaks of Influenza A H1N1 occur in late falls and winter months similar to seasonal flu. Transmission is mainly man to man through droplet infection and indirectly through fomites and contaminated hands. Infection spreads faster in overcrowded places. The virus survives longer outside the body in cold and dry weather hence, seasonal epidemic occurs during the winter months<sup>3</sup>. H1N1 virus is not transmitted by food. Properly handled and cooked pork & pork products do not transmit infection<sup>4</sup>.

**Some of the important outbreaks of H1N1 Influenza in the past :**

**1918 H1N1 flu pandemic :** Around 500 million people were affected causing 50 million deaths with a fatality rate of 0.2 to 0.5%<sup>5</sup>.

**1968-69 Hongkong Flu :** Around 500,000 individuals were affected with having a low death rate of 0.1%<sup>6</sup>.

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**1976 U.S outbreak :** A small outbreak in armed forces led to the vaccination of about 40 million people<sup>7</sup>.

**1977-78 Russian outbreak :** Mostly children and young adults under 23 years were affected<sup>8</sup>.

**2003-04 Fujian (H3N2) human flu :** The Fujian bird flu strain of H5N1 variety of Influenza A virus affected the residents of Taiwan<sup>9</sup>.

**2007 Philippines outbreak :** There was a 10% mortality among swine flu cases<sup>10</sup>.

**2009 H1N1 pandemic :** 29 countries were affected with H1N1 strain starting in Mexico with a total deaths of 14,286 worldwide<sup>3</sup>.

**2010 Indian outbreak :** A total of 44,987 lab confirmed cases and 2728 deaths reported in India<sup>11</sup>.

**2015 Indian outbreak :** “Swine flu in India : 2,035 succumb to the H1N1 virus”. The Health Site. March 30, 2015. Retrieved March 30, 2015.

H1N1 epidemics in India, a total of 35,521 cases with 2220 deaths<sup>12</sup>.



**VIROLOGY**

Influenza Virus belongs to the family of Orthomyxoviridae and are classified into three types—Influenza A, B and C. Influenza A virus is divided into subtypes on the basis of their surface Proteins-Haemagglutinin (HA) and Neuraminidase (NA). 16 H and 9 N subtypes of Influenza A virus are known. Four Influenza A subtypes isolated from Pigs are H1N1, H1N2, H3N1 and H3N2. The Swine flu virus undergoes constant genetic mutation with change in antigenicity. Antigenic changes result in the development of a novel virus which spreads very fast causing case fatality as the overall population has no immunity to this novel strain. Genetic re-assortment occurs in type A Influenza virus due to mixing of swine, avian and human influenza virus,

the pigs usually acting as “mixing bag” for the genetic re-assortment<sup>2</sup>.

This re-assorted virus has the unique ability to cause recurrent epidemics and global pandemics. The outbreak of Seasonal Influenza results due to Antigenic Drift i.e. continuous Amino Acid sequence mutations occurring in the Same (Intra) species<sup>13</sup>. Pandemic influenza results due to Antigenic Shift i.e. Genetic re-assortment in different (Inter) species where generally Pigs act as a “Mixing Bag” for genetic re-assortment<sup>14</sup>.

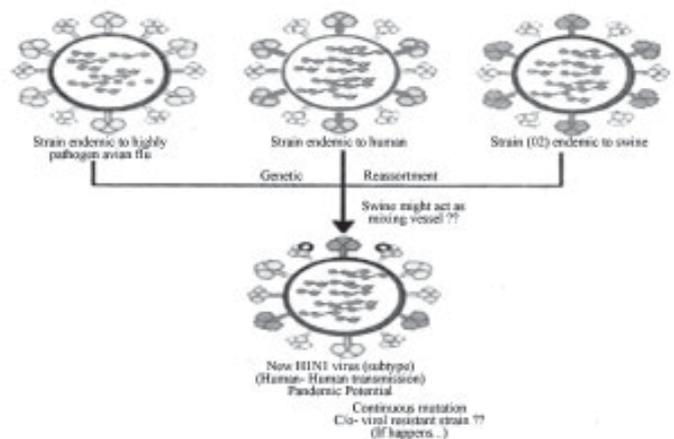


fig: Schematic Diagram of genetic re-assortment

**CLINICAL CHARACTERISTICS:**

**Symptoms include:**

- \* Fever, which is usually high, but unlike seasonal influenza, is sometimes absent.
- \* Cough, sore throat and bodyaches.
- \* Running nose or stuffy nose.
- \* Headache and chills, fatigue or extreme tiredness.
- \* Diarrhoea and vomiting (less common in seasonal flu).
- \* Sudden dizziness, shortness of breath and continuous vomiting.

Nearly everyone infected with H1N1 or swine flu shows *atleast two to three of these symptoms*.

**Complications (for all patients but especially for those at higher risk):**

1. Pneumonia
2. Bronchitis
3. Sinus infections
4. Ear infections
5. Myocarditis with CCF
6. Encephalitis

## **Diagnosis of Influenza A H1N1 -**

Influenza A H1N1 infection is diagnosed when an infected person is most likely to be shedding virus i.e, within the first four to five days of illness (children may shed virus for ten days or longer). During this period respiratory specimens are collected and sent for diagnosis to the designated labs.

### **Specific diagnostic tests:**

A quick test (for example, nasopharyngeal swab sample) is done to see if the patient is infected with influenza A or B virus. Most of the tests can distinguish between A and B type.

The test can be positive for type A and B. If the test is positive for type B, the flu is not likely to be swine influenza (H1N1). If it is positive for type A, the person could have conventional seasonal Influenza strain or swine Influenza (H1N1). Influenza A H1N1 is mainly diagnosed by identifying the particular antigens associated with this virus type.

#### **A. Direct detection of virus antigen**

1. Immuno-flourescent test
2. Antigen capture ELISA
3. Rapid test (Directigen)

#### **B. RT-PCR test for detection of viral RNA (H1N1)**

#### **C. Serological tests for antibodies in serum**

1. HAI test in paired sera samples,
2. IgM ELISA test

#### **D. Virus culture in respiratory specimens**

1. MDCK cell lines etc
2. Hen's Egg inoculation

**RT-PCR and IgM ELISA** are the commonly recommended tests for the diagnosis of Influenza A H1N1 infection. These confirmatory tests are carried out in specialized BSL laboratories. The National Institute of Virology, Pune is a level 4 and National Institute of communicable diseases (NICD), Delhi; Japanese Leprosy Mission (JALMA), Agra and NICED, Kolkata; Regional Medical Research Center (RMRC), Dibrugarh, Assam; King Institute of Preventive Medicine (KIPM), Chennai, Tamil Nadu and DRDE, Gwalior are BSL-3 laboratories in India.

### **Treatment : Symptomatic and specific with**

1. Rest and nutritious diet.
2. Anti-pyretics for fever.
3. Anti emetic for vomiting

4. Proper hydration and maintenance of Fluid and electrolyte balance, and

#### **5. Antiviral drugs**

*Antiviral treatment with Oseltamivir (Tamiflu) or Zanamivir (Relenza). Antiviral doses and schedules recommended for treatment of influenza A (H1N1) virus infection in Adults- tab Oseltamivir (Tamiflu) 75mg BD x 5days.*

#### **Mechanism of action:**

Oseltamivir is an acetamido cyclohexene that is a structural homologue of sialic acid and inhibits neuraminidase. Its effectiveness in terms of prevention of viral infection especially those who are in close contact of sick persons is 70% to 90%<sup>15</sup>. Oseltamivir is a prodrug usually administered as phosphate, it is hydrolysed in liver to the active metabolite, the free carboxylate of Oseltamivir (GS4071). Oseltamivir acts as a transition-state analogue inhibitor of influenza neuraminidase. These neuraminidase inhibitors prevent the virus to escape from the infected cell thereby, preventing the spread of infection.

Center For Disease Control (CDC, USA) recommend oseltamivir (brand name Tamiflu) both to prevent and treat Influenza A and B virus infection in people one year of age and older while Zanamivir (brand name Relenza) should be used to treat Influenza A and B virus infection in people 7 years and older and to prevent influenza A and B virus infection in people 5 years and older<sup>16</sup>.

#### **Drug Resistance:**

The mutational behavior of H1N1 is a major challenge for pharmacotherapy. Resistance to Oseltamivir has been reported from different countries<sup>17,18</sup>. It is therefore, ensured that drugs should be made available only on medical prescriptions. Government of India has also imposed a complete ban on sale of Tamiflu through retail outlets. It is essential as unnecessary consumption due to panic may result in development of drug resistance.

### **Ministry of Health and Family Welfare Guidelines for management of Influenza A H1N1 infection (Revised on 11.02.2015):**

- Guidelines on categorization of Influenza A H1N1 cases during screening for home isolation, testing, treatment and hospitalisation.

- At first all individuals seeking consultations for flu like

symptoms should be screened at healthcare facilities both Government and private or examined by a doctor and these will be categorized as under:

### **Category A**

Patients with mild fever plus cough/sore throat with or without bodyache, headache, diarrhoea and vomiting will be categorized as Category-A. They do not require Oseltamivir and should be treated for the symptoms above. The patients should be monitored for their progress and reassessed at 24 to 48 hours by the doctor.

- No testing for the patient for H1N1 is required.
- Patients should confine themselves at home and avoid mixing up with public and high risk members in the family.

### **Category B**

1) In addition to all the signs and symptoms mentioned under Category-A, if the patient has high grade fever and severe sore throat, may require home isolation and Oseltamivir.

2) In addition to all the signs and symptoms mentioned under Category-A, individuals having one or more of the following high risk conditions shall be treated with Oseltamivir.

- a. Children with mild illness but with predisposing risk factors
- b. Pregnant women.
- c. Persons aged 65 years or older.
- d. Patients with heart, lung or liver disease, kidney disease, blood disorders, diabetes, cancer and HIV/AIDS;
- e. Patients on long term cortisone therapy.

No tests for H1N1 is required for Category-B (i) and (ii) All patients of Category-B (i) and (ii) should confine themselves at home and avoid mixing with public and high risk members in the family.

Broad Spectrum antibiotics as per Guideline for Community acquired pneumonia (CAP) may be prescribed.

### **Category-C**

- In addition to the above signs and symptoms of Category-A and B, if the patient has one or more of the following:

- Breathlessness chest pain, drowsiness, fall in blood pressure, sputum mixed with blood, bluish discoloration of nails;
- Children with influenza like illness who had a severe disease as manifested by the red flag (Somnolence, high

and persistent fever, inability to feed well, convulsions, shortness of breath, difficulty in breathing, etc.

- Worsening of underlying chronic conditions.
- All these patients mentioned above in Category-C require testing, immediate hospitalization and treatment.

### **Preventions of Influenza A H1N1 infection:**

#### **a) Non pharmacological measures:**

1. Covering of mouth and nose while coughing and sneezing.
2. Washing hands frequently with soap & hot running water or application of an alcohol-based hand gel.
3. Person suffering from flu like symptoms should remain indoor and refrain from going outside.

#### **b) Pharmacological measures**

##### **H1N1 Vaccination:**

- The seasonal flu vaccine that are usually administered does not provide any protection against the H1N1 virus. H1N1 vaccination to protect against the H1N1 virus (sometimes called “swine flu”) have been produced.

- There are two kinds of H1N1 vaccines which are made by culturing the virus in chicken eggs. The vaccine can be given with a needle, usually in the arm or by a nasal spray.

**H1N1 vaccination** has been recommended for:

1. Health care and emergency medical personnel
2. Household contacts and cabdrivers for children younger than 6 months of age.
3. Pregnant women.
4. All children and young adults from 6 months through 24 years of age
5. Persons aged 25 through 64 years who have health conditions associated with higher risk of medical complications from influenza.
6. *CDC is now encouraging everyone to get vaccinated against H1N1 flu pandemic.*

##### **Side effects or H1N1 vaccines:**

Side effects of H1N1 vaccination are uncommon. However a small number of patients may develop pain, redness, tenderness, swelling and bruising at the site of injection. Less than 1% experiences a severe adverse reactions due to vaccination.

##### **Preparedness and capacity development for medical management of H1N1 in India:**

India is one of the most vulnerable countries of Asian subcontinent, that has been affected by Avian flu a number of times especially in Maharashtra, West Bengal and North-Eastern states during last three years. So far, the country has managed these incidences effectively by co-ordinated efforts of Integrated Disease Surveillance Programme (IDSP) run by Ministry of Health and Family, Ministry of Agriculture Department of Animal Husbandry and various laboratories. These incidences have been taken as indicators of present pandemic situation. The plan should be reviewed and made flexible and stringent enough to manage any such situation. Since it is a multi-disciplinary efforts with first line of defence with medical personnel, various inter departmental efforts are required to be taken to synchronize their actions.

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# Takayasu's Disease – Spectrum of Manifestations A Case Series

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### Abstract

Takayasu's Arteritis, formerly known as "pulseless disease", is a chronic idiopathic vasculitis which affects the large vessels in the body, This rare condition is more commonly found in Asian women in their 40's. The aorta and its main branches are the primary vessels affected, leading to a spectrum of manifestations, here we discuss four of our patients who were clinically suspected and investigated performing imaging modalities suggested Takayasu's arteritis.

**KEY WORDS :** AR: Aortic Regurgitation, TA: Takayasu's Arteritis.

### INTRODUCTION:

TA is a chronic idiopathic vasculitis which mainly involves aorta and its branches, inflammation results in stenosis, occlusion with aneurysms, it is usually most common in young women and adolescent girls<sup>1</sup>. 'Aortic arch syndrome' is the term given to disease affecting the upper extremities, heart, neck and head. Patients often complain of arm claudication, and on examination absence of peripheral pulses. Hence TA was previously called 'pulseless disease'. Blood pressure varies by more than 10 mmHg between the arms and a bruit may be audible over the artery. Aortic regurgitation, pulmonary hypertension, angina, congestive cardiac failure, vertigo, syncope, stroke and visual disturbance may occur. Descending aorta syndrome may cause renovascular hypertension, renal dysfunction, abdominal pain and acute abdominal bleeding or perforation of a viscus from infarction<sup>2,3,4</sup>. The finding of hypertension and arterial bruits in young adults necessitates the examination of pulses and blood pressures in different limbs in order to detect

asymmetry. So here we present series of cases of TA presenting with different manifestations.

### CASE 1:

Mr. JW a 22 yr old male patient presented with chest pain, difficulty in breathing and tingling sensation of left arm of the body since 4 months, there was no history of palpitations, giddiness, pedal oedema, discolouration of arms, no pain abdomen, blurring of vision. There was no history suggestive of hypertension and diabetes, no history of TB and there was no significant past history noted. On examining there was wide pulse pressure difference between arms, and there was radio radial delay. There was no bruit felt in the bilateral carotids and pulse volume were being equal in both the carotids, pulses were also normal at other peripheral arteries, there was no renal bruit. Respiratory and central nervous system were normal, Cardiovascular system examination revealed systolic murmur over pulmonary area with no other significant findings. On investigating ESR and CRP were slightly raised, rest of blood parameters were within normal limit. Doppler sonography of bilateral carotid, aortic arch and left upper limb showed: Circumferential arterial wall thickening in proximal left common carotid artery, left sub clavian artery. MR Angiography revealed features suggestive of type III aorto arteritis affecting the left sub clavian artery, mild affection of proximal left CCA, left vertebral artery origin with mild affection of renal and supra renal aorta and subsequent stenosis of

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left renal artery. Echo showed mild pulmonary hypertension and mild tricuspid regurgitation with Ejection fraction in normal limit. Aortic root angiography was within normal limit.

#### CASE 2:

Mrs JK a 40 yr old female patient presented with palpitation, giddiness and tingling sensation of left arm of the body since 1 year, there was no history of chest pain, pedal oedema, difficulty in breathing, discolouration of arms, no pain abdomen, blurring of vision. Patient is a known hypertensive and diabetic on regular medication, no history of TB and there was no significant past history noted. On examining there was wide pulse pressure difference between arms, and there was radio radial delay. A bruit felt in the bilateral carotids and pulse volume were being equal in both the carotids, pulses were also normal at other peripheral arteries, and there was no renal bruit. Respiratory and central nervous system were normal. Cardiovascular system examination revealed systolic and early diastolic murmurs over aortic and neo-aortic areas with no other significant findings. On investigating ESR and CRP were slightly raised, rest of blood parameters were within normal limit. Doppler sonography of bilateral carotid, vertebral and subclavian arteries showed: Diffuse thickening of aortic arch branches with focal stenosis of left sub clavian artery. MR Angiography revealed features suggestive of type II aorto arteritis affecting the ascending thoracic to upper abdominal aorta and affecting its major branches, Echo showed severe aortic regurgitation and mild mitral regurgitation with Ejection fraction of 67%.

#### CASE 3:

Mr.DM a 12 yr old male patient presented with tingling sensation of left half of the body and giddiness since 2 years, there was no history of chest pain, difficulty in breathing, palpitations, pedal oedema, discolouration of arms, abdominal pain, blurring of vision. There was no history suggestive of hypertension and diabetes, no history of TB and there was no significant past history noted. On examining there was wide pulse pressure difference between arms, and there was radio-radial delay. There was no bruit felt in the bilateral carotids and pulse volume were being equal in both the carotids. Pulses

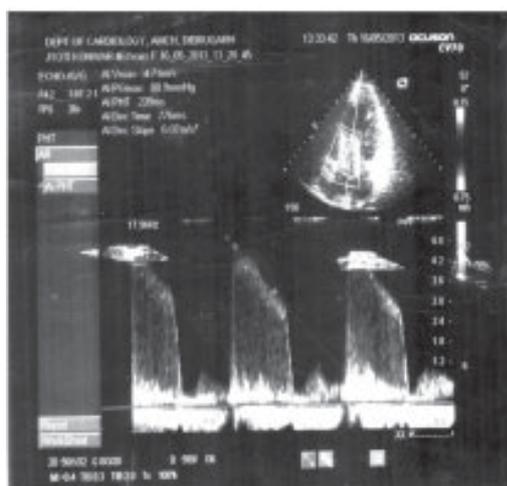
were also normal at other peripheral arteries bilateral dorsalis pedis, and there was no renal bruit. Respiratory and central nervous system were normal. Cardiovascular system examination revealed systolic murmur over aortic area with no other significant findings. On investigating ESR and CRP were slightly raised, rest of blood parameters were within normal limit. MR Angiography revealed features suggestive of type IIb<sup>12</sup>aorto arteritis affecting the left sub clavian artery, left axillary, thoracic and abdominal aorta and aneurysm formation in proximal thoracic aorta. Echo showed dilated aortic root and aortic arch with Ejection fraction in normal limit(66%).

#### CASE 4:

Mrs. MS a 34 year old female patient presented with chest pain, palpitations and weakness with tingling sensation of left half of the body since 1 month. There was no history of difficulty in breathing, giddiness, pedal oedema, discolouration of arms, abdominal pain, blurring of vision. There is no history suggestive of hypertension and diabetes, no history of TB and there was no significant past history noted. On examining there was wide pulse pressure difference between arms, and there was radio radial delay. There was no bruit felt in the bilateral carotids and pulse volume were being equal in both the carotids, pulses were also normal at other peripheral arteries, there was no renal bruit. Respiratory, central nervous system, and cardiovascular system examination were normal with no other significant findings. On investigating ESR was slightly raised rest of blood parameters were within normal limit. MR Angiography revealed features suggestive of type IIb aorto arteritis affecting mild dilatation of ascending aorta, occlusion of the left sub clavian artery, with tight stenosis of infra-renal aorta, superior mesenteric artery origin is occluded and focal aneurysm arising from branches of superior mesenteric artery. Echo showed mild aortic regurgitation with Ejection fraction in normal limit.



CASE 2



## DISCUSSION :

Takayasu's arteritis is a systemic disorder that affects multiple organs. The diagnosis of TA can be a challenge, especially in its initial phases and symptoms are generally constitutional, including malaise, fever, fatigue, and arthralgia and rest of the symptoms related to particular arterial involvement most commonly occur due to involvement of sub clavian artery and on examination there will be absence of peripheral pulses and presence of hypertension in 32-93%, similar to which 3 of our patients presented with symptoms due to involvement of sub clavian artery involvement and all of the patients had hypertension with absence of pulses. Elevated erythrocyte sedimentation rate is a common finding; which is seen in all of our patients however, caution is advised, because up to 50% of patients may have active TA disease and a normal sedimentation rate.

Confirmation of TA is best done by angiography or MRI angiography<sup>6,7</sup>. The most common lesion is a smooth, concentric, arterial or aortic narrowing (85%). Irregular narrowing, complete occlusion and fusiform or

saccular aneurysms are less commonly seen. Changes may be focal or segmental and are distinguished from arteriosclerosis and fibromuscular dysplasia. Contrast-enhanced magnetic resonance perfusion imaging, ultrasonography and positron emission tomography are new, non-invasive methods of assessment that are likely to replace conventional angiography<sup>8,9</sup>. Most commonly involved arteries are sub-clavian, followed by common carotid, abdominal aorta, renal and aortic root, most of our patients had involvement of subclavian, in 2 patients there is involvement of aortic root leading to aortic regurgitation and one patient was affected with involvement of abdominal artery and renal artery and in the other superior mesenteric artery involvement was present.

In regard to treatment options of Takayasu arteritis, corticosteroid remains the first-line medical therapy<sup>10</sup> in the active disease process. Surgical interventions such as angioplasty and vascular reconstruction are also recommended for severe stenosis or occlusion of critical arteries leading to Renovascular hypertension, coarctation of aorta, severe cerebral ischaemia, and severe aortic regurgitation causing congestive heart failure, or progressive aneurysmal enlargement or dissection may all require prompt surgical treatment between which surgical bypass is considered to have superior potency but more serious early postoperative complications as well<sup>11</sup>, all of our patients were managed with steroids, anti-hypertensive drugs and one patient was advised for surgery and the other patients were advised for follow up. So, If diagnosed at an early stage, the disease could be controlled with the standard therapies discussed earlier, as well as surgical intervention if critical vessels are involved, so that debilitating and irreversible complications can be prevented.

## CONCLUSION :

TA depending upon the artery involved can present with wide variety of clinical manifestations. So any patient of less than 40 years presenting with complaints of non-specific chest pain, giddiness, tingling sensation of left arm with radio-radial delay and a wide pulse pressure difference between the arms need to be investigated in the line of Takayasu's arteritis.

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## Clinical spectrum of non-compressive myelopathy in a tertiary care centre of north eastern India

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### ABSTRACT :

**Background :** Idiopathic acute transverse myelitis (ATM) is the most common cause of non-compressive myelopathy in India. Improved understanding of the differential diagnosis and improved investigative techniques have facilitated the diagnosis of patients with non-compressive myelopathy and reduced the proportion of patients who are labeled as having "idiopathic transverse myelitis." **Objective :** To study the clinical spectrum, etiology, and outcome after therapy of patients with non-compressive myelopathy. **Results :** Of 40 patients studied, 23 were male and 17 were female. Mean age was 34.73 years. Presentation was acute in 27, subacute in 9 and chronic in 4 patients and history of relapse and remission was present in 6 patients. 2 patients had low serum vitamin B12 level, 1 patient (2.5%) was HIV I positive, 1 (2.5%) was HTLV I antibody positive, 1 was Venereal Disease Research Laboratory (VDRL) test and Treponema pallidum haemagglutination (TPHA) test positive, 2 had elevated anti-thyroid peroxidase (TPO) antibodies and out of these 2 patients 1 was positive for anti-microsomal antibody and anti-thyroglobulin antibody. CSF analysis was done in all 40 patients, pleocytosis was seen in 10 (25%) patients, protein was elevated in 14 (35%) patients, ADA was elevated in 2 (5%), cryptococcal antigen was positive in 1 (2.5%), the CSF serum quotient for antibodies against varicella zoster virus (VZV) was elevated in 1 (2.5%). MRI of spine was done in all 40 patients. Multisegment (e" 3 segments) hyperintense lesion on T2W images, that occupied the central area on cross section was the most common abnormality. Out of 40 patients 9 (22.5%) patients revealed increased P-100 latency in VEP. 5 patients had bilaterally prolonged P-100 latencies. ATM was the commonest presentation with 13 patients, followed by NMO spectrum disorder with 9 patients, radiation myelitis (3), acute disseminated encephalomyelitis (ADEM) (2), Hirayama's disease (2), subacute combined degeneration (SACD) (2), varicella zoster myelitis (2), syphilitic myelitis (1), cryptococcal myelitis (1), anterior spinal artery ischemia (1), HIV associated myelopathy (1), Hashimoto's myelopathy (1), hereditary spastic paraparesis (HSP) (1) and HTLV-1 associated myelopathy (1). **Conclusion :** ATM followed by NMO spectrum disorder, is the leading cause of non-compressive myelopathy in the north eastern India. Clinical features combined with serology, MRI, VEP and CSF findings are helpful in defining the etiology of non-compressive myelopathy.

### INTRODUCTION :

Non-compressive myelopathy encompasses a large range of disease entities ranging from demyelination, infection, nutritional, toxic, hereditary to degenerative conditions. The disease spectrum is somewhat different in India as compared to the western countries, where infections and nutritional causes are less common and demyelinating and familial causes are the leading causes. Improved understanding of the differential diagnosis and improved investigative techniques, particularly neuroimaging and serologic testing, have facilitated the diagnosis of patients with acute and subacute myelopathy and reduced the proportion of patients who are labeled as having 'idiopathic transverse myelitis.'<sup>1</sup> Various studies on non-compressive myelopathy from India have been in the pre-magnetic resonance imaging (MRI)

era.<sup>2,3,4,5</sup> With the advent of MRI which is a very sensitive modality for the intramedullary spinal lesions it has become pertinent to have a relook at the profile of non-compressive myelopathies in India. Non-compressive myelopathy has particularly invoked great interest amongst neurologists as it strikes apparently healthy individuals in the prime of their lives, who are left with variable degree of sequelae. In this paper we want to present our experience with various non-compressive myelopathies with particular reference to Neuromyelitis optica (NMO) - spectrum of disorder and idiopathic acute transverse myelitis (ATM) encountered during the last one year in the north-eastern India.

### METHODS :

40 cases of non-compressive myelopathy admitted in the Neurology ward of Gauhati Medical College and hospital, Guwahati or attending Neurology OPD during August 2012 to September 2013 were included in the study. They were examined clinically and followed by laboratory investigations and neuroimaging studies. Details

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of onset of illness, antecedent events and grade of power (Medical Research Council) at admission and discharge, symmetry / asymmetry of symptoms, type of treatment given and complications were particularly recorded. CSF was done in all 40 cases. Estimation of serum anti-nuclear antibody (ANA), HIV I & II and thyroid function test were done in all cases and serum VDRL, TPHA, anti TPO, AMA, ATG, Vitamin-B12 levels, serum angiotensin converting enzyme (ACE) level, human T-cell lymphotropic virus (HTLV) I/II serology and lyme serology were done wherever suspected. MRI study of the brain was done in 25 patients & MRI of spinal cord was done in all the 40 cases. The vertebral segmental length of the high signal was estimated on the basis of findings on sagittal T2-weighted images. Cross-sectional location, size, and pattern of the high signal in the cord were determined by findings on the axial T2-weighted images. Evaluation of the abnormal signal intensity of the cord, segmental extent, and contrast enhancement was based on the initial MR examination; for the follow-up studies, these features were compared with the initial findings. Visual evoked potential was performed in all patients to rule out optic neuritis. Revised Wingerchuck's criteria (2006) was used for diagnosis of NMO and Transverse Myelitis Consortium Working Group diagnostic criteria was used for diagnosis of ATM.<sup>6</sup>

## RESULTS :

Of 40 patient studied, 23 patients were male and 17 were female. Mean age was 34.73 years. Presentation was acute in 27 (67.5%), subacute in 9 (22.5%) and chronic in 4 (10%) patients and history of relapse and remission was present in 6 (15%) patients. 23 patients (57.5%) presented with paraparesis, 15 patients (37.5%) with quadriparesis, 2 patient (5%) with bilateral upper limb weakness, involvement was symmetrical in 33 patients (82.50%) and most cases had maximum deficit at onset. Definite sensory level was present in 21 (52.5%) patients, and bladder was involved in 24 (60%) patients. Only pyramidal tract was involved in 5 (22.5%) patients.

All 40 patients were screened for anti nuclear

Table 1: Revised Wingerchuck's criteria-2006 (Weinshenker et al)

Absolute criteria	1 – Optic neuritis 2 – Myelitis
Supportive criteria (any 2 out of 3)	1 – spinal cord MRI lesion extending Å or equal to 3 contiguous vertebral segments. 2 – Initial brain MRI with fewer than 4 white matter lesions or 3 lesions if 1 is periventricular. 3 – NMO-IgG seropositivity.

Table No 2 - Criteria for Idiopathic Acute Transverse Myelitis<sup>6</sup>

Inclusion	Exclusion
Sensory, motor, or autonomic dysfunction attributable to the spinal cord	History of previous radiation to the spine within the past 10 years
Bilateral signs and/or symptoms (though not necessarily symmetric)	Clinical deficit consistent with thrombosis of the anterior spinal artery
Clearly defined sensory level	Abnormal flow voids on the surface of the spinal cord consistent with AVFs
Exclusion of extra-axial compressive etiology by neuroimaging (MRI, myelography; CT of spine not adequate)	Serologic or clinical evidence of connective tissue disease (sarcoidosis, Behcet's disease, Sjogren's syndrome, SLE, mixed connective tissue disorder, etc.)*
Inflammation within the spinal cord demonstrated by CSF pleocytosis or elevated IgG index or gadolinium enhancement	Clinical or laboratory evidence for syphilis, Lyme disease, HIV, HTLV-1, Mycoplasma, other viral infection (e.g., HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, enterovirus)*
If none of the inflammatory criteria is met at symptom onset, repeat MRI and lumbar puncture evaluation between 2 and 7 days following symptom onset	Brain MRI abnormalities suggestive of MS*
Progression to nadir between 4 hours and 21 days following the onset of symptoms (if patient awakens with symptoms, symptoms must become more pronounced from point of awakening)	History of clinically apparent optic neuritis*
*Do not exclude disease-associated acute transverse myelitis. AVFs, arteriovenous fistulas; MRI, magnetic resonance imaging; CT, computed tomography; CSF, cerebrospinal fluid; SLE, systemic lupus erythematosus; IgG, immunoglobulin G; HIV, human immunodeficiency virus; HTLV-1, human T-lymphotropic virus 1; HSV, herpes simplex virus; VZV, varicella zoster virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; HHV, human herpes virus	

antibody (ANA), human immunodeficiency virus (HIV) I & II and thyroid function test, 8 (20%) were ANA positive, 1 (2.5%) was HIV I positive, 1 (2.5%) was HTLV I positive and 9 (22.5%) patients had deranged thyroid function test, out of those 2 had elevated anti-TPO antibodies. Out of these 2 patients 1 was positive for anti microsomal antibody and anti thyroglobulin antibody. 29 patients were screened for serum VDRL and TPHA, and only 1 (2.5%) patient was found positive at presentation and also in the follow up.

CSF analysis was done in all 40 patients, pleocytosis was seen in 10 (25%) patients, protein were elevated in 14 (35%) patients, ADA was elevated in 2 (5%), cryptococcal antigen was positive in 1 (2.5%), the CSF serum quotient for antibodies against VZV was elevated in 1 (2.5%).

MRI of spine was done in all 40 patients. Multisegment (e" 3 segments) hyperintense lesion on T2W images, that occupied the central area on cross section was the most common abnormality, involved cervical cord in 16 (40%), cervicodorsal cord in 9 (22.5%) and dorsal cord in 12 (30%) patients. MRI showed cord swelling in 24 (60%), cord atrophy in 1 (2.5%), and was normal in 3 (7.5%) cases. Involvement of fewer than 3 vertebral segments was seen in 3 (7.5%) patients. Post gadolinium enhancement was seen in 14 (35%) patients in form of patchy or subtle enhancement. MRI brain was done in 25 patients. 1 patient showed bilaterally asymmetrical, multiple, ill-defined, T2 and FLAIR hyper-intense non enhancing lesion involving cortex and

subcortical white matter. Another patient with normal MRI spine showed thin corpus callosum on MRI brain.

Out of 40 patients 9 (22.5%) patients revealed increased P-100 latency in VEP. 5 patients had bilaterally prolonged P-100 latencies.

ATM was the commonest presentation with 13 patients followed by NMO with 9 patients, radiation myelitis (3), acute disseminated encephalomyelitis (ADEM) (2), hirayama's disease (2), sub-acute combined degeneration (SACD) (2), varicella zoster myelitis (2), syphilitic myelitis (1), cryptococcal myelitis (1), anterior spinal artery ischemia (1), HIV associated myelopathy (1), hashimoto's myelopathy (1), hereditary spastic paraparesis (HSP) (1) and HTLV-1 associated myelopathy (1).

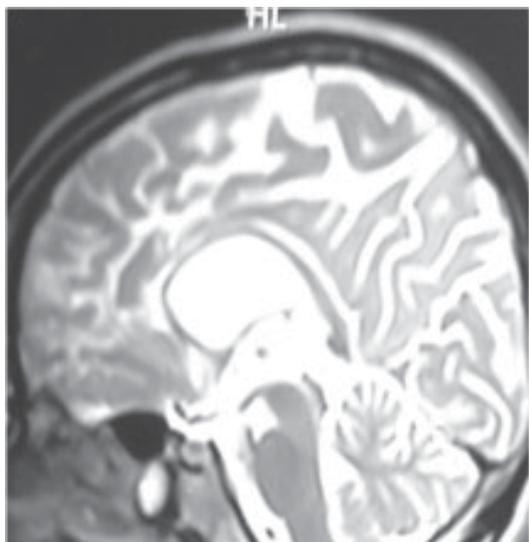


Fig 1 : MRI brain T2W coronal section of the HSP patient showing thin corpus callosum.

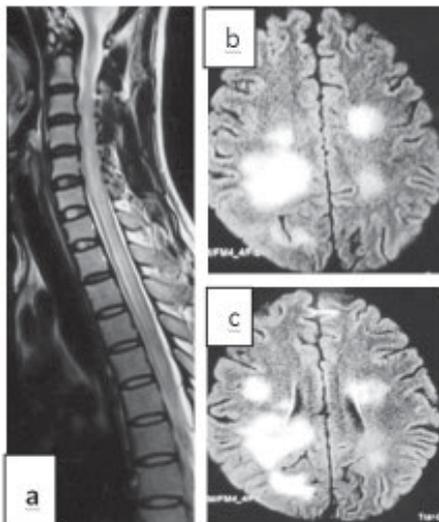


Fig 2: MRI of an ADEM patient. a) T2W sagittal section of MRI spine showing hyper-intense signal involving cervico-dorsal cord and cord swelling. b) & c) MRI brain axial section FLAIR images showing hyper-intense signals involving cortex & subcortical white matter bilaterally.

Out of 40 patients 21 patients were followed up, rest 19 patients failed to follow up. Follow up included 6 patients of NMO spectrum disorder, 4 patients of ATM, 2 patients of radiation myelitis, 2 patients of ADEM and 1 patient each of SACD, Syphilitic myelopathy, varicella zoster myelopathy, cryptococcal myelitis, Hashimoto's myelopathy, hereditary spastic paraplegia and HIV associated myelopathy.

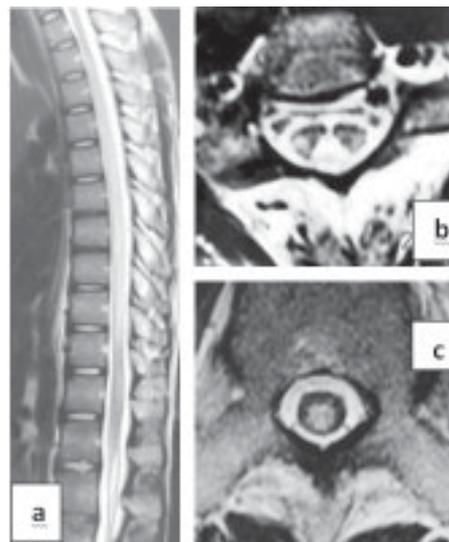


Fig 3: a) MRI spine T2W sagittal section of cryptococcal myelitis- showing long segment swelling of cord extending from D3 to D12 with hyperintense signals. b) MRI spine T2W axial section of NMO patient showing hyperintense signal from center of cord. c) MRI spine T2W axial section of SACD patient showing inverted "V" sign in posterior aspect of cord.

All 6 patients of NMO spectrum disorder received intravenous (IV) methyl prednisolone and continued on oral steroid and disease modifying therapy (5 on azathioprine & 1 on mycophenolate mofetil), 4 patients had relapses, 2 improved and 1 died secondary to aplastic crisis.

Among 4 patients of ATM and 2 patients with ADEM, 5 patient improved remarkably without any residual functional deficit after treatment with IV methyl prednisolone and tapering oral steroids and 1 patient of ADEM died secondary to sepsis and multi organ dysfunction.

IV methyl prednisolone followed by oral steroids were prescribed to both the patients with radiation myelitis and followed up monthly. Patient gradually deteriorated during follow up and became bed bound with a bone deep bed sore in the sacral area at the end of 6 month. The patient with SACD responded well to IM mehtylcobalamine and by the end of 3 months the patient became independent.

Intramuscular (IM) procaine penicillin was administered to the single patient of syphilitic myelopathy,

but patient remained serum VDRL & TPHA positive in the 3<sup>rd</sup> and 6<sup>th</sup> month of follow up. This patient showed minimal improvement, limbs were spastic, sphincter control was absent and patient was only could stand with support at the end of 6 month.

The patient with Varicella Zoster myelitis was treated with IV acyclovir for 2 weeks and steroids. Patient was followed up every month and showed gradual improvement in muscle strength. By the end of 6 months patient was able to walk with a four-wheel frame or a single-point stick for 10–20 meters and was independent for many activities of daily living.

The patient with cryptococcal myelitis was started on IV fluconazole for 10 days then continued on oral fluconazole. The patient was followed up every month and at end of sixth month patient was able to walk with some restriction, full sphincter control but dysesthesias persisted to some extent.

One patient of Hashimoto’s myeloneuropathy was started on IV methyl prednisolone for 5 days followed by oral steroid and thyroxine 150ug/day. There was marked improvement in muscle strength within a week, but the tingling and dysesthesias persisted. Patient was followed up every 1 month thereafter. At the end of 6 months, there was complete resolution of her paraparesis and sensory symptoms.

The patient with HIV associated myelopathy was started on anti retroviral treatment. During the monthly follow up no significant improvement was seen.

The young adult with HSP was given symptomatic treatment only and his functional status remained stable at 6 month follow up.

Table 3 - Outcome score

Score	Outcome	No. of Patients
0	Unrestricted walking, full sphincter control, no blindness	4
1	Restricted walking, full sphincter control and no blindness	6
2	Walk with support, no blindness	2
3	Can stand with support, not able to walk, no sphincter control, no blindness	4
4	Bed ridden	3
5	Bed ridden & blind	--
6	Death	2
	Total	21

## DISCUSSION:

This was a prospective study of 40 patients with non-compressive myelopathy seen within 1 year from North East India. Other series by Prabhakar S et al<sup>7</sup> from PGIMER, Chandigarh had reported 57 cases collected over a period of 2 years. Another series by Das K et al<sup>8</sup> reported 82 cases collected over a period of 2 years from Bangur Institute of Neurology and Institute of Postgraduate Medical Education and Research,

Department of Neuromedicine, Calcutta. ATM was the most common etiology of non compressive myelopathy in the previous two studies. In the present study also, acute transverse myelitis and NMO spectrum disorder formed the major bulk of non-compressive myelopathies comprising 60.86% together of all cases. NMO spectrum disorders were significantly common in our study compared to previous two studies. Hospital-based case series reported from India in the pre-MRI era<sup>9,10</sup> are often quoted in Western literature on NMO, to support the notion that NMO is common in India. The basis for this speculation could be possibly the disproportionate involvement of spinal cord and optic nerve reported in Indian MS. Optic spinal MS, loosely described in most Indian literature as MS, with attacks confined clinically to spinal cord and optic nerve were seen in 20 - 60% of cases.<sup>11</sup> The advance neuroimaging modalities have helped greatly to differentiate MS/ optico spinal MS from NMO spectrum disorders. The discovery of NMO-IgG, an autoantibody reported by Lennon and colleagues, played an important role in differentiating MS/ optico spinal MS from NMO spectrum disorders. NMO-IgG was found to be 73% sensitive and 91% specific<sup>12</sup> and had a predictive value<sup>13</sup> for NMO. We did not do NMO - IgG in any of our patient but we started disease modifying therapy in all patients who fulfilled revised wingerchuck’s criteria (2006) in the absence of NMO-IgG.

In the present study, apart from the common etiologies of non compressive myelopathy, we came across some rare causes like syphilitic myelitis, varicella zoster myelitis, cryptococcal myelitis, hashimoto’s myeloneuropathy, HTLV-1 associated myelopathy and HSP.

Syphilitic myelitis, now a days, is becoming a rare entity because of widespread use of antibiotics. We were, however, able to pick up one case because of routine testing for VDRL in the CSF of all cases of non-compressive myelopathy.

Cryptococcosis in the immunocompromised host has a high morbidity and mortality. Approximately 90% of cryptococcosis occurs in acquired immune deficiency syndrome (AIDS) patients. Cryptococcal myelitis is very rare, even in patients with AIDS. Cryptococcus infection presenting as a spinal cord syndrome has been reported, but all of these cases were vertebral osteomyelitis.<sup>14</sup> We reported an immunocompetent young male presenting with cryptococcal dorsal myelitis. Patient responded well to fluconazole, which again confirmed the cryptococcal

origin of the illness.

Varicella zoster virus (VZV) infection causes a variety of neurologic complications, including post-herpetic neuralgia, polyradiculoneuritis, transverse myelitis, vasculopathy, aseptic meningitis, leukoencephalopathy, dorsal root or cranial nerve ganglionitis, ventriculitis, necrotising angiitis and meningoencephalitis<sup>15,16</sup>. The frequency of transverse myelitis during or after varicella infection is 0.3%.<sup>17</sup> Onset is acute and occurs shortly after typical cutaneous rash in a dermatomal distribution with the development of paraparesis, sensory loss and sphincter dysfunction.<sup>18</sup> Patients with rapid progression and flaccidity below the level of the lesion have the poorest prognosis.<sup>19</sup> High suspicion is required for the diagnosis of varicella zoster myelitis. Early diagnosis and treatment can improve the prognosis.

Myelopathy associated with Hashimoto's disease is a rare. It is characterized by the presence of elevated anti thyroid peroxidase antibody and anti microsomal antibody. The exact role of the antibody in the genesis of the myelopathy is not clear although a vasculitic process as the basis of Hashimoto's encephalopathy has been proposed.<sup>20</sup> There are only two reported cases of Hashimoto's myelopathy until date.<sup>21,22</sup> Our patient had Hashimoto's disease with a marked increase in anti thyroid antibodies. The clinical picture of patient was suggestive of myelopathy with peripheral neuropathy. Peripheral neuropathy in this case was probably related to hypothyroidism. Myelopathy in our case seems to be related to Hashimoto's disease. The picture of myeloneuropathy can also be mimicked by vitamin B 12 deficiency, which was ruled out by relevant investigations. Though we could not exclude all causes of non compressive myelopathy, the clinical setting with the presence of high titers of anti TPO antibodies and response to steroids makes the diagnosis of myelopathy of Hashimoto's disease most likely. Diagnosis requires a high degree of suspicion and exclusion of other common causes. Besides periodic checking of autoimmune parameters and possible occurrence of another autoimmune disease should be sought for in all patients with autoimmune thyroid disease.

Finally we conclude that, ATM followed by NMO spectrum disorder are the leading causes of non-compressive myelopathy in north eastern India. High degree of suspicion regarding rare causes is necessary for early diagnosis and treatment, to improve prognosis. Clinical features combined with serology, MRI, VEP and CSF findings are helpful in defining the cause of non-compressive myelopathy.

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# Anomalous Origin of the Right Coronary Artery from the Left Anterior Descending Coronary Artery – a case report of two cases and review of literature

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### ABSTRACT :

Anomalous origin of the right coronary artery from the left anterior descending coronary artery is very rare and considered as a variant of single coronary artery. Typical course of this anomalous artery is anterior to the right ventricular out flow tract before it gains access to the right atrio-ventricular groove. Opinion varies regarding the clinical significance of this anomaly. We report two such cases of anomalous right coronary artery from our experiences.

**KEY WORDS :** *Anomalous coronary artery, left anterior descending coronary artery, right coronary artery.*

### INTRODUCTION

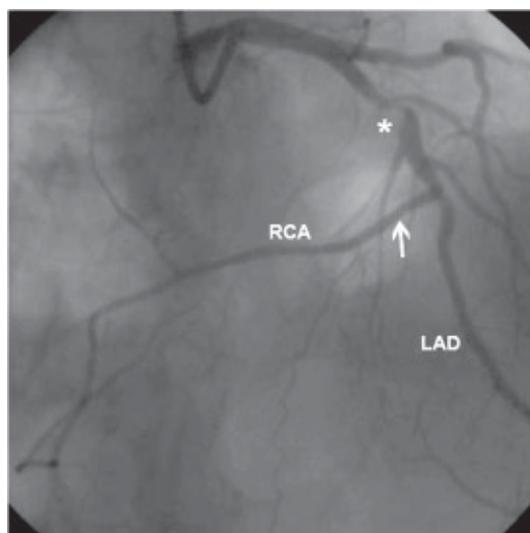
The coronary arteries normally arise from round or ovoid orifices located in the right and left sinuses of Valsalva. Any deviation of origin with or without the orientation of a coronary artery from the normal are considered anomalous. Anomalous origin of the right coronary artery (RCA) as a branch of the left anterior descending (LAD) artery is a rare variant of single coronary artery. Controversy remains regarding the clinical significance of this anomaly. We report two cases of anomalous RCA arising from the LAD artery. The first case is notable for the presence of significant coronary atherosclerotic disease in the LAD just proximal to the origin of the anomalous RCA, which was treated successfully by percutaneous intervention. In the second case, an anomalous non-dominant RCA is arising from LAD and supplying the proximal part of RCA territory, while the distal territory is receiving supply from the left circumflex coronary artery.

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### CASE REPORT

#### CASE I

A 53-year-old male presented with history of typical angina on minimal exertion of 7-days duration. He was a current smoker and hypertensive. Physical examination was unremarkable except for blood pressure of 150/90 mmHg. ECG at rest revealed sinus rhythm with T-wave inversion in chest leads (V1-V6). His left ventricular function evaluated by echocardiography was normal. Hematological evaluation by the Troponin-T marker study was positive for myocardial necrosis.

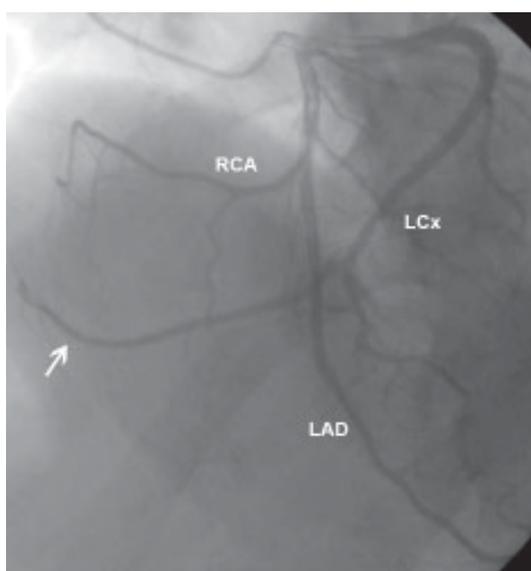


*Fig.1. Selective coronary injection showing the origin of an anomalous RCA from LAD distal to the third diagonal (asterisk) (D stands for diagonal branch of LAD)*

On selective coronary angiography from right radial approach, the left main coronary artery took origin from the left sinus of Valsalva, and was free of disease. The vessel bifurcated normally into LAD and circumflex coronary arteries. A 90% eccentric lesion was noted in the proximal portion of a type III LAD. The left circumflex coronary artery was normal. An anomalous RCA took origin from the LAD just after the second diagonal branch and major septal perforator (Fig.1). An aortic root angiogram did not reveal another right coronary artery. Successful percutaneous coronary angioplasty with stenting was carried out using 3.5 mm X 16 mm paclitaxel- eluting stent. At 3-year follow up, 64-slice CT-angiography revealed the course of the anomalous RCA and patent stent in the proximal LAD.

## CASE II

BR is a 54-year-old diabetic and hypertensive presented with a 5-months history of breathlessness on exertion NYHA class II. Clinical examination was unremarkable. ECG revealed left ventricular hypertrophy, and echocardiography showed good left ventricular function. Treadmill test was positive inducible myocardial ischaemia. Coronary angiography from right radial approach revealed normal left main artery with normal LAD artery and dominant left circumflex artery. An anomalous RCA originating from the LAD, was supplying the proximal RCA territory (Fig.2).



*Fig.2. Selective coronary injection showing the origin of an anomalous RCA from LAD distal to the third diagonal (asterisk) (D stands for diagonal branch of LAD)*

## DISCUSSION

Congenital anomalies of the coronary artery account for 1.3-3% of the routine cardiac catheterization procedures<sup>1</sup>, and anomalous origin of RCA from the left sinus of Valsalva has been noted approximately in 0.02-0.17% of cases. The right coronary artery may arise anomalously from various sites including the aorta, pulmonary trunk, left ventricle, the left main coronary artery, and from the left sinuses of Valsalva. The term single coronary artery is applicable when the right coronary artery arises from either the left main or the left circumflex coronary artery. Origin of the right coronary artery from the left anterior descending coronary artery is very rare and represents a variant of the L-II Lipton classification<sup>2</sup> as modified by Yamanaka and Hobbs<sup>3</sup> in the largest retrospective review of 1,686 coronary anomalies from series of 126,595 patients at the Cleveland Clinic. Single coronary artery has incidence of 0.008% and 0.067% in patients undergoing coronary angiography in large series 2, and accounts for between 1.1% and 8.8% of all coronary anomalies (excluding fistulae). The anomalous RCA is being described as an extension of the second diagonal<sup>4</sup> or as a branch of the first septal perforator<sup>5</sup>, and its course is usually anterior to the right ventricular outflow tract before it reaches the right atrio-ventricular sulcus. Although the vessel subsequently supplies the RCA territory as in the normal variant, the distribution is variable. An isolated report of an anomalous vessel from the LAD supplying the distal RCA distribution with an accessory branch originating in the right sinus of Valsalva to supply the proximal RCA territory has been reported<sup>1</sup>. The distribution noted in our second patient is unique with respect to the foregoing report. The anomalous RCA supplies the proximal part of the RCA territory, while the distal RCA territory is supplied by the distal extension of the left circumflex coronary artery.

In contrast to previous reports pertaining to the origin of the anomalous RCA from the LAD, in our cases, we have noted that the RCA took its origin quite distally in the LAD. In the first case, origin of the RCA is distal to the second diagonal branch and after the major septal perforator, while the anomalous RCA took its origin from the LAD distal to the third diagonal branch in the second.

The clinical significance of the anomalous RCA from the LAD is somewhat controversial. Several previous reports infer that such an anomaly is usually benign<sup>6</sup> and there appears to be no increased incidence of coronary artery disease. Other reports, however, suggest the contrary. Of 36 reported cases of anomalous RCA from LAD more than half the patients had obstructive lesion equal or greater than 50% in one or more epicardial coronary arteries<sup>7</sup> necessitating a revascularization procedures. Data regarding percutaneous revascularization in patients with anomalous RCA arising from LAD artery with a single coronary ostium is limited. Disease in the proximal segment of this artery puts a large area of myocardium into jeopardy and inadvertent dissection or spasm of the ostium during procedure might lead to catastrophe.

These case reports have demonstrated two very rare coronary artery anomaly. One of these had significant atherosclerotic coronary artery disease proximal to the origin of the anomalous RCAS, which

was successfully treated by percutaneous method with good immediate and long-term result.

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# Rare Neurological Manifestations of Insecticide Poisoning

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### ABSTRACT :

Ophthalmic effects in organophosphorus poisoning can be due to direct ocular exposure which can result in optic neuropathy, retinal degeneration, myopia, miosis and defective vertical smooth pursuit. There are case reports of extrapyramidal symptoms with organophosphorus poisoning, however optic neuritis is rare. We report this case as the patient had bilateral optic neuritis and extrapyramidal symptoms due to insecticide poisoning.

**KEY WORDS :** *organophosphorus poisoning, extrapyramidal symptoms, optic neuritis.*

### INTRODUCTION :

Organophosphate insecticides continue to be an important cause of poisoning in India.<sup>1</sup> Organophosphate insecticides have a triphasic effect on the central nervous system, namely acute cholinergic crisis, intermediate syndrome and delayed polyneuropathy. Although acute organophosphate poisoning is relatively common, case reports describing other neurological complications following an acute intoxication are limited.

### CASE REPORT :

A 29 year old male ingested alcohol with an unknown substance and was brought to hospital in a drowsy state. On admission patient was drowsy and had hypotension. He was admitted in ICU and was intubated in view of low GCS. In the setting of reduced pseudocholine esterase {1669 (N=5900 to 12,220)} with symptoms, a diagnosis of OP poisoning was considered and patient was treated.

As patient recovered haemodynamically extubation was tried. However patient had to be reintubated in view of respiratory distress. A diagnosis of intermediate

syndrome was considered. Patient was tracheostomised in view of prolonged ventilation and slowly weaned off from ventilator support.

During the course in the hospital patient complained of decreased vision in both eyes. On evaluation his pupils were sluggishly reacting and he was able to appreciate only light. A diagnosis of optic neuritis was considered and patient was started on injection methylprednisolone.

During the same period after closure of the tracheostomy it was noticed that patient had slurring of speech. On examination patient was found to have dysarthria and rigidity of all limbs with brisk deep tendon reflexes. MRI brain done showed bilateral symmetrical caudate and putamen hyperintensities. A diagnosis of extrapyramidal syndrome secondary to organophosphorus poisoning was made and patient was started on levodopa.

Patient's visual acuity and extrapyramidal symptoms improved marginally on discharge.

In our patient a diagnosis of poisoning by organophosphorus was considered based on clinical examination, low pseudocholinesterase levels and improvement with treatment. Intermediate syndrome and extrapyramidal symptoms are a known complication of organophosphorus poisoning however documented cases of optic neuritis are rare in literature. As the patient had consumed alcohol a possibility of toxicity secondary to methanol also has to be considered. However on admission arterial blood gas didn't show features suggestive of methanol poisoning. Organophosphorus

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compounds are combined with methanol, hence whether our patient had dual poisoning needs to be considered.



MRI brain showing bilateral symmetrical caudate and putamen hyperintensities.

## DISCUSSION :

There are few case reports on extrapyramidal manifestations of OP poisoning.<sup>2,3</sup> Extrapyramidal symptoms are a rare occurrence in OP poisoning in the intermediate phase.<sup>4</sup> This occurs after 4-40 days of intoxication and usually reversible within 8 weeks with or without treatment.<sup>4</sup> The extrapyramidal symptoms, which occur rarely as a part of the intermediate syndrome, are thought to be due to the inhibition of acetylcholinesterase in the human extrapyramidal areas.<sup>5,6</sup> Increased susceptibility of the basal ganglia nuclei to the toxic products, in the absence of efficient detoxification pathways, may also be responsible.<sup>7</sup>

Organophosphate poisoning causes irreversible AChE inhibition resulting in raised acetylcholine (ACh) concentrations. The striatum contains cholinergic

interneurons which are likely to stimulate efferent enkephalin-containing GABA projections to the globus pallidus externus leading via increased glutaminergic excitation in the subthalamic nucleus to a reduced cortical glutamate stimulation (indirect pathway of the corticostriatopallidothalamocortical circuit). Therefore, it can be speculated that reduced striatal AChE activity resulted in a decrease of cortical glutamate stimulation which clinically mimicked a dopamine deficiency syndrome. Extrapyramidal symptoms, a part of intermediate syndrome are characterized by dystonia, cogwheel rigidity and parkinsonian features.

## CONCLUSION :

It is important to recognise the rare neurological manifestations of insecticide poisoning as they can cause permanent neurological sequelae.

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# Ruptured hydatid cyst of lung

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### ABSTRACT :

Echinococcosis or hydatid disease is caused by larvae of Echinococcus. Pulmonary hydatid cysts are usually asymptomatic but patients may occasionally develop symptoms due to cyst rupture or compression of the surrounding structures by the cyst. We report a case of a 30 year old woman who had ruptured hydatid cyst of the right lung. The chest x-ray and CT scan features were suggestive of ruptured hydatid cyst with detached and collapsed membranes (Serpent's sign). Interesting Chest X-ray and CT appearance is the reason for reporting this case.

**KEY WORDS :** Ruptured hydatid cyst, Echinococcosis, serpent sign, Iceberg sign.

### INTRODUCTION :

Echinococcosis or hydatid disease is a parasitic infection caused by larva of Echinococcus. Four species are recognised, which are *E.granulosus*, *E.multilocularis*, *E.vogelli* and *E.oligarthus*<sup>1</sup>. The vast majority of human infections are caused by *E.granulosus*, which causes cyst formation in various organs of the body. The liver is the most common site followed by the lungs. Cystic echinococcosis is seen worldwide with endemicity in South America and Central America, the Middle East, sub Saharan Africa, Russia, China, Australia, New Zealand and Asia<sup>2</sup>. Hydatid disease of the lungs is usually asymptomatic for long time, and patients usually develop symptoms due to the cyst's compression to surrounding structures due to mass effect or due to cyst rupture which maybe spontaneous or secondary to an infectious process, trauma, or after needle aspiration<sup>3</sup>. Rupture is a frequent complication which may sometimes cause severe anaphylactic reaction. Hydatid disease of lung is comparatively rare and can be easily missed which leads to a delay in diagnosis and

presentation of patients with complications. Here we report one patient with ruptured hydatid cyst of lung who presented with symptoms of cough, chest pain, fever and shortness of breath and who had an earlier history of needle aspiration and being treated as tubercular pleural effusion in a peripheral centre.

### CASE REPORT:

A 30 years old female housewife from a rural setting and low socio-economic class presented to the out patient department of Pulmonary medicine in Gauhati Medical College and hospital with productive cough and right sided chest pain for the preceding one month and low grade fever, shortness of breath for last 20 days. Apparently her cough started 2 years back which was initially occasional but it increased in amount and frequency since last 20 days. Her sputum was salty in taste and she complained of expectorating some whitish material along with her sputum. There was no history of hemoptysis. However she had a history of previous pleural tapping which was done in a peripheral centre about 2 years back and afterwards treated as tubercular pleural effusion. But her symptoms still persisted even after antitubercular treatment. At the time of presentation to OPD, she was afebrile, conscious and oriented. Her pulse rate was 96/min, blood pressure was 110/80 mm of Hg, and oxygen saturation was 98%. She was tachypnoeic with a respiratory rate of 30/min and was using accessory muscles of respiration. On Respiratory

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examination her air entry was decreased in right interscapular and infraaxillary areas with crepitations in right infrascapular area. CVS, Neurological and abdominal examination was found to be normal. The laboratory tests revealed haemoglobin 11.7gm%, total cell count of 13,001/cu mm, platelet count 2.76 lacs/cu mm and ESR was 120 mm AEFH. Other routine investigations including renal function and liver function tests were within normal range. Her chest x-ray showed a thick walled cavitory lesion with air fluid level in the right lower zone of lung, demonstrating the “Iceberg sign” which indicates collapsed parasitic membrane which are partially submerged ( Fig: 1). CT- thorax was done which revealed a large cyst in the right lower lobe of lung measuring 9.7 \*6.6 cms. The cyst appeared ruptured with curvilinear crumpled membrane like structures which were detached, showing the ‘Serpent sign’ (Fig: 2).



Fig: 1: PA view chest showing iceberg sign.

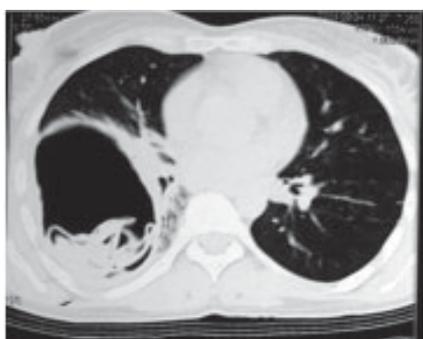


Fig:2: CT thorax showing serpent sign.

These features prompted us to do a hydatid serology test for her, which was positive (echinococcus IgG- 16.16 U/ml). USG of abdomen does not revealed any cysts in

the liver. Bronchoscopy was done and BAL fluid was sent for detection of brood capsules and scolices, but report was negative. She was initially started with antihelminthic (albendazole 400mg) in twice daily dose. CTVS consultation was taken and patient was planned for resection of the cyst.

## DISCUSSION :

Hydatid cyst disease is a zoonotic disease caused by the larval stage of *Echinococcus granulosus* (dog tapeworm), *E. Multilocularis* or *E. vogeli*. This disease occurs when humans ingest the hexacanth egg of the dog tapeworm. There are two main forms of the disease: the cystic unilocular form and the alveolar multilocular form<sup>4</sup>. The hydatid cyst caused by *E. granulosus* is usually solitary and occurs most commonly in the lower lobe of right lung, which was also the site in our case. Alveolar hydatid disease is caused by *E. multilocularis* and is characterised by formation of multilocular vesicles and has a grave prognosis. Cysts may initially be asymptomatic, and may be diagnosed incidentally during a radiological evaluation for other reasons. On the other hand, a hydatid cyst may present with symptoms, such as chest pain, hemoptysis, dyspnea, and fever. Kuzucu et al<sup>5</sup> reported chest pain (50%), cough (27%), dyspnea (18%), and fever (12%) as the most common presenting symptoms in patients with intact pulmonary hydatid cysts. However, 27% of patients were asymptomatic. Pulmonary hydatid cysts rupture in about a third of patients, releasing a highly antigenic fluid into the bronchus, which can cause secondary hydatid spread, asphyxia, anaphylactic shock, acute respiratory failure, massive hemoptysis, and circulatory collapse. Ruptured pulmonary hydatid cysts generally present with chest pain (49%), cough (46%), dyspnea (42%), hemoptysis (33%), fever (36%), and sputum production (33%), whereas only 3% of patients with ruptured pulmonary hydatid cyst are asymptomatic<sup>5</sup>. The patient in our case report had all of the above features except hemoptysis. In the majority of cases, a combination of imaging and serological methods usually yields the diagnosis of cystic echinococcosis. The different radiological signs found in ruptured hydratoid cyst are the ‘meniscus/crescent’ sign, the sign of the ‘rising sun’, the ‘serpent’ sign, the camalote or water lily’ sign, the ‘whirl’ sign, the ‘onion peel’ sign

and the 'cumbo' sign. In our patient the typical CT sign of ruptured hydatoid cyst "serpent sign" is present. A patient who has lung cysts should be investigated for associated liver cysts. Immunodiagnostic testing for serum antibodies or circulating antigen provides supportive evidence of pulmonary hydatid cyst.

The treatment of ruptured pulmonary hydatid cysts is principally surgical. However, pre- and post-operative 1-month courses of Albendazole and 2 weeks of Praziquantel should be considered in order to sterilize the cyst, decrease the chance of anaphylaxis, decrease the tension in the cyst wall (thus reducing the risk of spillage during surgery) and to reduce the recurrence rate post-operatively<sup>6</sup>. The surgical options for lung hydatid cysts include lobectomy, wedge resection, pericystectomy, intact endocystectomy and capitonnage.

#### CONCLUSION :

Ruptured hydatid cyst, at times may present with non specific respiratory symptoms. Correct diagnosis needs a high degree of clinical suspicion and can be

confused with pulmonary tuberculosis with superadded empyema. Appropriate medical management and early surgical intervention whenever feasible can help to decrease the morbidity and mortality.

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# Stroke Mimic : Neurotoxicity of Intrathecal Methotrexate

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### ABSTRACT :

Acute onset focal neurological deficit leads us to an alarming diagnosis of a stroke. But a variety of condition exists that mimic a stroke, thus leading to terms like “stroke mimic” and “stroke chameleon”. Keeping these terms in mind, we should approach a case of acute focal neurological deficit in the proper way.

**KEY WORDS :** *Stroke, Stroke mimic*

### INTRODUCTION :

The term “stroke mimic” was coined to describe a clinical syndrome suggestive of stroke, yet not actually caused by an ischemic event. Such conditions are usually seizures, systemic infections, brain tumor, toxic and metabolic disturbances.<sup>1</sup> Herein we report a case of stroke mimic caused by neurotoxicity of intrathecal methotrexate (IT-MTX). Methotrexate is a folate antagonist used in the treatment of lymphoblastic leukaemia and is effective in preventing recurrences of central nervous system leukaemia. We describe a 50 years old man who, developed acute hemiparesis seven days after receiving intrathecal methotrexate that alarmed us to investigate in the line of stroke.

### CASE REPORT :

A 50-year- old right handed man, non diabetic, non-hypertensive, non smoker or alcoholic, with acute lymphoblastic leukaemia who had received four cycles of chemotherapy consisting of intravenous vincristine 1.4mg/m<sup>2</sup>, oral prednisone 40mg/m<sup>2</sup>, intramuscular asparaginase 6000U/m<sup>2</sup>, IT-MTX 12mg/m<sup>2</sup>, and intravenous daunorubicin 30mg/m<sup>2</sup>. Seven days after the fourth cycle of chemotherapy he developed sudden onset

starring episode lasting for few seconds followed by left sided weakness. There was no history tonic clonic movements, loss of consciousness, clenching of teeth, frothing from mouth, up rolling of eyes and urinary incontinence. On examination, the patient was conscious and oriented. His blood pressure was 120/80 mm of Hg, pulse rate 70 beats per minutes and regular, normal carotid pulsation without bruits and he was febrile. On neurological examination higher mental functions were normal with dysarthria and left sided classical hemiparesis. Muscle power was grade 3/5 (MRC grade) in the left upper and lower limbs. Deep tendon reflexes were normal and symmetrical in all four limbs. Plantar response was equivocal on the left and flexor on the right side. There was no sensory loss. He had no signs of meningeal irritation or cerebellar involvement. His NIHSS score at time of presentation was 8.

Laboratory investigations showed a total leukocyte count 23,200/mm<sup>3</sup>, hemoglobin 10.8gm/dL, a platelet count 200,000/mm<sup>3</sup>. Liver function tests, kidney function tests and serum electrolytes were normal. Serum fasting lipid profile, serum homocystein levels were within normal range. Electrocardiography (ECG), 2D Echo and carotid Doppler study were normal. Electroencephalography (EEG) done on same day was normal. Non enhanced computed tomography (NECT) scan of the brain, done on the same day was normal. Magnetic Resonance imaging (MRI) of the brain showed multiple non-enhancing hyper intensities involving cortex, right corona radiata, corpus callosum, left cerebellar hemisphere and

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centrum semiovale on right side in T2 weighted and FLAIR images showing restricted diffusion on diffusion weighted image and ADC map, a constellation of findings suggestive of methotrexate induced toxicity (Figure 1). His magnetic resonance angiogram and magnetic resonance venogram were normal. The patient was treated symptomatically with steroid pulse therapy and folic acid in view of demyelination being one of the postulated mechanism of methotrexate induced neurotoxicity. His muscle power had subsequently improved to MRC grade 4+/5 and was discharged with a Modified Rankin Score (MRS) of 3.

## DISCUSSION :

Methotrexate therapy is known to cause acute, sub acute and chronic neurotoxicity ranging from symptomatic to asymptomatic findings. Sub acute neurotoxicity has been reported in 3-15% of patients after methotrexate administration. It is associated with its increased cumulative exposure with any route of administration but is primarily encountered with intrathecal exposure.<sup>2,3</sup> Neurotoxicity due to methotrexate usually manifests as seizures, headache, altered mental status or any focal neurological deficit occurring at a median of 10-11 days after intrathecal exposure.<sup>4</sup> When the clinical presentation is acute in onset as in our case stroke mimic should be brought into consideration. The pathophysiology has been explained by demyelination, cytotoxic edema or micro infarcts.<sup>5</sup> Toxic leucoencephalopathy is well known entity that occur following intrathecal methotrexate. However, the reason behind this structural alteration of cerebral white matter affecting the myelin sheath is multifactorial.<sup>6</sup> It has also been hypothesized that methotrexate inhibits dihydrofolate reductase, which elevates homocysteine level and its excitatory amino acid neurotransmitter metabolites (homocysteic acid and cysteine sulfinic acid), which may mediate neurotoxicity.<sup>7</sup> Methotrexate is also known to elevate the adenosine level which may dilate cerebral blood vessels, slow the release of neurotransmitters at presynaptic junctions, modify postsynaptic response and slow the discharge rate of the neurons.<sup>8</sup> Its excitatory effect on N-Methyl-D-Aspartate (NMDA) receptor, alteration in bipterin metabolism and inhibition of glucose metabolism has also been contributory to its neurotoxicity.<sup>9</sup> This toxic

leucoencephalopathy causes intramyelinic oedema and cytotoxic oedema leading to a restricted diffusion in neuroimaging thus mimicking a stroke but is usually transient and reversible.<sup>10</sup>

Methotrexate associated neurotoxicity is often treated with aminophylline, a competitive antagonist of adenosine. Leucovorin is used 24-36 hours after methotrexate administration to reduce its toxicity.<sup>11</sup> Our case developed acute onset focal neurological deficit (hemiparesis) seven days after his fourth cycle of chemotherapy. In a patient with no previous neurological symptoms, such a deficit may alarm us to treat in the line of stroke using antiplatelets and thrombolytics but in an appropriate clinical setting, we should keep in mind the differential diagnosis of stroke mimics. Neurotoxicity with intrathecal methotrexate is one such stroke mimic which may be reversible.

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# Posterior reversible encephalopathy syndrome in childhood Takayasu's arteritis with probable association with tuberculosis

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### ABSTRACT :

Takayasu's arteritis (TA) is a challenging diagnosis in children with unusual presentation and in the absence of typical signs. Posterior reversible encephalopathy syndrome (PRES) is an uncommon presentation of TA. Herein we describe a case of a 14-year-old girl with clinical features and neuroimaging consistent with the diagnosis of PRES. Evaluation of hypertension revealed right renal artery stenosis. TA was diagnosed as per EULAR/PRES consensus criteria for children. Interestingly, the girl had Mantoux induration of 25 mm and to our knowledge only one another case of PRES in association with TA and tuberculosis has been reported.

**KEY WORDS :** PRES, takayasu's arteritis, tuberculosis

### INTRODUCTION :

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological syndrome characterized clinically by headache, vomiting, confusion, seizures, visual abnormalities and reversible abnormalities in the posterior cerebral regions on neuroimaging.<sup>1</sup> Takayasu's arteritis (TA) is a vasculitis of unknown cause that chiefly affects the aorta and its major branches, most frequently in young women.<sup>2</sup> Renovascular hypertension and endothelial dysfunction in TA predisposes these patients to PRES. Herein we describe such a case and discuss pathophysiology.

### CASE REPORT :

A 14-year-old girl presented with severe headache, vomiting, altered sensorium and multiple attacks of generalized tonic-clonic seizures (GTCS). She had been symptomatic for over 1 ½ months with headache,

transient visual blurring and frequent attacks of GTCS. She was found to be hypertensive one month ago. The local physician had been treating her with analgesic (aceclofenac 100 mg) and antihypertensive (amlodipine 5 mg/day) with partial response.

On general examination, the girl had pulse 110/min, regular with no radio-radial or radio-femoral delay and all the peripheral pulses felt equal; blood pressure was 180/140 mm Hg in right upper limb without significant variations in other limbs. Nervous system examination revealed drowsy and disoriented patient with normal funduscopy and on subsequent examination had no loss of visual acuity, color vision or visual field defects and no focal motor-sensory deficits. Examination of the other systems was normal. There was no renal bruit.

Laboratory investigations showed normal blood counts, blood sugar, serum electrolytes, renal function tests, liver function tests and TSH. ESR (120 mm at one hour) and CRP were high. Urinalysis showed hematuria (5/hpf) and proteinuria (200mg/day). Serum ANA, ANCA and viral markers (HIV, HBsAg, Anti-HCV) were negative. Contrast enhanced CT scan of brain, done one month prior to admission, showed diffuse white matter hypodensities in the bilateral occipital lobes partially extending into the parietal lobes (Figure 1-A). Magnetic resonance imaging (MRI) of brain, one month

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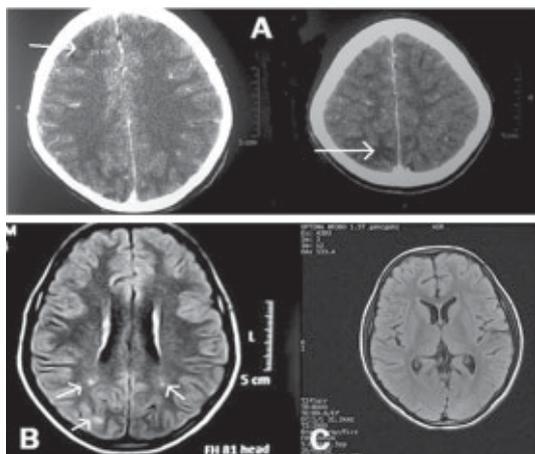


Figure 1 (A) CT brain showing parieto-occipital and frontal hypodensities (B) FLAIR MRI brain showing bilateral occipital hyperintensities (C) Resolution of lesions in MRI brain 2 weeks later

later, showed hyperintensities in bilateral occipital regions on T2-weighted and FLAIR images (Figure 1-B). Ultrasound abdomen with renal Doppler study showed stenosis of right renal artery. CT angiography confirmed renal artery stenosis without involvement of the rest of aorta and its other major branches (Figure 2). Chest X-ray and echocardiography were normal. Mantoux test was strongly positive (induration of 25 mm). Electroencephalography (EEG) showed diffuse cortical dysrhythmia in the form of slowing.

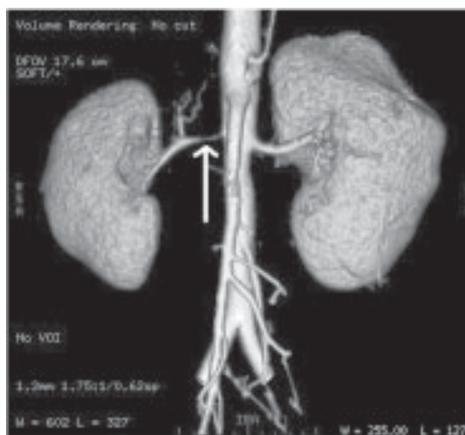


Figure 2. CT angiogram showing right renal artery stenosis

The girl responded to initial treatment with mannitol, furosemide and phenytoin (loading dose followed by 5mg/kg day in divided doses). Blood pressure control was achieved with nicardipine 20 mg/day, and prazosin 10 mg/day. Renal angioplasty and stenting was deferred in view of active inflammation (high ESR) and severe osteal stenosis (99%). She was started on prednisolone (1mg/kg day). In view of strongly positive Mantoux test and immunosuppressive therapy, anti-tubercular treatment

was also initiated. MRI brain, done 2 weeks later, showed resolution of the initial lesions (Figure 1-C). Prednisolone was gradually tapered after one month and now maintained at 20 mg daily. At 3-months follow-up, patient was asymptomatic.

## DISCUSSION :

The pathogenesis of PRES involves altered cerebral autoregulation. Normal cerebral vessels constrict in response to systemic hypertension. PRES occurs when hypertension exceeds this auto-regulatory capacity. The blood brain barrier gets disrupted leading to edema and micro-infarcts.<sup>3</sup> It is thought that the posterior brain is more vulnerable because the anterior circulation is richly innervated by sympathetic nerves from the superior cervical ganglion, while the posterior circulation is relatively devoid of sympathetic innervation. Hypertension may be absent in 20–40% of cases. Alternative mechanism of endothelial dysfunction has been proposed.<sup>3</sup>

TA is a panarteritis that is thought to result from an autoimmune process. Most TA patients possess anti-endothelial cell antibodies that can damage vessels by inducing endothelial inflammatory cytokine production, adhesion molecules, and apoptosis. Most patients of TA present with constitutional symptoms and symptoms and signs related to vascular stenosis/occlusion.<sup>4</sup> However, in children, hypertension is the most common mode of presentation and very often the only manifestation.<sup>5</sup> Hence, new diagnostic criteria for TA (table 1) have been advocated by European League Against Rheumatism/Paediatric Rheumatologic European Society (EULAR/PreS).<sup>6</sup>

Table 1. EULAR/PreS consensus criteria for diagnosis of TA in children  
Angiographic abnormalities (conventional, CT or MR) of the aorta or its main branches (mandatory criterion), plus at least one of the following four features:

1. Decreased peripheral artery pulse(s) and/or claudication of extremities
2. Blood pressure difference >10 mm Hg
3. Bruits over aorta and/or its major branches
4. Hypertension (related to childhood normative data)

Tuberculosis has been implicated in the pathogenesis of TA in view of the high prevalence of infection in affected patients in endemic areas.<sup>7</sup> Our patient had positive Mantoux test. Another case report of PRES with TA had abdominal tuberculosis.<sup>8</sup>

PRES has been reported with TA worldwide.<sup>9</sup> Most of these patients had renovascular hypertension, suggesting its important role in the development of PRES. Most of them had typical signs of TA and were diagnosed

as per American College of Rheumatology (ACR) 1999 criteria. Our patient, in contrast, had only hypertension in addition to neurological diagnosis. Cases have been reported with hypertension and angiographic abnormalities, in the absence of other signs, based on EULAR/Pres criteria.<sup>8, 10</sup>

MRI brain in PRES shows T2-weighted and FLAIR hyperintensities in parieto-occipital regions commonly, although lesions may be seen in the frontal lobe and the cerebellum. Cortical involvement is seen in up to 50 % of cases.<sup>11</sup> Management of PRES involves early recognition, anti-edema measures and adequate control of hypertension. Most patients respond to prompt treatment by 5 – 7 days. However, irreversibility and case fatalities have been reported, especially in children.<sup>12</sup>

TA is treated with steroids and steroid-sparing immunosuppressants.<sup>13</sup> However, the role of immunosuppressants in TA with PRES is controversial, since there are reports of PRES associated with these agents.<sup>14</sup> We used only steroid in our patient on account of her poor financial status. We thought it prudent to add anti-tubercular therapy based on strongly positive Mantoux test, requirement of immunosuppression and endemicity of tuberculosis in our country.

## CONCLUSION :

PRES needs to be recognized as an important presentation of TA. Diagnosis of TA in the children in the absence of typical signs requires high index of suspicion. We recommend screening for tuberculosis in these patients in endemic countries because of its association with TA and requirement of immunosuppression as treatment.

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