**CASE REPORT** **PROF-634**

# ATYPICAL HEPATITIS (OR A WILSON'S DISEASE);
## A DRASTIC HEREDITARY ACQUIRED FAMILIAL DISORDER?

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### INTRODUCTION

"If some doctor knows about diagnosis and treatment, for God's sake provide me a guide line to save my family". These are the words of cry from a poor father praying for health from nature.

It is our professional duty to listen to this voice. One among the authors of this report came across with this interesting (undiagnosed probably familial dominant) disorder leading to 4 deaths in a family and the 5th male child is now presenting the same symptoms and signs as were found in the previous four children (including 3 males and one female child) of different ages usually from less than one year to about 10-12 years.

The father of a family is a govt employee.. He is married to a house wife who is his 3rd cousin in relations. The affected children usually present with weight loss, anorexia and anaemia with or without constant low grade fever in early age. As the disease progresses, jaundice develops along with hapatospleenomagly Although the LFTs are abnormal, the tests for any type of viral hepatitis are negative. Ultrasonography shows diffuse enlargement without any focal lesions. The biopsy also shows infilterative inflammatory changes showing marked degree of cirrhosis. In the last child died recently, undiagnosed deposits in the liver biopsy tissue specimen were detected by Pathology Lab, Allied Hospital PMC Faisalabad.

They proposed that probably undetectable deposits were either glycogen or some minerals and advanced staining techniques were recommended. So the remaining specimen was sent to Agha Khan Hospital Lab. Karachi who were of the view that the copper deposits were there in the specimen.

The diagnosis was made of Wilson's disease in the last child who died during the treatment. In fact early treatment with D-Pencillamine did not improve the condition. This same history was repeated leading to death due to liver failure with ascities and hepatic encephalopathy as was seen in the previous children. Detail histories and investigations of all the family members are available and given below. The normal ranges are also mentioned for comparison of the results.

### CASE HISTORY OF FIRST CHILD (Male)

Presented at the age of 8, the jaundice developed

with epistaxis and abdominal pain off and on. Vomiting 1 -2 times daily, temp. 99° to 100° F. Mild ascites developed. Liver 10 cm below costal margin, spleen 8 cm, firm. At last acities and hepatic encephalopathy developed, became unconscious and died at the age of 8.5 years.

**ULTRASONOGRAPHY**

Liver enlarged, with minimal coarsening. Gall bladder partially contracted with thickening of the wall. Spleen moderately enlarged.

## CASE HISTORY OF SECOND CHILD

**(Female)**

She presented with severe cough on 12.10.1999 a few common antibiotics and decadron inj. were given, symptoms relieved. About 9 months after complained upper abdominal distension with colicky pain on feeding. Weight loss along with low grade fever 99° to 100°F with severe chill. Scanty bleeding through nose and vagina off and on at late stages. Pain in shoulders and legs with great emaciation. Ascites and then encephalopathy developed and patient died on June 1, 2000.

**LABORATORY FINDINGS, FIRST CHILD**

| Clinical Test | Normal Range[1,2,3] | Patient Value | | |
|---|---|---|---|---|
| | | Jan-97 | Feb-97 | May -97 |
| Total Bilirubin | 0.1-1.0mg/dl | 4.5 | 7.4 | 12.4 |
| Direct Bilirubin | 0.0-0.5 mg/dl | 3.4 | - | 10.4 |
| In-direct Bilirubin | 0.0-0.7 mg/dl | 1.1 | - | 12.0 |
| SGPT (ALT) | 0.0-41.0 iu/itr | 213.0 | 182 | 195182 |
| Alk. Phosphate | 10-286 iu/l | 112 | 86 | - |
| Hbs Ag | 2.00 (cutoff value) | 1.12 (Non -reactive) | - | - |
| Total protein | 5.01-7.75 g/dl | - | 7.9 G/DL | - |
| Albumim | 3.5-5.0 g/dl | - | 1.6 | - |
| Clobulin | 1.8-3.2 g /dl | - | 6.3 | - |
| A/G Ratio | 1.1-2.4 | | 0.3 | - |
| HCV | 2.0 Cut off value) | | 1.18 (patient value) | - |
| Hb. | 12-16 g/dl | 9.8 | 10.4 | 8.6 |
| TLC | 4000-11000mm$^3$ | - | - | 17.200 |
| DLC | | P-78%, L-22%, M-00%, E-00% | | |
| Blood Urea | - | - | - | 26.0MG |
| Sugar | - | - | - | 92.0 MG |
| Serum Na+ | - | - | - | 13.0 M.MOH/L |
| Serum K+ | - | - | - | 3.7" |

| | | | | |
|---|---|---|---|---|
| BT. | 3-5 Min | - | - | 4.25 |
| CT. | 5-7 Min | - | - | 5.5 |
| PT. | 0.0-16.0 Sec | 38.0 | 38.0 | - |

## ULTRASONOGRAPHY

Free fluid, spleen moderately enlarged. Moderate hepatosplenomegaly, which increases with passage of time and development of ascities.

## CASE HISTORY 3RD CHILD: (Male)

He was born normal. At the age of five month presented with diarrhoea along with chest infection and died after about a week therapy of the above ailment. No investigations were possible.

| LABORATORY FINDINGS, FIRST CHILD | | | | |
|---|---|---|---|---|
| Clinical Test | Normal Range[1,2,3] | Patient Value | | |
| | | 12,12,1999 | 29.12.1999 | 28.02.2001 |
| Total Bilirubin | 0.0-1.0 mg/dl | 2.0 | 1.8 | 1.4 |
| Direct Bilirubin | 0.0-0.5mg/dl | 1.5 | 0.9 | 0.8 |
| In-direct Bilirubin | 0.0-0.5mg/dl | 0.5 | 0.9 | 0.6 |
| SGPT (ALT) | 0.0-43.0 iu/L | - | 360 | 196 |
| Alkaline Phosphatase | 10-286 iu/L | - | 675 | - |
| Gama GT | 1.0-37.0 iu/L | - | 548 | - |
| PT. | 10-16Sec | | | 23.0 |
| Hbs Ag | 2.0 (cutoff value) | | 0.97 | - |
| Total protein | 5.7-7.5 g/d | - | - | 6.9 |
| Albumim | 3.2-2.5 g/d | - | - | 3.2 |
| Globulin | 1.9-3.65 g/dl | - | - | 3.7 |
| A/G Ratio | | | | 0.9 |
| HCV | 1.0 (cut off value) | -ve | -ve | 0.23 (Patient value) |
| Hb. | 11.5-15.5mg/dl | - | - | 12.1 |
| Hemocromatin | 35.0-45.0 | - | - | 36.3 |
| RBC | 5.2x10/$mm^3$ | - | - | 4.3x10 |
| TLC | 4000-11000/$mm^3$ | - | - | 15200 |

| | | | | |
|---|---|---|---|---|
| MCV | | - | - | 85.3 (FL) |
| MCH | 30-35 pg | - | - | 28.1 (PG) |
| MCHC | | - | - | 33.4 |
| ESR | 0.0-20.0 mmHg | - | - | 80.0 |
| Urobilinogen | | - | - | + Urine |
| Ca-Oalate | | - | - | + Urine |
| PT | 10-16Sec | - | - | 23 Sec. |
| ANA | | - | | |
| Asthma | | - | | |
| Fundoscopy for K.F Ring | For Wilson's Disease | Doubtful | | |
| Serum Copper | 80.0-190.0 ug/dl | | 122 | |
| Ceruloplasmin | 0.222-0.422 ug/dl | | .292 | |

**CASE HISTORY 4TH CHILD (Male)**

Presented at the age of 12,with weight loss, emaciation discoloration of skin and some times colicky pains. Lower lip dried in patches and bled off and on. Tab. Metronidazole and longifen syp was prescribed (for deworming), later high grade fever developed which was the main symptom along with hepatomegaly and ultimately developed encephalopathy, expired on 10-06-2001.

| LABORATORY INVESTIGATION, 4TH CHILD (MALE) | | |
|---|---|---|
| Clinical test | Normalrange[1,2,3] | Patient value |
| Hb | 14-18mg/dl | 9.6 |
| ESR | 3-15 mm Hg | 85 |
| TLC | 7000-11000/$mm^3$ | 8600 |
| NEUTROPHILS | 35-70% | 66 |
| LYMPHOCYTES | 25-40 | 22 |
| MONOCYTES | 1-6% | 02 |
| EPSINOPHILS | 1-5% | 0 |
| PLATELETS | 150,000-500,000/$mm^3$ | 500000 |
| TOTAL BILIRUBIN | 0.1-1.0 mg/dl | 1.6 |
| DIRECT | - | 1 |

| | | |
|---|---|---|
| INDIRECT | - | 0.6 |
| SGPT | 9-43 IUL | 515 |
| AL. PHOSPHATES | 80-25 IU/L | 778 |
| SERUM COPPER | 65-160 ug/dl | 88.33 |
| SERUM CERULOPLASMN | 15-60 mg/dl | 20.5 |
| 24 HRS URINE COPPER | 10-100mg/dl | 171.34 |
| URINE | | |
| FUNDSCOPY FOR F RING | For Wilson Disease | -ve |
| Hbs Ag | cutoff 2.000 | -ve (1.010) |
| HCV ANTIBODIES | cutoff.345 | -ve (.192) |
| SERUM IRON | 50-120 ug/dl | 71 |
| SERUM TIBC | 250-400 ug/dl | 164 |
| SATURATION TIBC | 20-45% | 43.3 |
| SERUM FERRITIN | 7-140 mg/dl | 322 |

**ULTRASONOGRAPHY**

Mildly enlarged liver, No focal mass seen, Intra-hepatic biliary ducts not dilated, Gall bladder contracted. Spleen enlarged about 12.7 cm.

**LIVER BIOPSY**

**Allied Hospital Faisalabad**

Tiny pieces, gray white Microscopic examination showed large polygonal cells with small centeral nuclei with foamy cytoplasm.

**Agha Khan Lab**

Presence of nodules exhibiting regeneration separated by thick fibrous bands revealed degenerative changes no evidence of any fatty changes or storage disorder eosinophilic intra cytoplasmic miliary bodies. Moderate degree of piece meal necrosis. Special stain for copper (Rubionic acid) is focally positive. Stain for iron and alpha anti-typsin were negative.

The child was under the treatment of a local child specialist. According to her views, although the serum copper 83.3 ug/dl (65-160 ug/dl normal) and serum ceruloplasmin was 36.5 mg/dl (15-60 mg/dl normal) but still the free copper calculation by subtracting ceruloplasmin bound copper (serum cesuloplasmin x 3.3) from total serum copper was greater i.e. 88.3-(22.5x3.3) = 21.3 ug/dl. It should always be less then 10 ug/dl. Other diagnostic criteria include serum copper < 80 ug/dl, 24 hour urinary copper more than 100 mg and liver copper content above 250 ug/gram dry weight[5].

The diagnosis was Wilson disease. The disease is caused as inheritence of a mutation on long arm q of chromosome 13 which decreases ceruloplasmin preventing excess copper elimination from body. About 50,000 -1,00,000 people in the world are suffering from this defect[1]. Too much copper damages the tissues especially the liver and lenticular part of brain. Treatment include restriction of copper rich food e.g. cocoa, nuts,

shellfish, chocolate and mushrooms along with chelating agent like penicillamin, trientime (syprime) and a drug tetrathiomolybdate. Salts of zinc in the form of ZnCoS and Zinc acetate are also recommended[1].

D-pencillamine was started at a dose of 5oo -750 mg / day form 2.5.2001 onward and zinc sulphate 400 mg/ day in divided doses. But no recovery was achieved. The symptoms increased till severe hepatospleenomagaly developed and died on 10.6.2001 due to liver failure.

**CASE HISTORY 5TH CHILD (Male)**

The parents of the diseased family were over conscious. So investigations were done in this case early and he at the age of 7 presented with abnormal LFTs. Tests analysis showed gradual increase of SGPT upto 205IU/L (Normal 0-43IU/L) Liver seemed somewhat enlarged but soft. The child is still alive.

The child is looking pale and somewhat yellowish. Appears weak and emaciated, no weight gain inspite of normal diet. The LFTs showing a rising trend with passage of time. HbsAg and HCV antibodies are not detected by even ELISA technique.

Keeping in view, the sad previous history of 4 other children, the advanced investigations were recommended at early stage which are shown below. Again Wilson's Disease is the provisional diagnosis and this time Zinc acetate salt at a dose of 10 mg/day was recommended.

After about two months treatment improvements in the symptoms along with recovery in LFTS has been observed.

The treatment is in progress. Recent SGPT estimation on 15.05.2002 again showed a rising trend (224 IU/L). The authors are very much worried at the recent rise in SGPT level. The treatment continues and further investigations are awaited.

**TABLE-IV. LABORATORY INVESTIGATION 5th CHILD (MALE)**

| Clinical test | Normal range [1,2,3] | Patient value | | | |
|---|---|---|---|---|---|
| Hb | 14-18mg/dl | 12.8 | 10.8 | 10.6 | 9.4 |
| ESR | 3-15 mm Hg | 18 | | | |
| TLC | 7000-11000/$mm^3$ | 7300 | 7500 | 11700 | |
| NEUTROPHILS | 35-70% | 63 | 67 | 66 | - |
| LYMPHOCYTES | 25-40 | 32 | 32 | 31 | - |
| MONOCYTES | 1-6% | 02 | 01 | 02 | - |
| EPSINOPHILS | 1-5% | 03 | 00 | 01 | - |
| PLATELETS | 150,000-500,000/$mm^3$ | 280000 | 208000 | 24000 | - |
| TOTAL BILIRUBIN | 0.1-1.0 mg/dl | 0.5 | 0.9 | 0.57 | 0.67 |
| DIRECT | - | - | - | .24 | .25 |

| | | | | | |
|---|---|---|---|---|---|
| INDIRECT | - | - | - | .33 | .42 |
| SGPT | 9-43 IUL | 125 | 186 | 205 | 92 |
| AL. PHOSPHATES | 80-25 IU/L | 232 | - | 630 | 543 |
| SERUM COPPER | 65-160 ug/dl | 93 | - | - | - |
| SERUM CERULOPLASMN | 15-60 mg/dl | 20 | - | - | - |
| 24 HRS URINE COPPER | 10-100mg/dl | 32 | - | - | - |
| URINE | | | - | | |
| FUNDSCOPY FOR F RING | For Wilson Disease | -ve | | | |
| Hbs Ag | cutoff 2.000 | -ve (1.020) | | | |
| HCV ANTIBODIES | Cut of.345 | -ve (0.146) | | | |

The authors are of the view that either this family is suffering from some atypical type of fatal viral hepatitis, which exclusively presents in early age and is un-detective with conventional laboratory tests. There is also possibility that the family is suffering from any type of dominant familial hereditary disorder leading to hepatic failure. This report is published with the view that the experts in the field of medicine, genetics, biochemistry, physiology and pathology can guide us to reach at a definite diagnosis and to save the last two children of the family, as the 5$^{th}$ child is also showing same symptoms as seen in previous family members. This will definitely be a great achievement if we are able to reach at a definite diagnosis as this is essential to treat this ailment properly. All those who are interested in the details of the previous cases or other members of the diseased family can contact the authors at above address. As God says *"He who save one life has actually save the whole universe".*

Any body who succeeds shall become a pioneer among universal savers.

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