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Cancer-Pain.org [Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/.

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CONTENTS

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ORIGINAL ARTICLE

CLINICAL PROFILE OF ACUTE PANCREATITIS WITH INFECTION DUE TO SALMONELLA TYPHI AND HEPATITIS-A IN CHILDREN

Dillip Kumar Das, Suprabha Shukla, Mangal Charan Murmu
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ABSTRACT

Background: Acute pancreatitis is the most common pancreatic disorder in children. The most common association which remains under-evaluation is association of Enteric fever and Hepatitis-A infections.

Objectives: To find out the frequency of acute pancreatitis in children who were admitted with the diagnosis of Enteric fever & Hepatitis -A.

Material & Methods: The present prospective study was conducted in the SVPPG Institute of pediatrics, SCB Medical College, Cuttack, a tertiary care referral institute of Eastern India. Acute pancreatitis was diagnosed by clinical features, biochemical changes (serum amylase and lipase) and ultra-sonographic evidence of pancreatic involvement. Serology for Enteric fever and Hepatitis-A was done

Results: Proportion of children with raised serum amylase in the typhoid fever group was 44.68% (n=21), in the Hepatitis A group was 41.67% (n=15). Comparing these values with the control group showed that the rise in serum amylase levels is statistically more significant ('p' value <0.05). The hyperamylasemia and hyperlipasemia was associated with both typhoid fever and Hepatitis A, but none showed clinical parameter consistent with the acute pancreatitis. The significant rise of pancreatic enzymes was more statistically significant in Hepatitis A group than in Enteric fever group.

Conclusions: Salmonella may be considered as a causative agent of subclinical pancreatitis with biochemical and radiological changes.

Keywords: Enteric fever, hepatitis, pancreatitis, serum amylases, serum lipase

Introduction

Pancreatitis is defined as inflammation of the pancreas resulting in acinar cell injury caused by the destructive effects of pancreatic enzymes. It is a relatively infrequent illness in pediatrics, affecting males and females equally and involving all ages. The etiology of pancreatitis in pediatrics is diverse in nature, with a grossly unpredictable clinical course and prognosis. The diagnosis requires a high index

of suspicion and should be considered in all children admitted with abdominal pain and elevated pancreatic enzymes. The disease is classified into acute and chronic forms or single and recurring episodes, respectively (1).

A wide variety of infectious agents have been associated with acute pancreatitis. Pathologic and radiological evidence of pancreatitis in the course of well documented infection has been associated with viruses, bacteria, fungi and parasites (2). In particular, a high incidence of acute pancreatitis in adult patients with Salmonella infection has been reported by Renner et al (3). In this study, although pancreatic enlargement was demonstrated by abdominal sonography in about half of patients, the course of pancreatitis was mild or moderate with complete recovery. However, many case reports of severe acute pancreatitis during salmonellosis have been reported, suggesting that serious pancreatic disease may represent a complication of Salmonella infection (4-6).

Viral infections may be associated with acute pancreatitis. The virus most commonly identified includes mumps, rubella, coxsackie B, Epstein-Barr and measles virus (7). Pancreatitis complicating infection with influenza A (8) and varicella (9) also has been observed. Hepatitis A was formerly known as infectious hepatitis or epidemic jaundice. It is acute infectious disease caused by Hepatitis A virus. The disease is heralded by nonspecific symptoms such as fever, chills, headache, fatigue, generalized weakness and aches and pains followed by anorexia, nausea, vomiting, dark urine and jaundice (10). Hepatitis A is endemic in most countries, with frequent outbursts of minor and major outbreaks. The exact incidence of the disease is difficult to estimate because of the high proportion of asymptomatic cases. However according to WHO about 10-50 persons per 100,000 are affected annually (11). The exact incidence of HAV in India is not known. The Indian literature is replete with numerous reports of sporadic and epidemic occurrence of the disease in various cities (12). Sood et al (13) presented a case of a 12 year old Indian girl with history of fever, generalized malaise and jaundice since 8 days, severe epigastric pain associated with nausea and vomiting for 1 day. Investigation revealed leukocyte count: 15×10^9/L, direct bilirubin: 3.47 mg/dL, aspartate aminotransferase (AST): 198 U/L (normal 0-38 U/L), alanine aminotransferase (ALT): 249 U/L (normal 0-39 U/L), alkaline phospatase: 459 U/L (normal 39-117 U/L), serum amylase: 2069 U/dL (normal: 0-220 U/dL), serum lipase: 2149U/ml (normal: 0-190 U/ml), IgM HAV antibodies: present. Plain film of abdomen showed distended small bowel loops with no fluid levels. Ultrasonography of abdomen revealed slightly enlarged pancreas with normal echogenecity. On supportive treatment patient started showing respond. After 15 days her biochemical and ultrasonographic parameters returned to normal.

Up till now, only few prospective studies have been reported on pancreatic abnormalities during typhoid fever and hepatitis A infection in pediatric population.

Objectives

To find out the frequency of acute pancreatitis considering clinical features, biochemical changes (serum amylase and lipase) and ultrasonographic evidence of pancreatic

involvement in pediatric population by estimating serum amylase and lipase level in children who were admitted with the diagnosis of either Enteric fever or hepatitis A. Children with fever for at least 3 days and /or jaundice of age group 1 – 15 years and of both sexes were selected randomly and allocated to study and control groups. Serum amylase and lipase level was done in all patients.

Materials and Methods

The present prospective study was conducted in the SVPPG Institute of pediatrics and SCB Medical College, Cuttack, a tertiary care teaching hospital of Eastern India. After obtaining clearance from institutional ethical committee, children in the age group 1 – 15 years and from both sexes attending the OPD and getting admitted were selected at randomly. The study period of study was from January 2017 to December 2019.

Children under study were divided into three groups:

A. Study group-1 (Enteric fever) - Those who had clinical features strongly suggestive of typhoid fever and subsequently confirmed by blood culture and / or Widal test.
B. Study group-2 (Hepatitis A) - Those who had clinical features strongly suggestive of Hepatitis A and subsequently confirmed by estimating IgM HAV in serum.
C. Control group - Those who admitted with fever and /or jaundice and subsequently diagnosed to have disease other than Enteric fever or Hepatitis A.

Inclusion criteria: Children with following conditions were included in the study group:

A. Study group-1 (Typhoid Fever)

Three Major Criteria and three or more Minor Criteria Major Criteria given as below.

Major criteria : (i) Fever, (ii) Headache, (iii) Relative bradycardia

Minor criteria : (i) Pain abdomen, (ii) Splenomegaly, (iii) Diarrhea, (iv) Chills, v. Vomiting

B. Study group-2 (Hepatitis A)- Sclera and skin shows jaundice, history of moderate fever, severe malaise, loss of appetite, nausea and upper abdominal pain, dark colored urine, clay colored stool, tender hepatomegaly, residence in a known typhoid endemic area / history of hepatitis A in other family member or in the community. No apparent source of infection (e.g., typhoid fever, malaria especially falciparum, dengue, leptospirosis as a cause of jaundice, marked elevation of SGOT/SGPT).
C. Control group-Those who admitted with fever and /or jaundice and subsequently diagnosed to have disease other than Enteric fever or Hepatitis A.

Exclusion criteria: Children with following conditions were excluded from the study group:

A. Study group-1(Typhoid Fever)

Past history of enteric fever; past history of pancreatic, renal, liver or salivary gland disease, history of any febrile illness prior to the present illness in the last 1 month, history of immunization with typhoid vaccine. Children who did not have fever during inpatient observation. Children once enrolled for the study were not enrolled for second time in the study.

B. Study group-2 (Hepatitis A)

Past history of jaundice due to any hepatitis virus; past history of pancreatic, renal or salivary gland disease. History of immunization with hepatitis A vaccine, and history of any biliary tract disease, intake of toxin or drugs that causes hepatitis. Children once enrolled for the study were not enrolled for second time in the study.

C. Control group

Past history of either typhoid fever or hepatitis A; past history of pancreatic, renal, liver or salivary gland disease; history of immunization with either typhoid vaccine or hepatitis A; children once enrolled for the study were not enrolled for second time in the study.

The following clinical and laboratory data were recorded in all patients: Detailed history including drug history, past history of suffering from similar illness, immunization history and family history of the concerned disease, and a thorough clinical examination.

The following laboratory investigations were done in all patients: HB, TLC, DC, ESR, Platelet, MP, RBS, CRP, Urea, Creatinine, Sodium, Potassium, Calcium, Liver Function Test including Total Bilirubin (conjugated and unconjugated), SGOT, SGPT and Alkaline Phosphatase.

Serum Amylase and Lipase: 1st time recorded on the 1st day of admission and 2nd time recorded 10 days after. CXR -PA view, straight X-ray Abdomen in erect posture, Mantoux test, Urine for RE/ME and C/S, Stools for RE/ME, USG of the abdomen (especially pancreas).

Special Tests

Blood culture for S.typhi on the 1st day of admission, Widal test on 8th day of fever and above.

For Hepatitis A: IgM anti HAV antibody

For Pancreatitis: Serum amylase estimation: EPS-G7 method, Serum lipase estimation : Turbidimetric method

Serum IgM HAV estimation: ELISA test

Serum amylase and lipase activity of each patient was recorded and methodically plotted. These values then statistically analyzed using the 'z' test. 'P' value less than 0.05 were considered statistically significant. Mean, ranges, standard deviation and frequency were used as descriptive statistics.

Results and Analysis

Table 1: Age group and sex wise distribution of Control group (n=44).

Age Group	Sex		%
	Male	Female	
1 year-5 year	1	2	6.8
6 year-10 year	9	7	36.4
11 year-15 year	14	11	56.8
%	54.54	45.46	-
Ratio	1.2	1	-

In the present study, there were 44 children who had a diagnosis other than enteric fever or hepatitis A. Among 44 children 24 cases (54.54%) were males and 20 cases (45.46%) were females. The male-female ratio was 1.2:1.The mean age of children in this group

was 9.52 years .The age and sex wise distribution of children in control group are shown in table 1 below.

The above table shows that maximum of cases under control group fall in the age group of 11 to 15 years and minimum number in the age group of 1 to 5 years. Of 44 control patients, the main final diagnostic groups were Acute respiratory tract infection (ARI) (17 or 38.6%), Acute Gastro-enteritis (AGE) (12 or 27.2%), Dysentery (9 or 20.6%), Tuberculosis (TB) (3 or 6.8%), Malaria (3 or 6.8%).

Table 2: The age and sex wise distribution of the patients with enteric fever (n=47).

Age Group	Sex		%
	Male	Female	
1 year-5 year	4	5	19.15
6 year-10 year	8	6	29.79
11 year-15 year	13	11	51.06
%	53.2	42.6	-
Ratio	1.14	1	-

A total of 83 cases were included in the study group. Diagnosis of enteric fever was made in 47 children (Study group-1), of whom 18 were blood culture positive and 29 were blood culture negative. Among 47 children diagnosed to have typhoid fever, 25 cases (53.2%) were male and 22 cases (46.8%) were female. The male-female ratio was 1.14:1. The mean age group of children in Enteric fever group was 9.16 years.

The above table shows that maximum number of cases under enteric fever group falls in the age group of 11 to 15 years and minimum number in the age group of 1 to 5 years, males are more affected than the female in enteric fever group.

Table 3: Analysis of Blood culture (Enteric fever) (n=47)

Sex	Blood culture		Total
	Positive	Negative	
Male	11	14	25
Female	7	15	22
Total	18	29	47

The above table shows out of 47 enteric cases 18 were culture positive of which 11 were male (61.11%) and 7 were female (38.89%). Among 25 male patient 11 cases (44%) shows positive result and among 22 female patient 7 cases (38.82%) shows positive result.

Table 4: The age and sex wise distribution of the patients with Hepatitis A (n=36)

Age Group	Sex		%
	Male	Female	
1 year-5 year	11	9	55.56
6 year-10 year	6	7	36.11
11 year-15 year	2	1	8.33
%	52.8	47.2	-
Ratio	1.11	1	-

Among 36 children diagnosed to have hepatitis A, 19 cases (52.8%) were male and 17 cases (47.2.4%) were female. The male-female ratio was 1.11:1. The mean age group of children in hepatitis A group was 5.92. The maximum number of cases under Hepatitis A group fall in the age group of 1 to 5 years and minimum number in the age group of 10 to 15 years. The above table 5 and chart-5 shows that males are more affected than the female in Hepatitis A group.

Table 5: Analysis of serum amylase in the control group (n=44)

Group	Serum Amylase	No of patient	%
A1	Normal	39	88.64
A2	Raised but less than 3 times the normal	5	11.36

A total of 44 patients were included in the control group. Of the 44 cases, only 5 patients had raised serum amylase levels at the time of initial assessment. They were divided into groups based on the magnitude of elevation of serum amylase depicted as follows:

1. Normal value of serum amylase (39 cases: 88.64%) (A1)
2. Serum amylase rose to less than 3 times normal (5 cases: 11.36%) (A2)

The magnitude of the rise in serum amylase levels in patients belonging to the group A2 varied from 103-153 U/L with a mean value of 128±20.66 U/L. On repeat evaluation of the serum amylase value after 10 days, 4 patients (80%) had normalized the raised values while in 1 (20%), the value remained raised to less than twice the normal.

Table 6: Analysis of serum amylase in patients with enteric fever (n=47)

Group	Serum Amylase	No of patient	%
B1	Normal	26	55.32
B2	Raised but less than 3 times the normal	16	34.04
B3	Raised more than 3 times the normal	5	10.64

A total of 47 patients were included in the study group -1 who were diagnosed as Typhoid fever based on blood culture and/or serology. Of the 47 enteric fever patient, 21 patients had raised serum amylase levels at the time of initial assessment. The cases were divided into groups based on the magnitude of elevation of serum amylase depicted as follows:

1. Normal value of serum amylase (26 cases: 55.32%) (B1)
2. Serum amylase rose to less than 3 times the normal (16 cases: 34.04%) (B2)
3. Serum amylase rose to more than 3 times the normal (5 cases: 10.64%) (B3)

The magnitude of the rise in serum amylase levels in patients belonging to the group B2 varied from 146-291 U/L with a mean value of 192±43.88 U/L and to the group B3 it varied from 307-452 U/L with a mean value of 376±47.50 U/L. Thus we find that in the enteric group 21 patients had raised serum amylase values while in the control group only 5 had raised serum amylase levels. Using 'z' test a 'p' value of less than 0.05 was obtained which was statistically significant i.e. hyperamylasemia was associated with a significant number of patients

in typhoid fever compared to the controls.

Serum amylase levels were repeated in these 21 patients after 10 days. The results in the case group are as follows:

1. Of the 16 patients included in the B2 group, 13 had normal serum amylase value; 3 patients showed values which were above the normal range but remained below twice the normal.
2. Of the 5 patients in the B3 group, 4 patients had values in the normal range while 1 had serum amylase value which was above the normal range but was below twice the normal range.

Table 7: Analysis of serum amylase in patients with Hepatitis A (n=36)

Group	Serum Amylase	No of patient	%
C1	Normal	21	58.33
C2	Raised but less than 3 times the normal	11	30.56
C3	Raised more than 3 times the normal	4	11.11

A total of 36 patients were included in the study group 2 who were diagnosed as Hepatitis A cases based on serology. Of the 36 hepatitis A patient, 21 patients had raised serum amylase levels at the time of initial assessment .The cases were divided into groups based on the magnitude of elevation of serum amylase depicted as follows:

1. Normal value of serum amylase (21 cases: 58.33 %) (C1)
2. Serum amylase rose to less than 3 times normal (11 cases: 30.56%) (C2)
3. Serum amylase rose to more than 3 times the normal (4 cases: 11.11%) (C3)

The magnitude of the rise serum amylase levels in patients belonging to the group C2 varied from 123-293 U/L with a mean value of 225±48.22 U/Land to the group C3 varied from 303-442 U/L with a mean value of 387±55.03 U/L.

Thus we find that in the Hepatitis A group 15 patients had raised serum amylase values while in the control group only 5 had raised serum amylase levels. Using ‘z’ test a ‘p’ value of less than 0.05 was obtained which was statistically significant i.e. hyperamylasemia was associated with a significant number of cases in those patients with Hepatitis A compared to the controls.

Serum amylase levels were repeated in these 15 patients after 10 days. The results in the case group are as follows:

1. Of the 11 patients included in the C2 group, 9 patients had values in the normal range while 2 had serum amylase value which was raised but was below twice the normal range.

2. Of the 4 patients in group C3, 3 patients had values in the normal range while 1 had serum amylase value which was raised but was below twice the normal range.

Table 8: Analysis of repeat serum amylase in Control group, Enteric fever patient and Hepatitis A patient in the study group

Group	Serum Amylase		No of patient
	Normal	Raised but less than 3 times the normal	
Control	4	1	5
Enteric fever	17	4	21
Hepatitis A	12	3	15

The above table shows that 5 control patient, 21 Typhoid fever patient and 15 Hepatitis A patient shows raised serum amylase level on initial assessment but on repeat assessment done 10 days after, only 1 control patient, 4 Enteric fever patient and 3 Hepatitis A patient shows mild elevation of serum amylase. Analysis of serum lipase in the control group: None of the patient under control group showed any elevation of serum lipase.

Table 9: Analysis of serum lipase in patients with Enteric fever (n=47)

Group	Serum Lipase	No of patient	%
D1	Normal	39	82.98
D2	Raised but less than 3 times the normal	8	17.02

Of the 47 Enteric fever patient, 8 patients had raised serum lipase levels at the time of initial assessment. The cases were divided into groups based on the magnitude of elevation of serum lipase depicted as follows:

1. Normal value of serum amylase (39 cases: 82.98%) (D1)
2. Serum amylase rose to less than 3 times the normal (8 cases: 17.02%) (D2)

The magnitude of the rise in serum lipase levels in patients belonging to the group D2 varied from 33-79 U/l with a mean value of 53±17.04 U/L. Serum lipase levels were repeated in these 8 patients after 10 days. All values came down to normal range.

Table 10: Analysis of serum lipase in patients with Hepatitis A (n=36)

Group	Serum Lipase	No of patient	%
E1	Normal	19	52.78
E2	Raised but less than 3 times the normal	10	27.78
E3	Raised more than 3 times the normal	7	19.44

Of the 36 hepatitis A patient, 17 patients had raised serum lipase levels at the time of initial assessment. The cases were divided into groups based on the magnitude of elevation of serum lipase depicted as follows:

1. Normal value of serum lipase (19 cases: 52.78 %) (E1)
2. Serum lipase rose to less than 3 times normal (10 cases: 27.78) (E2)
3. Serum lipase rose to more than 3 times the normal (7 cases: 19.44) (E3)

The magnitude of the rise in serum lipase levels in patients belonging to the group E2 varied from 35-87 U/L with a mean value of 57±16.98 U/L and to the group E3 varied from 107-143 U/L with a mean value of 122±14.27 U/L.

Serum lipase levels were repeated in these 17 patients after 10 days. The results in the Hepatitis A group are as follows:

1. Of the 10 patients included in the E2 group, 9 patients had values in the normal range while 1 had serum lipase value which was raised but was below twice the normal range.
2. Of the 7 patients in group E3, 5 patients had values in the normal range while 2 had serum lipase value which was raised but was below twice the normal range.

Table 11: Analysis of repeat serum lipase in patients with Enteric fever and Hepatitis A

Group	Serum Lipase		No of patient
	Normal	Raised but less than 3 times the normal	
Enteric fever	8	0	8
Hepatitis A	14	3	17

The above table shows that 8 Typhoid fever patient and 17 Hepatitis A patient shows raised serum amylase level on initial assessment but on repeat assessment done 10 days after, only 3 Hepatitis A patients show mild elevation of serum amylase.

Table 12: Analysis of serum Amylase and Lipase in the Control group, Enteric fever patient and Hepatitis A patient in the study group

Group	Serum Amylase			Serum Lipase		
	Normal	(↑)	(↑↑)	Normal	(↑)	(↑↑)
Control	39	5	-	-	-	-
Enteric Fever	26	16	5	39	8	-
Hepatitis A	21	11	4	19	10	7

[(↑↑) = more than 3 times the normal; (↑) = less than 3 times normal; (-) = no rise]

It shows 88.64% (n=39) patients under Control group are of normal serum amylase level and 11.36% (n=5) shows mild elevation of serum amylase. In Enteric fever group, 55.32% (n=26) patients shows normal serum amylase, 10.64% (n=5) patients shows significant rise of serum amylase (more than 3 times the normal) and mild rise of serum amylase (raised but less than 3 times normal) found in 34.04% (n=16) patients. In the same group mild rise of serum lipase found in 17.02% (n=8) patients and serum lipase level was normal in 82.98% (n=39) patients. In Hepatitis A group, 58.33% (n=21) patients shows normal serum amylase, 11.11% (n=4) patients shows significant rise of serum amylase and mild rise of serum amylase (raised but less than 3 times normal) found in 30.56% (n=11) patients. In the same group significant rise of serum lipase found in 19.44% (n=7) patients, mild rise of serum lipase found in 27.78% (n=10) patients and serum lipase level was normal in 52.78% (n=19) patients.

Table: 13- Analysis of serum Amylase and Lipase in Enteric fever patient when considered together

Group	Serum amylase	Serum lipase	No of patient	%
F1	N	N	26	55.31
F2	↑↑	↑	4	8.51
F3	↑↑	N	1	2.13
F4	↑	↑	4	8.51
F5	↑	N	12	25.53

[(↑↑) = more than 3 times the normal; (↑) = less than 3 times normal; (N) = normal]

Enteric fever patients were divided into groups based on the magnitude of elevation of

both serum amylase and lipase when considered together depicted as follows:

1. Both the serum amylase and lipase values were within normal range (n=26: 55.31%) (F1)
2. Serum amylase was significantly raised (more than 3 times the normal) with or without rise of serum lipase (n=5: 10.64%) (F2&3)
3. Serum amylase was significantly or mildly raised with mild rise of serum lipase (n=8: 17.02%) (F2&4)
4. Both Serum amylase and lipase was raised mildly (less than 3 times normal) (n=4: 8.5%) (F4)
5. Serum amylase was mildly raised (less than 3 times the normal) without rise of serum lipase (n=12: 25.53%) (F5):

Table 14: Analysis of serum Amylase and Lipase in Hepatitis A patient when considered together.

Group	Serum amylase	Serum lipase	No of patient	%
G1	N	N	19	52.77
G2	↑↑	↑↑	3	8.33
G3	↑↑	↑	1	2.78
G4	↑	↑↑	4	11.11
G5	↑	↑	7	19.4
G6	N	↑	2	5.56

[(↑↑) = more than 3 times the normal; (↑) = less than 3 times normal; (N) = normal]

[(↑↑) = more than 3 times the normal; (↑) = less than 3 times normal; (N) = normal]

Hepatitis A patients were divided into groups based on the magnitude of elevation of both serum amylase and lipase when considered together depicted as follows:

1. Both the serum amylase and lipase values were within normal range (n=19: 52.77%) (G1)
2. Serum amylase and lipase was significantly raised (more than 3 times the normal) (n=3: 8.33%) (G2)
3. Either Serum amylase or lipase was raised significantly (more than 3 times the normal) (n=5: 13.89%) (G3&4)
4. Both Serum amylase and lipase was raised mildly (less than 3 times normal) (n=7: 19.4%) (G5)
5. Only mild rise of serum lipase (less than 3 times normal) (n=2: 5.56%) (G6)

Table 15: Analysis of Ultrasonography of abdomen in the Control group, Enteric fever patient and Hepatitis A patient in the study group.

Group	No of patient showing abnormal pancreas	No of patient	%
Control	0	44	00.00
Enteric fever	2	47	4.26
Hepatitis A	3	36	8.33

The above table shows that none of the patient under control group shows any abnormality on ultrasonography. Among 47 patient of enteric fever only 2 cases (4.26%) shows bulky pancreas whereas only 3 cases (8.33%) out of 36 hepatitis A patient shows bulky pancreas.

Discussion

In the present study, among 47 children diagnosed to have Enteric fever, 25 cases (53.2%) were male and 22 cases (46.8%) were female. The mean age group of children in Enteric fever group was 9.14 years. In our study, of 47 Enteric fever patients, 38 cases (80.85%) were above 5 years of age of which the maximum number of Enteric fever patients (51.06%; n=24) fall in the age group of 11 to 15 years and minimum number (19.15 %; n=9) in the age group of 1 to 5 years. This finding is corroborated with those obtained by Sekarwana et al (14) in their study that 64% of enteric fever patient were above 5 years of age and 51.2% were males. Out of 47 enteric fever patients, only 18 cases (38.3%) were blood culture positive and 29 cases (61.7%) were blood culture negative which corroborated with the observation of Haque et al (15) that the sensitivity of blood culture in typhoid fever was 34.1% where as Tanyigna et al (16) found 28.6% positive & Mogasale et al (17) found 61% positive for blood culture. Our study is similar to the study done by Haque et al (15).

In the present study, the incidence of hyperamylasemia and hyperlipasemia was noted in 44.68% and 17.02% respectively in the Enteric fever group. The mean serum amylase in patients with Typhoid fever with pancreatic involvement was 246.8±82.83 U/L and means serum lipase was 53±17.04 U/L. This figure stands in contrast to the study done by Tossiti et al (5) in which they noted an incidence of 10.2%. None of the patients in the present series developed acute pancreatitis as defined previously. In the observation made by Tossiti et al (5), although hyperamylasemia over four times the normal values was found in three cases in a total of 507 patients, the clinical features of acute pancreatitis were recorded in only one case (0.1%). In another study done by Pezzili et al (18), where they prospectively evaluated the frequency of acute pancreatitis, pancreatic enzyme elevation and morphological pancreatic abnormalities in patients with salmonella infection, the incidence of hyperamylasemia in the case group was calculated to be 6.7%. None of the patients developed acute pancreatitis. The incidence of hyperamylasemia in the control group in this study was also noted to be 6.7% while the same in the present study conducted by us was 11.36%. We found that elevated serum lipase levels above the normal range were 17.02% in the Enteric fever group and in the control group no patient had elevated serum lipase levels. This pattern matches with those, found by Pezzili et al (18) in which they noted elevated serum lipase levels above the normal range in 16.7% in the study group while 3.3% of the patients in the control group had elevated serum lipase values.

Another observation made by Hermans et al (8) in 14 adult Enteric fever patients, clinical pancreatitis was noted in 28.57% (n=4) of cases and biological signs of pancreatitis was noted in 50% (n=7) of cases. In this study, the mean amylase levels noted was 81 IU (range: 30-201 IU) whereas the mean lipase value was 949 IU (range: 468-2000 IU). Renner et al (6) in their study of adult patients demonstrated that 62% of them infected with salmonella had raised amylase and lipase levels. In this study, although pancreatic enlargement was demonstrated by abdominal ultrasonography in about half of patients, the course of pancreatitis was mild or

moderate with complete recovery.

In the present study, 4 patients (8.51%) with Enteric fever showed serum amylase above three times the normal and serum lipase elevation less than three times. In this group, 2 (4.26%) had morphological alteration in the pancreas demonstrated by ultrasonography. In the Enteric fever group, there were 21 patients (44.68%) who had raised serum amylase levels initially. Repeat serum amylase after 10 days revealed that only 4 of them (8.51%) had persistently raised levels of the parameter but none had raised values above three times the normal. Similarly the raised serum lipase values initially were present in 8 patients (17.02%) but repeat examination failed to reveal raised values in any of them. The discrepancy of findings between the previous studies and our study may be explained by the fact that only pediatric population was included in our study as well as there may be other nonspecific infections of gastrointestinal tract which may have infected the pancreas causing hyperamylasemia and hyperlipasemia in patients with Typhoid fever. In the control group, 5 patients (11.36%) had raised amylase levels initially but on repeat examination after 10 days, only one (2.27%) had raised values which were less than thrice the normal values. The serum lipase values were not raised in any of the patients belonging to the control group.

The above noted findings may be explained by the fact that there may be prevalence in the environment of other unknown organisms which may have infected the pancreas but could not be detected. These organisms may be responsible for chronic low grade inflammation of the pancreas which may be present in the asymptomatic form. The elevation of serum pancreatic enzymes during the course of Enteric fever due to Salmonella infection could be explained in several ways. Intestinal inflammation could lead to an increased permeability which allows the reabsorption of macromolecules such as amylase as suggested by Gnadinger et al (19). These authors demonstrated an increased intestinal permeability for oral 51Cr-EDTA in two patients with elevated serum amylase levels in the course of entero-invasive salmonellosis. Hyperamylasemia and hyperlipasemia could also be the result of a reduced excretion due to either impaired renal or liver function (20,21).

Hyperamylasemia and hyperlipasemia could represent the effect of direct pancreatic localization of bacteria through a haematogenous route as suggested by Schmid et al (22). This hypothesis was not confirmed; in fact, Tositti et al (5) found that, in those patients in whom Salmonella typhi was isolated from blood cultures, hyperamylasemia was not detected. Finally, there is also some evidence that Salmonella are present in bile fluid and gallstone cultures (23,24), in this way, bacteria may directly infect the pancreas via the biliary duct system (25). This may explain, at least in part, the presence of hyperamylasemia and hyperlipasemia in our patients infected by salmonella typhi.

Among 36 children diagnosed to have Hepatitis A, 19 cases (52.8%) were male and 17 cases (47.2%) were female. The mean age group of children in hepatitis A group was 5.92 years. The present study shows that maximum number of Hepatitis A patients (55.56%; n=20) fall in the age group of 1 to 5 years and minimum

number (8.33%; n=3) in the age group of 11 to 15 years. This finding is corroborated with those obtained by Singh et al (26) in their study which showed the incidence of Hepatitis A was highest among less than 5 years of age and declined progressively and significantly thereafter. The low incidence of Hepatitis A patient after 10 years of age (8.33%; n=3) may be explained by the fact that very high infection rates in the first few years of life and most of the population acquiring antibodies to HAV by 10 years of age as suggested by Batra et al (27).

In our study hyperamylasemia and hyperlipasemia were recorded in 41.66% and 47.22% of patients with Hepatitis A, respectively. Four patients (11.11%) had serum amylase levels more than thrice the normal values while 7 patients (19.44%) had serum lipase levels three times above the normal range. Only 3 patients (8.33%) in this group had both serum lipase and amylase three times above the normal levels. Morphological alteration in the pancreas was present in all these three patients (8.33%). None of the patients with raised serum amylase and lipase value had significant clinical findings of acute pancreatitis. The mean serum amylase in patients with Hepatitis A with pancreatic involvement was 268.2±76.54 U/L and the mean lipase value was 83.8±35.48 U/L. Repeat serum amylase and lipase was done after 10 days which revealed that out of 15 patients (41.66%) with raised serum amylase level only 3 of them (8.33%) had persistently raised whereas 3 patient (8.33%) out of 17 patient with raised serum lipase level had persistently raised but the repeat values were always less than three times the normal. The above noted finding may be explained by the fact that there may be some degree of cholestasis occurred in Hepatitis A infection.

Very few studies have been done to confirm the association of Hepatitis A with acute pancreatitis. Sporadic case reports have been documented in the existing literature. Therefore, it will be very difficult to compare the findings of the present study with the previous case reports available. However, it has been shown from the present study that there is indeed a correlation between pancreatic involvement and acute Hepatitis A, although the incidence of acute pancreatitis clinically is absent.

Basaranoglu et al (28) reported a young woman with gallbladder sludge and acute pancreatitis due to acute hepatitis A (HAV). A magnetic resonance cholangiopancreatography (MRCP) revealed imaging features of an acute stage of pancreatitis and gallbladder wall thickness with coexisting sludge in the gallbladder lumen. HAV infection was diagnosed by the detection of immunoglobulin M against HAV in the serum. In this case, they observed reversible changes in the hepatobiliary and pancreatic system, which was related to the severity of hepatic necro-inflammation. HAV-associated pancreatitis may be due to the formation of biliary sludge during the acute phase of the viral illness.

Sood et al (13) presented a case of a 12 year old Indian girl with history of fever, generalized malaise and jaundice since 8 days, severe epigastric pain associated with nausea and vomiting. IgM HAV antibodies were present. Ultrasonography of abdomen revealed slightly enlarged pancreas with normal echogenecity. On supportive treatment patient

started showing respond. After 15 days her biochemical and ultrasonographic parameters returned to normal.

Lopez Morante et al (29) reported a boy with fever and jaundice, with distended, tender abdomen and absent bowel sound. IgM HAV antibodies were present. The 24 hours urinary amylase content was 27,600 U/L and the amylase/creatinine clearance ratio was 7.1% (normal <5%). On discharge, bilirubin and amylase returned to normal values.

Shrier et al (30) described a 4-year-old Korean girl who was admitted in hospital for intermittent severe supraumbilical pain radiating to periumbilical region for 1 day. On examination she was found to have jaundice, mild periumbilical tenderness with hepatomegaly. IgM and IgG HAV antibodies were present. Ultrasonography of abdomen revealed increased echogenecity and thickening of entire pancreas and a prominent pancreatic duct. Computed tomography scan showed a diffusely swollen pancreas. On supportive treatment patient started showing respond from 4th day. After 1 month of discharge, ultrasonographically pancreas appeared normal. By 11 weeks of onset, liver functions and pancreatic enzyme findings were within normal limits.

Even if the mean elevation of serum amylase and lipase in our patients with Hepatitis A was lower than that reported by others (13,29,30), our study confirms that hyperamylasemia and hyperlipasemia can be found in patients with hepatitis A.

The mechanism by which hepatitis A virus may cause pancreatitis is unknown. The cytopathic effect may be direct or it may be mediated through the patient's immune response. Animal studies of other viral infections and pancreatitis have suggested either direct inflammation and acinar cell destruction (31,32) or edema of the ampulla of Vater causing obstruction of pancreatic outflow (33). When acute pancreatitis is associated with fulminating hepatitis, the virus may cause tissue damage directly, but there are several other factors which can play an important role in the development of pancreatitis and these include acute liver failure, hypotension and drug induced disease. These factors were not operated in our present study and the pancreatic damage could only have been caused by HAV. Autodigestion may play a role in potentiating pancreatic damage (34). In our study no coincidental causes of acute pancreatitis, such as alcohol abuse, gallstone disease, drug or toxin induced pancreatic injury, trauma, or anomalies of the panereaticobiliary tree, were evident.

Conclusions

The hyperamylasemia and hyperlipasemia was associated with both Enteric fever and Hepatitis A patients but none showed clinical parameter consistent with the acute pancreatitis and the significant rise of pancreatic enzymes was more statistically significant in Hepatitis A group than in Enteric fever group.

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ORIGINAL ARTICLE

THERAPEUTIC HYPOTHERMIA IN ASPHYXIATED NEONATES USING PHASE CHANGING MATERIAL

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ABSTRACT

Background: Birth asphyxia leading to Hypoxic Ischemic Encephalopathy (HIE) is a common problem in our country. Therapeutic Hypothermia (TH) for management of birth asphyxia and HIE has been used since 2005 and has become a standard of care for these babies in developed countries.

Objective: To assess whether phase changing material using Mira Cradle can provide Therapeutic Hypothermia (TH) for 72 hours and to determine short term outcome in babies with Hypoxic Ischemic Encephalopathy (HIE) in our population.

Methods: This was a 3 year retrospective study from March 2016 – March 2019 carried out in a tertiary care NICU in Rourkela. 72 babies having HIE II or HIE III with pre-defined inclusion criteria were given TH compared with 97 babies having HIE II or HIE III who could not be given TH. The efficacy of Mira Cradle was judged by time taken to reach target temperature and percentage of deviations from the same. The efficacy of TH was judged by mortality, need for ventilation, Anti Epileptic Drugs (AED) usage, feeding and neurological status at the time of discharge. Pearson's Chi Square Test for independence using statistica 8.0 (StarSoft Inc.) was used to analyze differences between groups.

Result: The results show that Mira Cradle is an effective equipment for TH. The average time taken to reach target temperature of 33.5^0C was 39.2 minutes. It reduces mortality and morbidity and leads to better neurological outcomes especially in HIE II babies.

Conclusion: Mira Cradle to provide TH is an excellent alternative in financially constrained tertiary care NICU's. Short term outcomes in HIE II babies are favorable and strongly advocated as an additional treatment modality in Birth Asphyxia. However better outcomes are still awaited in HIE III babies.

Keywords: Birth Asphyxia, Therapeutic Hypothermia, Phase Change Material, Mira Cradle, HIE

Background

Birth asphyxia leading to Hypoxic Ischemic Encephalopathy (HIE) is a common problem in our country with incidence reported to be about 16-20/1000 live births (1,2). Therapeutic Hypothermia (TH) for management of birth asphyxia and HIE has been used since 2005 and has become a standard of care for these babies in developed countries (3-5) In India it has been used since 2009 in some form or the other in a few places (6-8) There are various reasons why it has not come into vogue in our country and one of the important factors is the cost of imported servo controlled equipment like Tecotherm/ Criticool (9,10). This exorbitant cost may not be viable for many NICU's especially in semi urban areas. Now with the availability of Indian made Mira Cradle (manufacturer Plus Advance Technologies) using phase change material, it has become possible to start using TH for these babies, the cost and maintenance being easy and affordable (8,9).

The objectives of our study was whether phase change material using Mira Cradle can provide effective TH for 72 hours and whether, in our population TH actually helps babies with HIE at least in the short term.

Materials and Methods

A retrospective study design was used on data collected from the period of March 2016 – March 2019. The study setting was a tertiary care neonatal centre in Rourkela called Aastha Mother & Child Care Hospital. The NICU temperature was kept between 26^{o}C to 28^{o}C.

The inclusion and exclusion criteria were based on guidelines given by the manufacturer (Plus Advance Technologies) in association with CMC Vellore (9) in which the neonates had any one of the following criteria: >35 Weeks, Birth Weight >1800 gms, Apgar score <5 at 5 min / <6 at 10 minutes, did not cry at birth/ required resuscitation for at least 10 minutes (out born), moderate to severe encephalopathy (modified Sarnat) / altered state of consciousness at presentation, pH < 7.1 at 1 hr of life, base deficit >12 at 1 hour of life, h/o acute perinatal event – fetal distress with abruption placenta/cord prolapse/ uterine rupture **and** at least **one** of the following: hypotonia, abnormal reflexes including oculomotor/pupillary abnormalities, absent or weak suck, or clinical seizures.

The exclusion criteria were: >6 hrs of birth, birth weight <1800 gms, life threatening coagulopathy or imperforate anus.

A total of 240 babies were studied, the details of whom studied are provided in Table 1. Of these babies, 72 babies met the criteria for Therapeutic Hypothermia. TH was performed in three phases namely induction phase, maintenance and rewarming. They were maintained at a temperature of 33.5^{o}C ± 0.5^{o}C for 72 hours with gradual rewarming over 8 – 12hrs (0.2–0.5^{o}/hr) till 36.5^{o}C rectal temperature was reached. The rectal temperature was further monitored for a period of 24 hours to prevent overshoot hyperthermia.

The indications to stop cooling prior to 72 hrs are as follows: persistent hypoxemia in 100% O_2, life threatening coagulopathy, arrhythmia requiring medications, irreversible brain death or PPHN.

Table 1: Details of babies with birth asphyxia in the present study

	Number of babies (%)
Total with birth asphyxia with HIE II/III	240 (100%)
TH given (HIE II – 37 HIE III -35)	72 (30%)
Within those given TH	
Male	51 (70.83%)
Female	21 (29.17%)
LAMA	14 (19.44%)
Ventilation given	20 (27.78%)
TH not given (HIE II -68 HIE III – 29)	168 (70%)
Within those not given TH	
LAMA	36 (21.43%)
Bleeding complications/ congenital anomalies/ preterm	35 (20.83%)

Babies were assessed by a Pediatrician on being admitted to the NICU and categorized as HIE II or HIE III based on modified Sarnat Staging (moderate/severe encephalopathy). There could be some error in the assessment as many of the babies especially those reaching late were already given Anti Epileptic Drugs (AED) or having metabolic complications by the time they reached the hospital. If required the babies were put on invasive ventilation. Once decision and consent were taken the rectal temperature was measured and arterial blood gas (ABG) done. The babies were put on the Mira Cradle as per the instructions of the manufacturer. The Mira cradle is a polyethylene based cradle manufactured by Plus Advance Technologies Pvt Ltd., based in Gurgaon, India. It is supplied with two types of phase change material (PCM) packs, FS29 and FS21 and a conduction mattress. The packs are kept in the refrigerator and made ready for use utilizing the temperature indicator provided on the PCM packs. Both rectal and axillary temperatures were measured every 15 minutes for 1 hour, and hourly thereafter. If by 30 minutes, the target temperature was not reached FS21 was used. Neonates having temperatures less than 32.5^0C were initially gradually warmed under radiant warmer till they reached the target temperature. Investigations and monitoring were done as per protocol and necessary action taken.

Table 2: Investigations and Lab Monitoring

	Baseline	24 Hrs	48 Hrs	72 Hrs
ABG	+	+		+
S. Electrolytes		+		+

S. Creatinine		+	+
PT/PTT	+	+	+
Hb/TC/DC/Plt	+	+	+
SGPT/SGOT	+		+
ECG	Any time if HR < 80/min or arrhythmia		

After completion of TH and rewarming, the babies were followed up closely in the NICU/wards and neurological assessments done daily as well as at the time of discharge. Important evaluations were use of AED/ feeding/NNR especially Moro's reflex/tone. The short-term outcomes of those babies with HIE II/III during the same period who could not be given TH which were mostly due to delayed referral or other co-morbidities. The babies with bleeding and congenital anomalies were excluded from the study.

Efficacy of Mira Cradle was judged by time taken to reach target temperature (rectal) and percentage of deviations from the desired temperature range (33□ - 34□) Effect of TH on short term neurological outcomes in HIE II/III babies was assessed by mortality, use of AED, feeding (tube or breast and spoon), tone and NNR esp. Moro's reflex and sucking reflex.

Statistical Analysis

For analysis of whether the two groups differed based on a criterion, Pearson's Chi-Square tests for Independence were conducted using Statistica 8.0 (StatSoft Inc.). A difference between the groups, significant at $p<0.05$, was considered indicative of a statistically significant difference.

Results

Effectiveness of Mira Cradle: The time taken to reach target temperature ranged from 15mins – 2hrs, average time being 39.2 mins. This depended on the rectal temperature at admission which varied from 28.8^{o}C to 37.5^{o}C. The average temperature recorded on admission was 35.3 ± 1.8^{o}C. This is better than servo controlled systems which took 90 mins to reach target temperature (3). The percentage of temperature fluctuation (<33^{o}C - >34^{o}C) when measured hourly was only 3.02%. This is also better then the servo-controlled systems in the TOBY and NICHD trails (10%) (3,11,12). 25 babies were hypothermic on admission.

The time after birth to start TH and their outcome is represented in Table 3.

Table 3: Effect of time after birth to start TH on outcomes in babies with birth asphyxia

Outcomes	Time after birth to start TH		Pearson Chi-square	Effect of time on outcome (p-value)
	< 3 hrs (N = 50)	**3 - 6 hrs** (N = 21)		
Death	12.00%	14.29%	0.07	p = 0.79

Complications	18.18%	16.67%	0.02	p = 0.89
AED Required	2.00%	4.76%	0.41	p = 0.52
Tubefeeding Required	5.56%	26.67%	4.55	p = 0.03*
Abnormal Neurological Examination	38.89%	40.00%	0.01	p = 0.94

**P < 0.05.*

When babies were started on TH early, i.e. < 3 hours after birth, the feeding outcomes were significantly better (Table 3) reflecting a better long-term neurological outcome (13, 14). Outcome of Babies of Birth Asphyxia with HIE II/III: While comparing the outcomes of babies with HIE II/III given TH it was found that there was a significant difference in all parameters measured except complications (Table 4). As expected, the outcomes of babies with HIE III were poorer than HIE II.

Table 4: Difference between outcomes when given TH to babies at different stages of HIE.

Outcome	Stage of Disease		Pearson Chi-square	Difference between stages when given TH (p-value)
	HIE II	**HIE III**		
Death	6.06%	27.59%	5.29	p = 0.02*
Ventilation	10.81%	45.71%	10.92	p <0.01*
Complications	11.43%	18.52%	0.62	p = 0.43
AED Required	3.70%	21.43%	3.29	p = 0.07*
Tube feeding required	7.41%	35.71%	5.22	p = 0.02*
Abnormal Neurological Examination	14.81%	71.43%	13.14	P = 0.002*

**P< 0.05.*

TH had to be stopped in 9 babies for the following: persistent bleeding (6), persistent bradycardia (1), and irreversible brain death (2).

The outcomes of babies who could not be given TH were also compared. It can be clearly seen (Table 5) that there is a significant effect of TH on outcomes in babies with HIE II. However, when comparing HIE III babies, though there is no statistical significance, the trends show a promise that TH has resulted in more positive outcomes (Table 4). Given that the sample sizes for these groups were fairly low, this hypothesis can be validated better with larger sample sizes.

Table 5: Difference between outcomes when TH given or not given to babies at different stage of HIE.

Outcome	Therapeutic Hypothermia given/not given		Pearson Chi-square	Effect of TH on Outcome (p-value)
	Given	**Not Given**		
Death	6.06%	8.8%	0.59	p = 0.44
AED Required	3.70%	38.81%	11.58	P<0.01*
Abnormal Neurological Examination	14.81%	44.78%	7.48	P<0.01*
	Given	**Not Given**		
Death	27.59%	34.14%	0.09	p = 0.76
AED Required	21.43%	36.36%	0.90	p = 0.34
Abnormal Neurological Examination	71.43%	81.82%	0.53	p = 0.47

**P< 0.05.*

Discussion

Birth asphyxia leading to HIE is an important cause of morbidity and mortality faced by most Pediatricians in our daily practice (1,2,12). Over the years, apart from supportive care, only one definite modality of treatment has emerged that is Therapeutic Hypothermia which has now become the mandatory standard of care in developed countries (3-5). We in India face a larger burden of this problem and there is an urgent need to implement the same in our settings. This study demonstrates that using more economical alternatives like Phase Change Material (Mira Cradle) it is very much feasible to practice TH with well defined protocols in tertiary care NICU's (9). Our study also had a controlled group of neonates who could not be given TH mostly because of delayed referral to our center. It is extremely important to sensitize our Pediatricians to transport all such babies urgently so that they reach the center definitely within 6 hours (13,14). This will also call for better Neonatal transport facilities and can be worked upon with the baby being transported in Mira Cradle as it also doesn't require electricity. We had a fairly large number of babies given TH with HIE III (35) which could be compared with HIE II (37). The study showed that the HIE III babies do not fare as well as HIE II babies despite TH. More controlled studies for additional interventions in this group are ongoing in various centers and hopefully may benefit these neonates (15-17).

This study had some limitations such as absence of Amplitude-integrated EEG (aEEG), effect of confounding factors such as sepsis. The

study has also not dealt with long term follow up data as it has only looked at the feasibility and easily appreciated short term outcomes which could be practiced by any Pediatrician.

Conclusions

Mira Cradle using PCM technology to provide TH is an excellent alternative in financially constrained tertiary care NICUs where the population requiring treatment for Birth asphyxia are largely from extremely disadvantaged backgrounds.

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REVIEW ARTICLE

INFLUENZA VACCINATION IN PREGNANCY AND ITS BENEFITS ON FETUS AND INFANTS

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ABSTRACT

Influenza occurs in all ages. For infants under 6 months of age the infection is pretty serious. The rate of hospitalization in infants <6 months of age due to Influenza and associated illness is similar to that of adults and older children. The Influenza vaccine is available only after 6 months of age. Severe maternal influenza results in increased incidence of stillbirth, infant death, emergency caesarian section delivery, low birth weight and small for date neonate delivery. Studies have demonstrated that in case of 83.3% of severe maternal influenza illness the infants either required ICU admission or died due to severe illness. The WHO and ACOG recommended the use of inactivated influenza vaccine as an essential element of prenatal care during pregnancy. Studies reported that vaccinating pregnant women with inactivated influenza vaccine during 2nd and 3rd trimester is safe and provides protection to the mother, the fetus, the neonate and infants under 6 months of age. The CDC recommends immunizing pregnant women with inactivated influenza vaccine, as soon as it is available, during any trimester of pregnancy to protect the mother against influenza illness and their to-be-born babies until 6 months of age through trans-placental transfer of antibodies.

Keywords: Influenza, Immunization, Pregnancy, Newborn outcomes, Vaccine safety, Maternal influenza, TIV (trivalent inactivated vaccine), QIV (quadrivalent inactivated vaccine), LAIV (Live attenuated influenza vaccine).

Introduction

Influenza, commonly known as “the flu” is an infectious disease of the respiratory tract. In most cases (90%), it is a self-limiting benign respiratory febrile illness with duration of 1-2 weeks but some high risk groups manifest more severe illness with high case fatality such as pregnant ladies and very young child below 2 years. It is a dreaded illness for infants under six months of age. Infants of less than six months of age have the highest rate of hospitalization due to influenza and associated illness (1), with estimates of 9-10 per 10,000 infants of less than 6 months of age which is similar in comparison

to rates reported in adults above 80 years of age (2). Influenza vaccine is not effective at this age and is recommended only at the age of 6 months (3,4). The most favored evidence-based strategy is to immunize pregnant women with inactivated influenza vaccines which help in protecting the babies from flu illness for the first several months after birth (3). Millions of pregnant women have been immunized with influenza vaccine over several decades with a good safety record (5).

Epidemiology

Influenza occurs mainly due to the most important human respiratory pathogens namely Influenza A and B virus. These viruses are usually transmitted by aerosols and droplets, originated from the respiratory secretions of affected persons. It may also spread through contact with fomites contaminated with the virus. Both type A and type B influenza viruses are capable of causing seasonal influenza epidemics as well as non seasonal sporadic cases and outbreaks (6-8). Tropical countries like India experience influenza infection perennially with more irregular outbreaks. In temperate regions, during the winter, the seasonal epidemics are usually encountered.

Influenza A viruses are also capable of causing pandemics globally by rapid spread of new influenza A subtypes through person-to-person transmission and are altogether different from the already circulating strain to escape control by strain-specific immunity existing in the general population. Major pandemics have occurred at intervals of 10-40 years since the middle of the 18th century. Notable pandemics in 20th century were H1N1 (designated as Spanish flu) during the year 1918, H2N2 (known as Asian flu) during 1957 and H3N2 (Hong Kong flu) during 1968. Spanish flu pandemic of 1918 was very severe resulting in an estimated 20-40 million or more deaths globally. The global outbreak in 2009, due to A(H1N1) strain nomenclature as A(H1N1)pdm09 acquired pandemic status but it gradually receded to a seasonal form of influenza in 2010. The first positive case of pdm H1N1 was recorded in May 2009 in India which resulted in 20,604 cases and 1,763 deaths by the end of 2010 (9). During the pandemic period of 2009-2010, India experienced three waves, 1st one in September, 2nd one in December and the 3rd and final peak in August 2010 culminating the end of pandemic4.

Pathogen

Influenza virus, an orthomyxovirus and capable of affecting humans, birds and animals, is characterized by a single-stranded, segmented RNA genome. The influenza viruses are classified as type A, B and C according to their nucleoprotein basis. The subtypes are determined on the basis of hemagglutinin (HA) and neuraminidase (NA). Type A virus causes moderate-to-severe illness in humans affecting all age groups and also in other animals where as type B causes milder disease in humans particularly affecting children. Type C virus rarely causes illness in humans and also does not produce epidemics.

These viruses possess high mutation rates contributing to significant variability of the HA and NA antigens. Minor mutations resulting very little changes in the HA gene and known as “Antigenic drift” occur frequently enabling the virus to escape immune recognition and causing seasonal outbreaks during inter-pandemic years.

Re-assortment of genetic material (the HA gene in particular) from different A sub types mainly causes major changes in the HA antigen known as "Antigenic shift". The absence of viral reservoirs in animals prohibits the type B influenza virus to exhibit antigenic shifts. Though the type B viruses do not divide into subtypes, co-circulation of two antigenically distinct lineages has been documented from different parts of the world (6-8).

Disease burden

Globally the estimated annual attack rate of influenza is around 5-10% in adults and 20-30% in children3. Children under the age of 5 years particularly those aged less than 2 years, have a high incidence of influenza. A systematic review of global influenza disease burden in a total of 8 million children aged <5 years in 2008 estimated existence of 90 million (95%, CI 49-162 million) new cases of seasonal influenza, 20 million (95%,CI 13-32 million) cases of influenza-associated acute lower respiratory infections (ALRIs), including 28,000-111,500 deaths (6). The incidence of influenza episodes and death due to influenza was found to be much higher in developing countries as compared to developed nations (6). A systematic review covering a span of 30 years of seasonal influenza epidemiology in sub-Saharan Africa demonstrated, influenza on average accounting for approximately 10% (range 1%-25%) of all out patients visits and for about 6.5% (range 0.6%-15.6%) of hospital admissions for acute respiratory infections in children (7). A recent systemic review demonstrated association of influenza with 10% (95% CI, 8-11%) hospitalization due to respiratory illness in children aged <18 years globally, ranging from 5% (95% CI, 3-7%) among children <6 months to 16% (95% CI, 14-20%) among children 5-17 years. It was estimated that influenza occurs approximately in 374,000 (95% CI, 264,000-539,000) hospitalization in children of <1 year and that too 228,000 (95% CI, 150,000-344,000) in children aged <6 months annually (8). The rates of pre-school-aged children hospitalization in USAare similar to that of persons aged 50-64 years. In one study by Neuzil et al hospital admission rates were found to be 240/100,000 among infants <6 months and 20/100,000 among children 2-5 years of age (1).

There is lack of adequate data on the prevalence and disease burden of influenza in India. However as per the published data influenza contributes to approximately 5-10% of all ARIs. One report published in 2009described contribution of influenza in almost 1.5%-14.5% of all ARI episodes (9). A recent study by Saha et al in 2018 from rural North India found ILI in children aged <5 years to be 13 (95% CI, 4%-29%) per 1,000 person years.

There is increased risk of severe illness and death among pregnant ladies due to influenza which in turn may also cause complications like stillbirth, neonatal death, pre-term delivery and decreased birth weight (10).

Influenza Vaccine

Two types of vaccines i.e. Inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV) are available. The trivalent influenza vaccine (TIV) incorporates antigens from two influenza A strains H1N1 and H3N2 and one from influenza B strains either Yamagata or Victoria where as two influenza A strains and both Yamagata and Victoria strains of type B are present in the quadrivalent

inactivated vaccine which offers protection against both the B-type lineages, responsible for infection in humans (11). In USA, one quadrivalent live attenuated vaccine containing two influenza type A and two type B strains was licensed in 2012 for intranasal application. Only TIVs are licensed to vaccinate children under 2 years of age, persons aged 50 years or more and pregnant women. Non-pregnant persons of 2-49 years of age can be vaccinated with either TIV or LAIV depending upon their country's national immunization policy. The LAIV influenza vaccine manufactured in Russia has been licensed for use for individuals of 3 years of age or more (3).

Impact of influenza on Outcomes of Pregnancy

Pregnancy itself is considered as a high risk for severe illness. Influenza can result in serious illness and the effect on pregnancy outcome is quite detrimental (12). Zaman et al reported fetal malformations and other illnesses due to influenza infection in pregnancy (13). As per a study by Newsome et al in USA, 63.6% of influenza infected severely ill pregnant women had preterm deliveries and 43.8% had low birth weight babies as compared to the national averages (14). Also severe maternal influenza during pregnancy results in stillbirth, infant death, emergency caesarian delivery, low birth weight and decreased weight for gestational age babies (12).

Impact of Maternal Influenza During Pregnancy on Newborn

It is a well known fact that infants, during their early months of life, are protected against infection through placentally transferred maternal antibodies. Maternal influenza infection during pregnancy adversely affects the infants. Creanga et al in a study reported that infants of 83.3% of severely infected mothers, either required ICU treatment or died (15). Prematurity and/or complications during delivery results in prolonged hospital stay of the affected infants. Non-specific symptoms like poor feeding, vomiting, diarrhoea, fever, dyspnoea and irritability are also encountered (16). A study from Bangladesh, a perennially influenza affected country, showed about 33% of infants below 6 months as serologically positive for influenza virus infection (17). In case of these influenza virus positive infants,occurrence of pneumonia is very common, and this co-infection with pneumococcus is very much detrimental for them.

Protection from Influenza in Infants <6 months of Age

The inactivated influenza vaccine, TIV or QIV, is safe and has played a major role in providing effective means to combat influenza in infants and children of 6 or more months of age (12,18). But in infants below 6 months of age who are at highest risk for severe disease, preventing influenza is quite tedious and difficult as influenza vaccines are not licensed or recommended for infants below 6 months of age (19) and Walter et al in a study pointed out their variable immune response and unclear vaccine effectiveness (20). Besides practicing exclusive breast feeding, meticulous hand hygiene and maintaining physical distance from and avoiding contact with influenza infected people, two different immunizationstrategies have been undertaken like 'cocooning' (immunization of postpartum women and the household contacts

of the particular infant) and immunization of women during pregnancy. Cocooning programs are difficult to carryout in real set up and is not cost effective and have met with limited success. The maternal immunization during pregnancy provides the major portion of infant's protection against influenza (21).

Maternal Influenza Vaccination During Pregnancy

Since 2005, WHO has recommended vaccination of pregnant women with inactivated influenza vaccine (22). Another WHO position paper in 2012 again emphasized the importance of vaccination in pregnant women (3). The Advisory Committee on Immunization Practices (ACIP) has recommended use of inactivated influenza vaccine during pregnancy without any specific formulation (23). The American College of Obstetricians and Gynecologists (ACOG) also recommends administration of inactivated influenza vaccine to all pregnant women during the influenza season (24). The influenza vaccination has been designated as an essential element of prenatal care. To assess the clinical effectiveness of influenza vaccine, during the period of August 2004 to May 2005, a randomized trial named as The Mothers Gift, was carried out in Bangladeshconsisting of 340 randomized pregnant women who received one dose of inactivated influenza vaccine in third trimester. Results showed a significant (63%) reduction of laboratory-confirmed influenza, 29% reduction in febrile respiratory illness in infants and also less maternal respiratory illness with fever (36%) as compared to the control group (13,16).

Safety of Vaccine

The trivalent inactivated influenza vaccine has been reported to be safe for administration during pregnancy. Numerous clinical trials and observation studies and data from safety reporting systems have shown consistently the safety of influenza vaccination to pregnant women (25-29). Regan et al in a study, conducted in 2012-2013, demonstrated significantly fewer hospitalization incidence in vaccinated pregnant women than non-vaccinated pregnant women (30). Several observational studies and four large-scale randomized control trials reported neonatal protection due to influenza vaccination of pregnant women (13,31-33). Reduction in incidence of influenza infection related hospitalization was reported in infants born to influenza vaccinated mothers during pregnancy (34,35). RCT studies conducted in USA and Bangladesh did not report any significant adverse effects, nor any increase in the likelihood of fetal, perinatal or infant complications as a result of vaccine administration (3). The CDC recommends a flu shot in any trimester of pregnancy to the pregnant women to protect themselves and their, to be born babies till 6 months of life through transplacental transfer of protecting antibodies (36). Till date no scientific evidence has been found regarding causation of any adverse outcome of pregnancy due to presence of thiomersal, a mercury-containing preservative in the multi-dose vials. Therefore, ACIP does not recommend any preference for vaccines not containing thiomersal (23). The ASO3 adjuvant, present in the vaccine formulations used in Nordic countries in the pandemic period and responsible for more cases of narcolepsy/cataplexy, is not present in any currently available vaccine (3). A small

retrospective case-control study by Donahue et al suggested a possible co-relation between administration of A/H1N1 pdm component influenza vaccine in the 1st trimester of pregnancy in the previous influenza season and subsequent spontaneous abortion (37). This co-relation has not been reported during other seasons and other versions of influenza vaccine. Due to several significant flaws in this study, lack of evidence of biological plausibility and other data showing no association, influenza vaccine is recommended in any trimester (37,38). At present, a pregnant woman should be immunized with any licensed, recommended, age-appropriate, inactivated influenza vaccine during any trimester (39). Both, the tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine and influenza vaccines can be administered in the same sitting at different sites. Breastfeeding women if not vaccinated during pregnancy, can safely receive influenza vaccine (24). CDC recommends to vaccinate breast feeding mothers against flu to protect the mothers against acquiring the disease themselves and passing influenza to their infants (23,36). Currently, quadrivalent inactivated influenza vaccines are available. Both trivalent and quadrivalent inactivated vaccines can be used because ACIP does not preferentially recommend a specific formulation (23). The ACOG and CDC recommend that all pregnant women and to be pregnant women should be immunized with inactivated influenza vaccine during the influenza season as soon as the vaccine is available (14).

Conclusion

It has been proved beyond doubt that influenza illness has a deleterious effect both on the pregnant women and their infants. No vaccine is available to protect the infants from birth till 6 months of life as the earliest recommended age of first flu shot is at 6 months. Immunization of pregnant women with inactivated flu vaccine has been well studied and found to be safe and has protective effects both for the mother and the child before birth and till 6 months after birth because the infant is protected against flu through placentally transferred antibodies from the mother. Therefore, the best evidence-based strategy is to immunize pregnant mothers with QIV or TIV to protect infants below 6 months of age against flu. However, other preventive strategies like exclusive breastfeeding, maintenance of scrupulous hand hygiene, maintaining physical distance from and avoidance of contact with flu infected individuals and immunization of close contacts of the infant should be meticulously followed to protect the vulnerable group.

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Conflict of Interest- Nil

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PERSPECTIVE

SLEEP DEPRIVATION: THE NEW TRIGGER FOR CHILDHOOD OBESITY

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ABSTRACT

Childhood obesity is a newly emerging pandemic in the current scenario. It is one of the most evident, yet neglected public health problems. In the past few years, the burden of childhood overweight and obesity is on the rise not only in developed countries, but also in developing countries. Unlike the non-modifiable risk factor like genetic inheritance, we have a long list of modifiable risk factors that can be timely intervened. Numerous studies have been conducted to establish this fact. Sleep deprivation is one of the major risk factors for obesity and obesity in turn leads to sleep problem. In this COVID era, children are bearing the major brunt, being restricted at home, plugged onto hours of online classes and wavered off all extra-curricular physical activities, which has implications for getting them put extra weight resulting in obesity.

Keywords: Obesity, sleep problems, modifyble risk factors, non-communicable disease.

Childhood obesity is a newly emerging pandemic in the current scenario. It is one of the most evident, yet neglected public health problems (1). In the past few years, the burden of childhood overweight and obesity is on the rise not only in developed countries, but also in developing countries. Unlike the non-modifiable risk factor like genetic inheritance, we have a long list of modifiable risk factors that can be timely intervened. Eating junk food, drinking carbonated beverages, limited physical activity and prolonged screen time are the already known culprits, contributing to the alarming rise in childhood obesity. Since time immemorial, the conventional focus is on nutrition and physical activity as preventive measures (2,3). Numerous studies have been conducted to establish this fact.

In the recent few years, researchers have come up with a unique co-relation between sleep duration and childhood obesity. Both extreme ends of sleep; inadequate sleep and excessive sleep are detrimental to physique by contributing to obesity. Earlier, excessive sleep duration, thereby prolonged periods of physical inactivity, was associated with obesity, in contrast to our

present belief that sleep deprivation is also a major factor. Many studies done outside India and few within the country bear witness to this fact. In concordance with the growing burden of overweight and obesity, the incidence of chronic sleep deprivation is on the rise (4). This is a major breakthrough on account of the fact that sleep is a modifiable risk factor and active interventions to maintain sleep hygiene can go a long way in preventing childhood obesity.

A large North Indian study based on Global School Health Survey, conducted among 13 to 15 years old age group by Faizi et al (5) at Aligarh, found that inadequate sleep is a triggering factor for obesity, even in developing countries. Gujarati adolescents between 16 - 18 years old , who had sleep deprivation at night suffered from high body fat percentage and total body fat mass (6). Based on International Obesity Task Force (7) standards, overweight was detected in South Indian children between 6 - 16 years age group who slept inadequately. Various studies from developed countries have also reported the same among comparable age groups in Germany (8), the USA (9,10), Vietnam (11), Taiwan (12) and the UK (13).

Sleep deprivation may have a causal relationship with overweight and obesity. The increased BMI in children with short sleep duration may be on account of decreased leptin levels, increased ghrelin levels along with increased hunger and appetite (14,15). An alternative hypothesis is that short sleep disrupts circadian rhythm, leading to the release of adipokines as a result of abnormal timing of adipocyte differentiation (16,17). In a large scale study on 66,817 Chinese adolescents, conducted by Wu et al (18), an interesting "U" shaped association emerged between sleep duration and childhood overweight/ obesity; an optimal sleep duration of 7.0 to 8.0 hours sleep may prevent overweight/obesity. In yet another study, 18,403 Chinese students in 442 schools were recruited and surveyed by Wang, et al (19) and published their finding; the same "U"-shaped relationship emerged between sleep duration and obesity risk among girls, with the lowest risk among those who slept for 8 hours; but not among boys. These studies believed adequate sleep duration may be an important preventive factor for obesity in children, especially adolescents.

In the present day, many "New World" diseases are emerging due to the major paradigm shift in lifestyle; childhood obesity is one amongst them (20). It's time to focus on sleep hygiene - one of the invisible modifiable contributors apart from the already known risk factors like diet and physical exercise. The need of the day is to inculcate good sleep hygiene starting from early childhood. An appropriate sleep duration of an average of 8 hours a day needs to be established. Such small measures can go a long way in preventing this new growing epidemic of childhood obesity.

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CASE REPORT

A STITCH IN TIME SAVES NINE: AN INTERESTING CASE OF VARICELLA ENCEPHALITIS

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ABSTRACT

Acute viral encephalitis causes high morbidity and mortality in children. Before the 1995 era, varicella was a universal communicable disease of childhood. Now, varicella zoster virus (VZV) is a rare cause of encephalitis. We descrivbe an 11 year old child who presented with classical picture of varicella encephalitis and finally recovered and discharged.

Keywords: VZV - varicella zoster virus, encephalitis, immunocompetent child

Background

Before the 1995 era, varicella was a universal communicable disease of childhood. Humans are the exclusive host for the neurotrophic alpha herpes virus VZV (1). The pre-school and school going children are mainly affected. VZV primarily manifests as extremely infectious, generalized "dew drop" like vesicular exanthems. Post the primary infection, the virus may stay latent in the spinal and cranial ganglia neurons for years. Neurological complications post VZV infection, is as rare as 0.01%-0.03% (2). A wide spectrum of central nervous system (CNS) manifestations are encountered during primary infection or later on reactivation, such as encephalitis, cerebellitis, meningitis, vasculitis, stroke, polyneuropathy (1). Amongst these, the most serious secondary CNS complication is encephalitis (2). 30% of the cases occur under 15 years age group. It is commonly seen in immunocompetent patients (3). Symptoms are commonly seen after 10 days of onset of typical vesicular rash or after varicella vaccination (4). Meningitis and encephalitis are seen in >50% and around 40% of the affected patients (4) respectively. Earlier, VZV was recognized as the second most common virus causing encephalitis, after herpes simplex virus (1). This scenario has changed after the introduction of VZV vaccination in 1995. Now, the incidence of VZV encephalitis is as rare as 1 per 50,000 unvaccinated cases (3).

Case presentation

An eleven years old, Hindu male child, from Midnapur, West Bengal, presented with chief complaints of disorientation for 5 days and

two episodes of generalized tonic clonic seizures in last 3 days. He was apparently alright till 13 days back when he developed multiple, small, fluid filled vesicular lesions all over his body associated with low grade fever, itching and severe myalgia. The vesicles were centrifugal in distribution, gradually enlarged and then became crusted. After 8 days of appearance of vesicles, he became disoriented. Subsequently, in a couple of days, he had two episodes of generalized tonic clonic seizures followed by post-ictal phase. Fever was not accompanied. Treatment in a local health facility did not cause any relief of symptoms.

On arrival, the child had crusted skin lesions, disoriented with normal motor and sensory system examination; and without any cranial nerve deficit, cerebellar or meningeal signs. A probable diagnosis of Varicella encephalitis was kept. After sending relevant laboratory investigations, he was started on IV Acyclovir, IV Ceftriaxone, IV levetiracetam and other supportive management. Blood picture revealed normal leucocyte count with lymphocyte predominance, mildly raised CRP and ESR with normal serum electrolytes and liver function tests. CSF study was done after 12 hours of admission (due to sedation issues) and revealed lymphocytic pleocytosis with marginally elevated protein and normal sugar level. Absence of a close contact with a case of Tuberculosis, a non-reactive Mantoux test and normal Chest X-ray ruled out TB. CSF for AFB stain, Gram stain and culture were negative. IV Ceftriaxone was stopped within 48 hours; and IV Acyclovir continued. MRI brain and screening spine did not reveal any abnormality. EEG was abnormal showing intermittent frontal delta activity predominantly with burst suppression pattern. CSF for virological study revealed negative DNA PCR for HSV-1&2, JE and Varicella. The child showed good response to IV acyclovir; we continued it for 10 days. He responded well and remained seizure free and was discharged on oral anti-epileptics on day 11 of admission and advised for regular follow up. The child had normal EEG on first follow up within 2 weeks of discharge. We planned to continue anti-epileptics for a total of 3 months and then stop (in view of secondary seizures). Currently, he is under our regular follow up.

Discussion

CNS complications caused by VZV is rare in pediatric population, though infection is commonplace. Various types of CNS presentations are cerebellar, encephalitic and immune-mediated, which manifests within 8 to 12 days of illness. Presence of characteristic skin lesions with CNS symptoms, mononuclear pleocytosis, without significant change in protein and glucose in CSF are the hallmark of clinical diagnosis, which can be confirmed by virological studies like IgG/ IgM against VZV or RTPCR, though they may not be positive in all cases.

Our case had all the clinical manifestations. Other common etiology like dyselectrolytemia, blood glucose abnormalities, brain oedema, ADEM, intoxication or drug reaction, etc. were excluded through appropriate laboratory tests and neuro-imaging. Since our hospital does not have any virology set up, CSF sample was sent to state pathology laboratory for virological analysis for common viruses. The result of CSF DNA PCR for HSV (1&2), JE and varicella were negative. This might be due to

faulty or delayed collection and transport method. Such negative results have also been described by other researchers. Burst suppression pattern in EEG supports our diagnosis.

Review of literature revealed very few case studies and case reports on varicella encephalitis in immunocompetent host, rarer in children. The pathophysiology of VZV encephalitis is still not clear. Demyelinating disease, vasculopathy and acute infectious encephalitis of undetermined pathophysiology are the three main types of pathophysiological involvement(6). Of these, multifocal subacute demyelinating disease and VZV-induced vasculopathy are widely encountered in immunocompromised and immunocompetent hosts respectively.

In a prospective cohort study done by T. De Broucker, et al, on 20 immunocompetent patients with varicella encephalitis, VZV was identified in 16 of 20 cases by DNA PCR detection in the cerebrospinal fluid. In the remaining four patients, the clinical signs, response to treatment and out-come strongly suggested a causative link between VZV and the encephalitis, and the negative result of the PCR might be related to the early CSF sampling, or to the administration of acyclovir before CSF sampling (7,8). Neuro-imaging in these children were either normal or revealed non-specific findings.

V. B. Voitenkov, et al (9) examined EEG in 35 children suffering from different forms of varicella-induced encephalitis. With the exception of one child, slow-wave EEG components were present in almost all the children irrespective of the disease pattern; out of which two-thirds appeared within first five days from the onset of neurological symptoms.

Varicella encephalitis is a rare cause of acute infectious encephalitis in the post vaccination era. This diagnosis should be considered in any child, especially unvaccinated, who presents with seizures and altered sensorium following typical vesicular skin lesions, and revealing lymphocytic aseptic pleocytosis in CSF study and burst suppression pattern in EEG. The failure to establish positive varicella DNA PCR should not be considered as evidence excluding the diagnosis of VZV encephalitis. The case fatality rate remains high and sequelae are frequent. Acyclovir treatment should be promptly prescribed to these patients, because of its antiviral effectiveness against VZV.

Conclusion

Our case re-inforced this age old adage - “A stitch in time saves nine”. We need to emphasize the importance of optional vaccines like varicella in all children. Physicians need to be aware that varicella encephalitis, though rare, can occur in an immunocompetent host. Early clinical recognition and timely intervention in a case of varicella encephalitis can reduce long term sequelae and may be life-saving.

Conflict of Interest: None

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Fig "1": Picture of our child

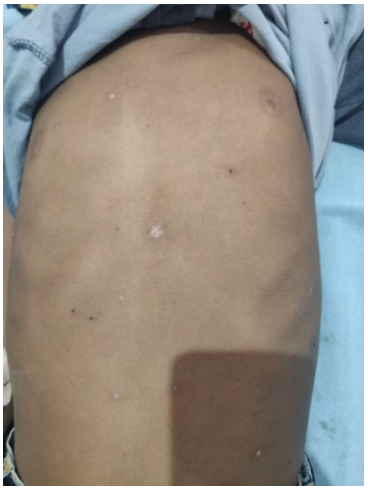

Fig "2" : Skin lesions on trunk

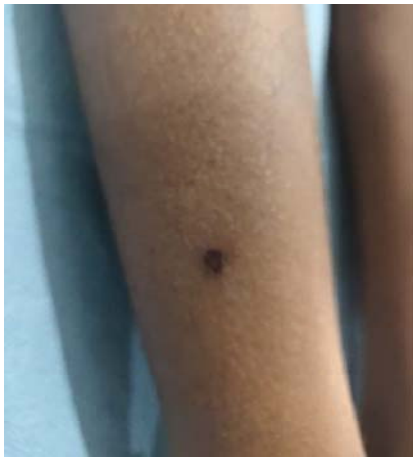

Fig “3” : Skin lesions on legs

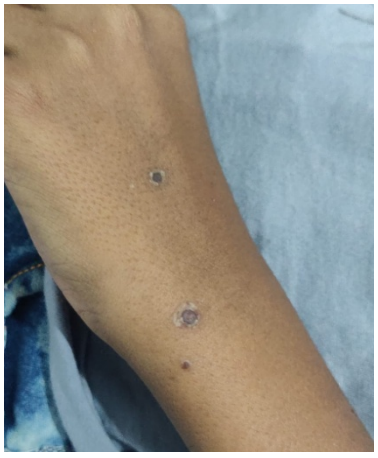

Fig “4” : Skin lesions on hands

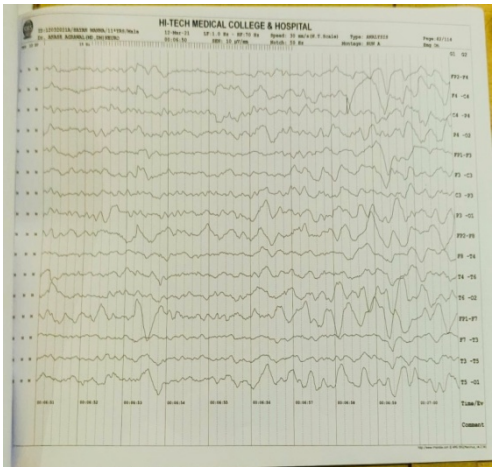

Fig “5” : EEG - Burst suppression pattern

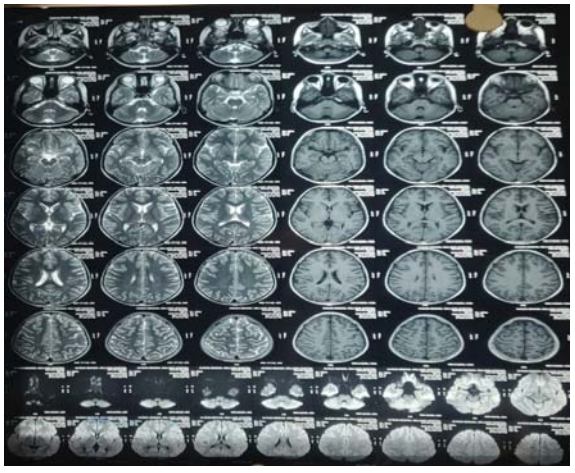

Fig “6” : MRI Brain - Normal

Fig “7” : MRI Screening Spine – Normal

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CASE REPORT

CONGENITAL ADRENAL HYPERPLASIA WITH SEVERE HYPONATREMIA, A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders due to deficiencies steroidogenesis enzymes. CAH is characterized by low blood levels of estrogens, androgens and cortisol, which leads to a compensatory increase in adrenocorticotropic hormone levels that stimulate the production of mineralocorticoid precursors. CAH due to 21-hydroxylase deficiency is accounting for 90% of cases. There may be classical/ non-classical variety of 21-hydroxylase deficiency. The classical form usually manifest since birth and if not detected may have fatal outcome in first few weeks of life. Here we present a case of 12 days old male baby with CAH with severe hyponatremia. The diagnosis was based on clinical presentation and raised 17-hydroxyprogesterone level. The baby was on treatment with fludrocortisone and hydrocortisone. He is doing well in the follow-up visits.

Keywords: Adrenal insufficiency, infants, newborn screening, hyponatremia, corticosteroid.

Introduction

Congenital Adrenal Hyperplasia (CAH) is a family of autosomal recessive disorder characterized by deficiency of 21-hydroxylase attributed to mutations in CYP21P and CYP21A2 gene (1). Due to deficiency of 21-hydroxylase, there is decreased cortisol levels, and leads to excess ACTH production as there is no negative feedback control of adrenocorticotropic hormone (ACTH) production (2). So, there is overproduction of steroid precursors like 17-hydroxyprogesterone. There may/may not increase in the aldosterone level. The clinical presentation is due to the levels of the intermediates in the steroid biosynthetic pathway and the level of deficiency of cortisol and aldosterone. CAH with the salt-wasting variety may present in emergency with

shock with severe hyponatremic dehydration and hyperkalemia (3). There may be associated hyperpigmentation of genitalia. On the other hand non-salt wasting variety may have ambiguous genitalia or clitoral hypertrophy (4). Here we report a case of 12 days old male baby with CAH with severe hyponatremia and hyperkalemia.

Case report

A 12-day old male baby was brought to the emergency department in a condition of lethargy, high pitched cry, icterus zone 5 with shock. There was a wide open anterior fontanelle and excessive weight loss. The baby had fever, cough and multiple episodes of vomiting on day 9 of life for which child received iv antibiotics (inj ampicillin, inj gentamycin), iv fluids and domperidone drop. The vomiting was projectile, non-bilious, non blood stained and associated with decreased urinary output.

He was a singleton term, vaginal delivery weighing 3500 gms at the gestational age of 37+1 weeks. The baby had delayed cry after birth might be due to prolonged labor. Mother was 22 yrs, P2L1, spontaneous conception and had no history of PIH, GDM, bleeding per vaginum, PROM, or hypothyroidism. Baby was on exclusive breast feeding till date. History of death of first baby at day 28 of life probably due to respiratory problem. Antenatal fetal anomally scan was normal, and no history of genetic diseases in the family.

On examination baby was lethargic, dry oral mucosa, shunken eyes and large depressed with anterior fontanelle. Baby was febrile (100.2^0F), feeble pulse and unrecordable blood pressure. Examinations of the respiratory, cardiovascular and gastro-intestinal system revealed no abnormality. On examination normal male genitalia but hyperpigmentation was marked.

On investigation there was severe hyponatremia (Na^+-119 mEq/dl) and hyperkalemia (K^+- 8.2 mEq/dl). Random blood sugar was 54 mg/dl. Serum ammonia was 118 umol/L (10-40 umol/L), serum cratinine 0.6 mg/dl and Lactate 19.1 mg/dl (<4 mmol/L), Base excess -11 mmol/L (−4.0 to +4.0 mmol/L) with PH- 7.33. Liver function test was within normal range. USG abdomen and pelvis revealed no significant abnormality and there by pyloric stenosis was excluded. Suspecting a case of CAH, 17-OH progesterone was done and found to be 400 ng/ml (0.53-1.86 ng/dl). Serum aldosterone was 73.1 ng/dl (5-90 ng/dl) and serum cortisol was 1.58 ug/dl (morning hour 4-23µg/dl), which was very much lower than physiological range. CSF study and thyroid screening were normal. Basing on investigation and clinical findings the baby was diagnosed as a case of congenital adrenal hyperplasia with the salt-wasting crisis.

The baby was treated with fluid bolus of 20ml/kg of 0.9% saline, and started with continuous salbutamol nebulisation. He was started with intravenous hydrocortisone 2 mg/kg 6 hourly and fludrocortisone acetate at 0.3mg/day. Though the initial screening for sepsis was negative, blood culture showed growth of staphylococcus epidermidis sensitive to linezolid. So, injection Linezolid was given 10mg/kg per dose 12 hourly for 7 days. His blood sugar, Na^+, K^+ were monitored regularly and by 5^{th} day there was a remarkable

improvement of the general condition. Electrolytes become normal and the treatment was adjusted according to the body weight. The baby was discharged with an advise of exclusive breast feeding for 6 months, 3ml of 3% normal saline in each feeding to continue, fludrocortisone 100 mcg once daily and tab hydrocortisone 2.5 mg twice a day. The baby came after 10 days in follow up clinic and there is progressive weight gain (3.8kg).

Discussion

This case presented in the emergency department mimicking a case of late onset sepsis with shock. Being a male child initial thinking of congenital adrenal hyperplasia is less likely compared to a female child. However, the suspicion was increased after the finding of hyperpigmented genitalia and laboratory reports of severe hyponatremia with hyperkalemia and features of severe dehydration with shock. This case has typical low serum cortisol and very high 17-OH progesterone level to establish the diagnosis of CAH.

The incidence of severe classic form of CAH is 1:10,000- 1:20,000 birth through out the world (1). In the Indian sub-continent, every 1 in 5762 cases was positive in a study that had done screening of 104,066 babies (5). At present, prenatal genetic diagnosis as well as post-natal screening for CAH is available. A high level of blood 17-hydroxyprogesterone (> 242 nmol/L, normal < 3 nmol/L) is characteristic of classic 21-hydroxylase deficiency (1). Possibility of false positive CAH out of neonatal screening are there in cases of preterm infants. Corticotropun stimulation test or genetic study will establish the diagnosis in these cases (6).

The classic variety usually presents with failure to thrive, moderate/severe hyponatremia and hyperkalemia. CAH in a female baby present with ambiguous genitalia due to excessive androgen exposures in utero (7). She may have enlarged clitoris, common urogenital sinus and partial fusion of labia majora. CAH in male infant present with hyperpigmented genitalia and sometimes penile enlargement (8). Both boys and girls with the salt-losing form manifest vomiting, weight loss, lethargy, dehydration, hyponatraemia, and hyperkalaemia in 2nd week of life and may leads to shock as in our case (7). The non-salt-losing form usually virilisation is found by the age 3 years (8).

Treatment consists of glucocorticoids in dose enough to suppress adrenal androgen secretion partly, but not in excess for suppression of the HPA axis. To maintain the electrolyte balance mineralocorticoids are needed. The dose of hydrocortisone is 12–18 mg/m^2/day in two divided doses (7). Sometimes infants may experience the hypoglycaemia. To prevent it higher dose of hydrocortisone may be administered. However, the dose of hydrocortisone should not exceed 25 mg/m^2/day. Regular measurement of weight and length along with plasma renin activity, and serum electrolyte levels are needed. Longer-acting glucocorticoids, like prednisone (5·0–7·5 mg/day in devided doses) or dexamethasone (0·25–0·50 mg at bedtime) may be given to the adults but not preferred in children due to its side effect like growth suppression [7]. Mineralocorticoids fludrocortisone at a dose of 100 µg to 200 µg irrespective of body weight is needed [1]. Moreover, higher does is required during early infancy. Classic CAH needs regular supplementation of sodium chloride (1–2 g

daily)for first year of life. Further, extra salt may be taken in condition like hot weather. Most importantly close clinical assessment and frequent laboratory investigation in every 4–6 weeks is needed.

In cases of ambiguous genitalia surgical management is an option. But it needs a multidisciplinary approach involving endocrinology, genetics, paediatric surgery and urology department.

Conclusion

Though CAH cases are rare in male infants, hyperpigmention of genitalia and presenting with hyponatremia and shock, suspicion of CAH should be kept in mind. Quick investigation for electrolytes and 17-hydroxyprogesterone levels is needed to make a diagnosis and early management of the patient to prevent a morbidity.

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Consent: Consent was obtained from the parent after due explaination regarding non publication of personal data and identity of the baby.

Conflict of Interest: None

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Figure 1 The child with CAH in follow-up OPD, KIMS on day 34 of life. Baby is active and gaining weight. His sodium and poatassium are within normal limit with fludrocortisone and hydrocortisone.

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Biostatistics in Clinical Research

ODDS RATIO

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ABSTRACT

Odds Ratio is commonly used in clinical research especially in case control studies. The understanding of odds ratio, how it is calculated, what the values mean, finding out its confidence interval and p value is essential for deriving any inference from it.

Key words: Odds Ratio, Odds, Confidence Interval, Case Control Study

Introduction

Odds Ratio is commonly used in clinical research especially in case control studies (1). The understanding of odds ratio, how it is calculated, what the values mean, finding out its confidence interval and p value is essential for deriving any inference from it. This article will discuss the basics of Odds ratio.

What is Odds ?

Odds are usually used in gambling and statistics. It is the ratio of the number of positive outcomes to that of negative outcomes, or the ratio of Success to Failure, or Wins to Loss (2).

In case of a tossing a coin, there can be two outcomes – head or tail. The odds in favor of getting head is 1:1. The odds against getting a head is also 1:1. If we are rolling a 6 sided dice, the odds of getting a 4 is 1:5 (1 event out of six where we get 4 and in 5 events we do not get 4). If the probability of an event occurring is p, then the probability of the event not occurring is (1-p). So the odds in favor is $\frac{p}{1-p}$, or the odds against is $\frac{1-p}{p}$.

The probability of an event is different. It is the ratio of number of outcomes of the particular event to the total number of outcomes that can occur (sample space). In case of rolling a 6 sided dice, the probability of getting a 4 is 1:6 or $\frac{1}{6}$.

The probability of an event can be calculated if the odds is known and vice versa (3).

What is Odds Ratio ?

Odds Ratio is the ratio of two odds, as the name implies.

Odds Ratio is used quite commonly in case control studies and cross sectional studies (3,4). Case control studies are retrospective in nature, where the investigator intends to find the

degree of association between the outcome and exposure. The investigator takes up a sample and divides them two groups, cases (with outcome) and control (without outcome), and finds out whether each had an exposure or not.

Odds Ratio quantifies the association between two events, A and B (outcome and exposure). It is the ratio of Odds of A (outcome) in presence of B (exposure) with the Odds of A (outcome) in absence of B (exposure). For the purpose of illustration, let us take an example. The data is not from any real study. Suppose an investigator intends to study the association of maternal smoking with Low Birth Weight. He collects data from a hospital, with his focus on two variables that is birth weight of new born and mother's smoking status. Low Birth weight is the outcome variable and maternal smoking is the exposure. A 2 by 2 contingency table is created.

	LBW	NBW
Smoking	25 (a)	110 (b)
No smoking	5 (c)	205 (d)

If a mother is smoking, the odds of having a LBW baby is 25/110, and if mother is not smoking the odds of having a LBW baby is 5/205. Odds ratio is ratio of these two odds.

So our Odds Ratio= $\frac{25/110}{5/205} = \frac{25\ X\ 205}{5\ X\ 110} = \frac{5125}{550}$ = 9.32 or = $\frac{ad}{bc}$ (cross multiplication of the cells in our contingency table)

The odds of a LBW baby for smokers is 9.32, which more than the odds of a LBW baby for non smokers. A large value indicates strong association between the exposure and outcome.

Another value usually used is the log (Odds Ratio). Here**,** log (OR) = log (9.32)= 2.23 . The log (OR) is used in logistic regression.

The range of OR is from zero to infinity with 1 as middle point. It is a skewed distribution. But log (OR) is a symmetric distribution around 0.

OR=1 Exposure does not affect odds of outcome.

OR> 1 Exposure associated with higher odds of outcome.

OR <1 Exposure associated with lower odds of outcome.

Confidence Interval of OR (Odds Ratio), measure of significance or p value

The Odds ratio in the above case has been calculated from one sample. We do not know the true Odds Ratio in the population. The confidence interval will give us the range of values within which the true population Odds ratio resides (4).

A 95% confidence interval is commonly accepted in most of medical scientific research. OR is a skewed distribution with a range from 0 to ∞ (1 in middle). But log(OR) is normally distributed. We calculate the confidence interval of log(OR) and for CI of OR we raise it power of exponential. The mathematical formula to calculate the upper and lower limit of 95% confidence interval (CI) of Odds ratio is –

We know CI = $\bar{x} \pm Z\ X\ SE$, SE= standard error, Z= z score for confidence interval

Upper limit of

CI = $e^{\log(OR)+1.96\ X\ sqrt(\left(\frac{1}{a}\right)+\left(\frac{1}{b}\right)+\left(\frac{1}{c}\right)+\left(\frac{1}{d}\right))}$

Lower limit of

CI= $e^{\log(OR)-1.96\ X\ sqrt\ (\left(\frac{1}{a}\right)+\left(\frac{1}{b}\right)+\left(\frac{1}{c}\right)+\left(\frac{1}{d}\right))}$

Where a, b, c, d are the values in each of the cells in our contingency table.

SE = $sqrt(\left(\frac{1}{a}\right) + \left(\frac{1}{b}\right) + \left(\frac{1}{c}\right) + (\frac{1}{d}))$

The Z value for our CI of 95% is 1.96. By putting the values from our hypothetical contingency table, the range of 95% Confidence Interval (CI) for our Odds ratio is (3.47, 25.03). One need not calculate these values manually; there are software available for calculation.

Inference of significance of association from Confidence interval (CI)

We had seen before that Odds Ratio of 1 indicates that there is no association between the exposure and outcome. If the Confidence Interval contains the value 1, then the Odds Ratio is not significant, and the reverse is, if the confidence interval does not contain the value 1 then the Odds Ratio is significant.

In the above example the CI (3.47, 25.03) does not contain the value 1, so the Odds Ratio is significant.

The other method of finding significance is by finding out the p value by chi-square test. If the calculated p value is less than 0.05 (our significance level), then the association is significant.

Caution while deriving conclusion from OR

1) OR is used in case control studies, which is one of the observational studies. In observational studies, the inference that can be drawn is whether the two variables (exposure and outcome) are associated or not. It must always be remembered that "Association does not necessarily mean causation." To prove causation, an experimental study is required.
2) Confounding variables – In our hypothetical example, we had taken two variables, which is maternal smoking and birth weight of babies. We all know that there are many other variables that affect birth weight of babies, like maternal age, maternal nutrition, height, weight, gestational age, parity, pollution etc. They are all confounding variables that we have not accounted for. Adjusted OR is used in logistic regression modeling where other confounding variables are kept constant.

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OVERARCHING QUESTIONS

NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM

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ABSTRACT

World-wide, congenital hypothyroidism (CH) has an incidence of 1: 3000-4000 live births. It is one of the most common preventable causes of mental retardation. It can be prevented by universal screening at 3-4 days of post-natal age. Confirmation should be done by taking venous sample and interpreting results as per age-wise cut-offs. After confirmation, treatment (L-thyroxine) should be started at a dose of 10- 15µg/kg/day. Outcome of CH depends on the time of initiation of therapy (best outcome if treatment started before 2 weeks of age).

Keywords: hypothyroidism, newborn, mental retardation, thyroxine, TSH

Introduction

World-wide, congenital hypothyroidism (CH) has an incidence of 1: 3000-4000 live births (1). It is one of the most common preventable causes of mental retardation (2,3). It can be prevented by universal screening at 3-4 days of post-natal age. Confirmation should be done by taking venous sample and interpreting results as per age-wise cut-offs. After confirmation, treatment (L-thyroxine) should be started at a dose of 10- 15µg/kg/day (3,4). Outcome of CH depends on the time of initiation of therapy (best outcome if treatment started before 2 weeks of age) (3,5). There are some questions which need to be answered specifically to educate the pediatricians for proper understanding and care of infants and children with CH.

The questions and their answers (1-5)

1. How common is congenital hypothyroidism ?
   - ✓ Congenital hypothyroidism occurs in 1:4000 newborns.
2. Why is it important to treat early ?
   - ✓ Early therapy within 14 days prevents brain damage.
3. Why should neonatal screening for hypothyroidism be universal ?

There are two reasons:

- ✓ Unrecognized congenital hypothyroidism leads to mental retardation
- ✓ Clinical symptoms and signs are subtle in neonatal period

4. What are the major strategies for

newborn screening ?

- ✓ Estimation of T4 levels
- ✓ Estimation of TSH levels
- ✓ Estimation of both T4 and TSH levels

5. What are the pros and cons of measuring T4 levels ?
   - ✓ T4 estimation will diagnose all causes of congenital hypothyroidism including central hypothyroidism and also cases of primary hypothyroidism including those babies who have a late rise of TSH.
   - ✓ It misses neonates with compensated forms of congenital hypothyroidism who have normal T4 and high TSH
   - ✓ It has the disadvantage of false positivity in TBG deficiency and in preterm and sick neonates
6. What are the pros and cons of measuring initial TSH ?
   - ✓ Initial TSH estimation has the advantage that it would detect all cases of primary hypothyroidism including subclinical and mild and transient cases
   - ✓ But the disadvantage is it will not detect central hypothyroidism
7. Which is the most sensitive test ?
   - ✓ Estimation of TSH is more sensitive and specific test for primary CH then T4 screen
8. What is the type of sample used for screening ?
   - ✓ Either cord blood or postnatal heel prick filter paper Dried blood sample [DBS] can be used.
9. What is the timing of test ?
   - ✓ The timing of test is either cord blood or post-natally at 48 -72 hrs of age. ISPAE guidelines recommend either cord blood or day 3 to 5 postnatal sample for screening
10. What is neonatal surge of TSH ?
    - ✓ In healthy term neonates serum TSH rises to 60-80mIU/L within 30-60min after birth, it then rapidly decreases to 20mIU/L by 1 day and then slowly to 6-10mU/L by 1 week of age
11. Is cord blood spared of neonatal surge ?
    - ✓ The TSH surge starts 30mins after birth and so cord blood [placental end [immediately after delivery] can be used for NBS as it is spared of neonatal surge.
12. What is the TSH cut-off which is considered positive in screening tests ?
    - ✓ Baby with TSH >20mIU/L on cord blood and postnatal screen sample after 48hrs need to be recalled for confirmation or repeat screening [ISPAE guidelines]
13. How are the units for dried blood sample and serum sample of TSH different ?
    - ✓ The TSH measured from a DBS is expressed in whole blood units. Serum units may be derived by multiplying the whole blood unit value by 2.2 [to adjust for the hematocrit] The ISPAE recommends using serum units for all to maintain uniformity. The ISPAE guidelines are based on serum units of TSH.
14. What are ISPAE guidelines for screen positives ?
    - ✓ TSH 20-40mIU/L: the baby need to be recalled in second week for repeat screening. The reason being most of the mildly high TSH reports due to unresolved neonatal TSH surge would have normalized in a few days, if the repeat screen TSH >20mIU/L for <2 weeks and >10 for >2 weeks of postnatal age then confirmatory venous sample for

FreeT4/T4 and TSH are to be taken.

- ✓ TSH >40mIU/L: an immediate venous sample should be taken for freeT4/T4 and TSH.
- ✓ TSH > 80mIU/L: very likely to have low T4 levels and therapy should be started after drawing a venous confirmatory sample without waiting for results.

15. What are the criteria for starting treatment based on venous confirmatory sample results ?
    - ✓ Low T4 (<100 nmol/L or <8 microgm/dl) or low free T4 (< 12 pmol/L or < 1.1 ng /dl) irrespective of TSH levels
    - ✓ Mild low T4 (< 128 nmol/L or < 10 microgms/dl) or low FT4 (< 15 pmol/L or <1.17ng/dl) with TSH >20mIU/L if age is less than 2 weeks and >10mIU/L if age is more than 2 weeks
    - ✓ Normal T4/FT4 with persistently elevated TSH >10mIU/L at age more than 3 weeks
16. What is the level of cutoff to be used if sample is taken between 24-48 hrs?
    - ✓ Interpretation is based on age related cutoff of TSH which is > 34 mIU/L.
17. Who should be reevaluated even after starting treatment?
    - ✓ Reevaluation should be done when there has been no definitive diagnosis in neonatal period regarding the cause.
    - ✓ It is also done in infants with persistently elevated TSH >10mIU/L after 3 weeks of age with normal T4 /FT4 levels who have been started on levothyroxine therapy.
    - ✓ In babies with normal confirmatory TSH with definitely low T4<8microgms/dl or T4<1.1ng/dl who are started on treatment.
18. When should reevaluation be done ?
    - ✓ At the age of 3 yrs.
19. Who do not need reevaluation ?
    - ✓ Those who have a definite diagnosis such as thyroid agenesis, ectopic thyroid, dyshormonogenesis with DUOX2 mutation.
    - ✓ No need to revaluate if TSH is rising with age even if it is due to insufficient dose or poor compliance.
20. What is the treatment of congenital hypothyroidism ?
    - ✓ Levothyroxine in dose of 10-15 microgms/kg/day as a single morning dose preferably in empty stomach.
21. How is the monitoring done after starting treatment ?
    - ✓ Monitoring to be done by measuring free T4 levels and TSH levels
    - ✓ First test is done after 1-2 weeks after initiation and then every 2 weeks till TSH is completely normalized
    - ✓ Every 1-3 months till the age of 12 months and every 2-4 months between 1-3 yrs and every 3-12 months till growth is completed
    - ✓ If there is change in dose T4 should be done after 4-6 weeks of change of dose
22. When should preterm /LBW/VLBW babies undergo screening ?
    - ✓ Babies who are preterm or LBW should be screened at 48-72 hrs
    - ✓ Sick neonates should be screened at least by 7 days of age
    - ✓ Second screening is recommended at 2-4 weeks of age
23. In which babies should we ask for freeT4 levels ?
    - ✓ In most situations Total T4 is sufficient

for diagnosis and monitoring treatment,

- ✓ Free T4 should be done in following conditions;
  - o in preterm babies as total T4 may be low because of low levels of TBG [thyroid binding globulin]
  - o in babies with low T4 with normal TSH as it could be due to two reasons;
    - Firstly If free T4 is normal it could be due to TBG deficiency - referral to paediatric endocrinologist is recommended
    - Secondly If free T4 is low also with low total T4 with normal TSH, central hypothyroidism needs to be suspected

Conclusions

The diagnosis, approach and management of congenital hypothyroidism have been simplified in this paper. A timely diagnosis and intervention would help children with CH thereby preventing life-long disability.

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Conflicts of interest: None

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