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Hereditary Spherocytosis in North India:
Need for More Extensive Data

Sir,

We read with interest the paper “Clinical profile of hereditary spherocytosis in north India” by Panigrahi et al. In the paper itself some of their data are self-contradictory; for example in the abstract 35 out of 50 patients presented with jaundice where as in Table 2, 32 patients had jaundice at presentation and icterus was present on evaluation only in 9? Similarly spherocytosis was found on smear in 19 out 42 patients in the abstract section whereas that number has become 22 out of 50 in Table 3.

It was surprising to see normal red cell survival curve in 3/12 patients studied. If their red cell survival was normal why did they have reticulocytosis, splenomegaly etc. The autohaemolysis results are also confusing. 20/31 patient had increased autohaemolysis but nothing was written as to the correctability of increase autohaemolysis by addition of glucose or ATP, which are traditionally done to discriminate between hereditary spherocytosis and other congenital non-spherocytic haemolytic anaemia. The very fact that in many of these patients spherocytosis was not evident on smears brings suspicion whether really all the patients studied had hereditary spherocytosis or not? None of these patients were properly investigated for red cell enzymopathies, no studies are available on membrane cytoskeleton of the affected red cells. MCHC is regarded as a useful pointer to hereditary spherocytosis in a screening test if the value has been obtained in a good quality red cell counter as has been used in these cases but MCHC (mean + 1SD) of 33±5.1 (Table 3) inspires little confidence in the whole data. In this paper none of the pedigrees described autosomal dominant inheritance is conclusively proved and in the second family there was a consanguinity too. In all these three family pedigrees (Fig. 2) one of the parents were shown to be normal and this was on the basis of negative smear, osmotic fragility and clinical examination and we all know all these investigations may miss a patient with small number of spherocytes in the circulation. In each of the pedigrees there were deaths and these deaths have not been satisfactorily explained.

The authors have discussed about co-inheritance of Gilbert syndrome as a cause of increased propensity to develop gall stones but they themselves did not care to do certain simple investigations to include or exclude this condition in the series of their patients.

It may not be out of place to mention here that there are many causes of spherocytosis with haemolytic anaemia of which hereditary spherocytosis is but one. Except doing Coombs test to rule out immunohaemolytic anaemia no other investigations were done to exclude other cause of spherocytosis.

This paper has come from the genetics department of one of the elite medical institutes in India and we expected some cytogenetic studies in HS. The literature cites in this disease patients with abnormalities in chromosome 8,12,2,3 No molecular genetic studies have been done in any of these cases.

Hereditary spherocytosis is not a common cause of haemolytic anaemia (1:5000 population) but any Institute or Hospital which has kept a record over years may get a large series of hereditary spherocytosis as was reported from this institute.

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Reply from the authors

Sir,

We thank Jihina et al for reading our paper critically. We accept the error in the abstract where presenting feature was jaundice was said to be in 35 cases while as rightly mentioned in Table 2, it was really 32. We regret about the similar numerical error of number of spherocyte positive cases. By jaundice as a presenting feature we mean that the patient contacted doctor because of episode/episodes of jaundice while cases with icterus mean the cases who had icterus at the time of examination. Hence, the numbers with jaundice and icterus are different.

In our experience we did not find autohemolysis test very informative and hence, the data about correctability is not mentioned. Autohemolysis test results are known to vary from lab to lab and also in a person repeated at different times. Correctability also depends on the number of reticulocytes and may lead to confusion.

Absence of spherocytes is not against the diagnosis of spherocytosis as in many cases spherocyte are sparse and
peripheral smear may be considered normal even by experienced observer.\textsuperscript{1,2}

Increased osmotic fragility with negative Coomb's test and clinical presentation suggestive of hereditary spherocytosis are taken as diagnostic. Enzymopathies do not cause shift in osmotic fragility. However, G6PD was studied in all cases and we have mentioned about one case with G6PD deficiency on page 1366. Pyruvate kinase was studied in cases where the shift in OF curve was minimal. General blood picture, blood counts, reticulocytosis, direct combs test, serum bilirubin and OF curve after 24 hours incubation are the investigations suggested fro the diagnosis of hereditary spherocytosis.\textsuperscript{2} Membrane studies are not routinely indicated. With this approach rare cases with unusual manifestations will be missed. Portal hypertension was ruled out by ultrasonography to look for collateral vessels and ascitic fluid in all cases and if there were some unusual features like very large spleen, endoscopy was done to rule out esophageal varies as an evidence of portal hypertension. During the course of evaluating these cases, we diagnosed two cases of autoimmune hemolytic anaemia, but none with portal hypertension. Other causes of spherocytosis like clostridial sepsis, transfusion reaction, burns, or insect bites can be ruled out clinically. MCHC as shown in Table 3 was very variable and there were cases with microcytosis and some with macrocytosis. This may be due to associated iron deficiency and folic acid deficiency respectively. Serum iron and total iron binding capacity was done in all cases and we found iron deficiency in seven cases.

We advise investigations of parents and siblings of all cases of hereditary spherocytosis. However, only a few families get it done. The pedigrees which we have given are from the families where all members were clinically examined and investigated with hematological tests including OF curves and the affected members were proved cases of HS. In the AD family with consanguinity, the father had characteristic features an test results suggestive of his and mother was clinically and investigation-wise normal. The cooccurrence of consanguinity, we had already explained. All disorders do occur in consanguineous families and presence of consanguinity does not confirm AR inheritance.

We have not evaluated the patients for Gilbert syndrome. The RBC half-life and splenic sequestration studies done in other cases of hemolytic anemia and splenic sequestration have shown false-negative results in our experience. We are analyzing data related to this aspect.

Cytogenetic studies are never indicated in genetic disorders which are known to be monogenic disorder. If two or more monogenic disorders are seen in a patient or a known monogenic disorder is found in association with mental retardation, then only karyotyping is indicated. Such are rare cases but very useful for gene mapping. We had one child of HS with developmental delay, whose karyotyping did not reveal any abnormality.

HS is one of the common genetic disorders as most of the genetic disorders have prevalence of 1 in 10,000 to 1 in 40,000.

The aim of the paper was to document clinical and hematological features of Indian cases of HS as mentioned in our paper. Protein and molecular abnormalities need to be in Indian patients. The journal might have accepted the paper as there is scarcity of data about genetic disorders form India.

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**Acinetobacter Infection in Hickman’s Catheterized Patient of Multiple Myeloma**

Hickman’s catheter is commonly used in cancer patients requiring long term venous access for chemotherapy or total parenteral nutrition.\textsuperscript{1} Intravascular devices (IVD) are associated with risk factors such as mechanical trauma, thrombosis and nosocomial bacteremia. We report Hickman’s catheter Acinetobacter related infection in a multiple myeloma male patient, aged 38 years registered in IRCH, AIIMS, New Delhi. Patient reported episodes of high-grade fever (> 102°F) accompanied with rigors and chills (catheter had been in situ for 6 months). Because of seasonal predisposition (April) and endemicity of malaria, chloroquine was given. Patient became symptom-free. TLC, blood urea and serum creatinine was 8,700/cumm, 22 mg% and 1.2 mg% respectively and PBF was negative for MP. A week later patient came back with repeat symptoms. TLC was 18,000/cumm and was prescribed ciprofloxacin-500 mg bid for 5 days. Patient became afebrile but reported back after 7 days with dyspnea at rest, puffiness of face, generalized weakness and difficulty in walking with high-grade fever, rigors and chills. Detailed history revealed a concomitant and instantaneous occurrence of fever and shivering accompanied by extreme weakness when the catheter was flushed with normal saline. This prompted investigation for catheter-related bacteremia. TLC, blood urea and serum creatinine were 25,000/cumm, 43 mg% and 1.7 mg% respectively with normal X-ray chest. Catheter was removed and tip was sent for culture and anti-microbial sensitivity.

Patient showed dramatic improvement in symptoms and was prescribed cefuroxime 500 mg bid for 5 days. Microbiological report showed *Acinetobacter* species. Sensitivity in decreasing order was ceftoperazone plus sulbactam, ciprofloxacin, piperaclillin and moncef plus cefazidine combination. Sensitivity to cefuroxime was not
Infections and is the second most commonly isolated non-infection is a less common cause (< 5%) of the catheter related species. Gram-negative organisms are less commonly involved in catheter-related infections. Acinetobacter infection is a less common cause (< 5%) of the catheter related infections and is the second most commonly isolated non-fermenter in human bacteriological specimens. Pneumonia is most common followed by urinary tract and soft tissue infections. Mere presence of Acinetobacter species in human specimens does not imply infections. A positive blood culture from the peripheral lines and clinical co-relation is essential to prove catheter-related infection. We obtained a positive culture from blood as well as the catheter tip along with symptoms. Symptoms of Acinetobacter catheter infection resembled those of malaria and therefore it is important to differentially diagnose it from malaria. This case report highlights that recurrent febrile episodes of fever in patients with indwelling catheters for long duration should raise suspicion of catheter-related infection. Though the patient was treated with ciprofloxacin to which bacteria were sensitive, infection persisted till the catheter was removed. Therefore, removal of catheter is necessary to eliminate the nidus of infection.

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Received : 5.7.2001; Revised : 13.11.2001; Re-revised : 5.2.2002; Accepted : 11.8.2003

REFERENCES

Poetic Voice of Obstructive Sleep Apnea

Sir,

The prevalence of obstructive sleep apnea (OSA) is increasing mainly due to increased awareness of the disorder in society. (Snoring in sleep is not a sign of sound sleep). OSA is recognised as a risk factor for the development of hypertension, ischemic heart disease, strokes and diabetes. Vehicular accidents are also common due to excessive daytime sleepiness. OSA is being summarised in a poem which is as follows.

OSA Voice
Can’t sleep to the core
I know it is the snore,
People around can’t sleep,
The snore is the alarm beep,
It stops for sometime to recur again,
Oxygen required again and again,
Not only I disturb all people around,
I too get up to visit the urinal around,
Too tired in the day inactive and depressed,
Constantly look around for a place to rest,
I haven’t slept for many years,
It does bring in some tears,
Would prefer to sleep rather than to weep,
Throughout the day consuming tea and coffee,
The real answer is polysomnography,
Titration study gave the solutions,
Which dissolved all the complications,
Feel fit, fresh, active all the day, without a gap,
The night is welcome but not without the CPAP.

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Received : 21.7.2003; Accepted : 11.8.2003

REFERENCES

Endobronchial Metastases from Renal Cell Carcinoma

Sir,

The lung is an extremely common site for metastases from extra-pulmonary tumours. The endobronchial metastases, however, is quite rare and occurs in only 2-5% of patients according to autopsy findings. Amongst all solid tumours, renal cell carcinoma is the most common tumour to involve the bronchus secondarily. We describe a case of endobronchial metastasis six years after the primary tumour for its rarity. To the best of our knowledge, no such case has yet been reported from our country.

A 70-year-old nonsmoker male was an old case of renal cell carcinoma managed by right nephrectomy followed by radiotherapy and chemotherapy in 1994. He was symptom-free till October 2000 when he was admitted in the same hospital with complaints of productive cough, fever and progressively increasing breathlessness of one week duration. There was no history of haemoptysis, chest pain or significant weight loss. On clinical examination, his pulse rate was 110/min, BP-120/70mmHg and respiratory rate 26/min. He had pallor, mild
bilateral pedal oedema and there was no lymphadenopathy. Chest examination revealed tracheal shift to right, dull percussion note with reduced intensity of breath sounds and crackles over right infracavicular and interscapular areas. Examination of other systems was essentially normal. Investigation revealed polymorphonuclear leukocytosis, anaemia (Hb-10 gm%), with normal metabolic parameters. Sputum examination was negative for acid-fast bacillus and malignant cells. Chest radiograph (Fig. 1) revealed collapse of anterior segment of right upper lobe and patchy acinar opacities at right upper and lower zones. The bronchoscopic examination revealed polypoidal growth almost completely occluding the right upper lobe bronchus. The histopathological examination of bronchial biopsy showed malignant clear cells of renal cell carcinoma in sheaths. He was initially managed with broad-spectrum parenteral antibiotics and oxygen therapy. He later developed features of septicemia with severe hypoxaemia, hypotension, altered sensorium and expired after one week.

The symptoms of endobronchial metastases are usually indistinguishable from primary bronchogenic carcinoma and most of endobronchial metastases are initially diagnosed as primary bronchial tumours until histopathological examination confirms the diagnosis. However, haemoptysis has been found to be the most common symptom, occurring in 62% of patients in one of the case series.1 Our patient, however, did not have haemoptysis and instead presented with features of atelectasis and post-obstructive pneumonia. Radiologically the most common sign is atelectasis due to endobronchial obstruction, as also seen in our patient. Most endobronchial lesions can be viewed via bronchoscope and diagnosis established by bronchial biopsy. However, at times bronchial biopsy may not prove diagnostic and thoracotomy is required for an accurate diagnosis.2 The tumour usually involves submucosal lymphatics rather than the surface of the mucosa and this probably explains the failure of bronchial biopsy and need for thoracotomy for establishing the diagnosis.2 The time interval between the diagnosis of renal cell carcinoma and endobronchial metastases is quite variable and the longest interval of 13 years has been reported.3 The time interval in our patient was 6 years. The possible route of spread of renal cell carcinoma to bronchus seems to be through bronchial or pulmonary arteries.3

In conclusion, in a case of renal cell carcinoma with a long symptom-free interval after nephrectomy, the appearance of cough, haemoptysis and atelectasis on chest radiograph may point to the underlying endobronchial metastases.

**REFERENCES**


**Effect of Lemon-Honey in Lukewarm Water on Hyperacidity**

Milk is effective at neutralising acid, that is why a diet with a high milk content is often advised for patient with acid peptic disease; but such a diet stimulates significantly greater production of acid than a normal diet, thereby putting a question mark against the role of such a diet.1 Keeping in view the above facts, and patient’s experience with lemon-honey in luke warm water, getting relief of acid eructations and rertostrernal burning, initiated us to note the effect of this combination in various symptoms of hyperacidity.

Twenty patients suffering from acid eructations, retrosternal burning, dyspepsia, postmeal heaviness, nausea, vomiting, upper abdominal discomfort, drug-induced or alcohol-induced gastritis etc. were included in the present study. There were only six female patients. Fourteen patients were males, and belonged to 4th and 5th decade of life. All the patients aged from 32 to 64 years of life. Age and sex distribution is shown in the Table 1. They were allowed to take everything in their routine diet including fruit, vegetables, cereals etc. except for reduction in number of cups of tea from 6-10 to maximum two per day. A glass of milk at bed time was
fixed and lesser consumption of fried foods were advised. None of the patients were put on any kind of antisecretory, antacids, anti-spasmodic or peptic ulcer healing agents like cinmetidine, ranitidine, bismuth salts etc. Juice of one lemon, a tsf of honey in a glass of lukewarm water was taken as and when required. The follow up was done for 6 weeks, interrupted by 2 weekly reporting. None of the patients underwent any kind of investigations like routines, radiological or endoscopic. Various clinical observations have been tabulated in Table 2 without any quantification. Those continuing alcohol were barred and those taking drugs were advised to take these after meals. None of the patient was smoking.

An open, uncontrolled; pilot study, is based purely on clinical presentation and evaluation. Hyperacidity symptom complex is a day to day problem with every clinician. In nearly 50% cases of non-ulcer dyspepsia, a spiral organism, \textit{Helicobacter (Campylobacter pyloridis)}, has been suspected to be the possible cause\(^2\) further confirmed by an experimental study on a normal volunteer, developing an acute self-limiting dyspeptic syndrome with acute gastritis after swallowing the bacteria. Milk which is not helpful in the process of healing peptic ulcer in patient of acid peptic disease even if it is dispensed by intragastric milk drip. Milk has been in the use since long because of the instant relief of pain offered by it. The controversial association of \textit{Helicobacter (Campylobacter pyloridis)} and gastritis and its interesting relation with the peptic ulcer\(^2,3\) opens a new phase of its association with lemon honey in lukewarm water because of the relief of symptoms in all the patients, although it may look too early to make such a comment.

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Received : 26.9.2001; Revised : 24.1.2002; Accepted : 11.8.2003

### Table 1: Age and sex distribution

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<th>Decade of life</th>
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<td>5th</td>
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<td><strong>Total</strong></td>
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<td>14</td>
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</table>

### Table 2: Response

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No of patients</th>
<th>After 2 weeks</th>
<th>After 4 weeks</th>
<th>After 6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>12/20</td>
<td>10/12</td>
<td>12/12</td>
<td>12/12</td>
</tr>
<tr>
<td>Acid eructations</td>
<td>20/20</td>
<td>14/20</td>
<td>16/20</td>
<td>18/20</td>
</tr>
<tr>
<td>Upper abdominal discomfort</td>
<td>16/20</td>
<td>6/16</td>
<td>10/16</td>
<td>10/16</td>
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<tr>
<td>Postmeal heaviness</td>
<td>14/20</td>
<td>8/14</td>
<td>8/14</td>
<td>10/14</td>
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<tr>
<td>Retrosternal burning</td>
<td>20/20</td>
<td>16/20</td>
<td>16/20</td>
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</table>

### References

### Gelatinous Transformation of Bone Marrow

Gelatinous transformation (GT) is a condition in which there is fat atrophy, narrow hypoplasia and replacement of these cells by an amorphous extracellular material.\(^1\) The percentage of GT was approximately \(0.2 \pm 0.08\)% in all age groups with a slight peak of incidence in young adults. The spectrum of underlying diseases is heterogenous and age-dependent. In younger ages (<40 ages), anorexia nervosa, acute febrile states and AIDS; in middle ages, alcoholism and lymphomas and in older ages, carcinomas, lymphomas and CHF were more commonly associated with GT.\(^2\) It occurs in association with tuberculosis, kala-azar, renal failure, celiac disease, in patients in intensive care,\(^2\) severe hypothyroidism, at sites exposed to high dose X-irradiation and Hodgkin’s disease.\(^1\) It develops rapidly in acute severe illness with multiple organ failure, severe acute infections or acute febrile states\(^2\) and in association with myeloid leukemoid reaction.\(^3\) Majority of cases have weight loss (78%) and anaemia (82%).\(^2\) Peripheral blood film (PBF) shows variable cytophenias. Bone marrow aspirate may not spread normally on film preparation. It contains amorphous material, sometimes fibrillar or finely granular which stains pink or pinkish purple with Romanovsky stains. In bone marrow histology the changes are usually focal. There is atrophy of fat cell, which are both reduced in number and are variable-size with mild to moderate hypoplasia of hemopoietic cells along with the presence of amorphous material which on hemotoxyline and eosin stain has a light blue to pale pink color and a finely granular appearance.\(^1\)

A 12 years male presented with 4 months history of moderate to high-grade continuous fever associated with rígors and chills and joint pain. There was swelling of big joints (knee, elbow, ankle and wrist) for 15 days, with restricted joint movements. Patient was moderately build and nourished, anemic and had hepatosplenomegaly along with inflammation of the joints. Cardiovascular system examination revealed a pansystolic musical murmur over the mitral area. Hematological investigations revealed Hb 5.5 gms/dl. Peripheral blood film revealed dimorphic red blood cells (RBC) with mild to moderate degree of anisocytosis and poikilocytosis. Rare nucleated RBCs were present. TLC was 23000/cumm with neutrophilic leucocytosis with shift to left (neutrophils 28%, stab forms 36%, metamyelocytes 8%, myelocytes 6%, lymphocytes 20%, eosinophils 2%). Platelet count - 95000/cumm, reticulocyte count - 1.2% and ESR - 160 mm 1st hour. CRP +ve, ASO +ve, antinuclear antibodies
negative, SGOT 54 IU/L. Bone marrow aspiration study revealed scanty marrow diluted with peripheral blood. The cellularity was poor, mainly constituted by myeloid series of cells. Erythroid series of cells were markedly reduced. No megakaryocyte was seen. Interspersed in the smear was present pinkish granular necrotic material (Fig. 1). Myelogram revealed blasts 0%, myelocytes 6%, metamyelocytes 12%, stab forms 24%, polymorphs 30%, lymphocytes 22% and eosinophils 2%. Trephine biopsy was not done. A diagnosis of acute rheumatic fever with leukemoid reaction, anaemia and thrombocytopenia with gelatinous transformation of the bone marrow was made. The patient was given antibodies and supportive care to which he responded well.

The blood cell counts in cases with GT depends on the extent of marrow involvement. Bohm J2 found 155 cases of GT among 80000 marrow biopsies, out of which 6 cases were of severe acute infections or acute febrile states of unknown cause. Our case had acute rheumatic fever, which was a severe clinical disorder. This resulted in myeloid leukemoid reaction and bicytopenia, which was due to GT and literature, quotes GT in acute febrile states or acute infections. Among young patients (<40 years) severe infections (e.g., AIDS and acute febrile states) represented 28.5% of the cases of GT. Stress factors may play a role in the development of GT as is suggested by GT in severe chronic heart failure. Similar factors explain the finding of GT in patients under intensive care and in patients with a substantial weight loss. It appears that any severe underlying illness that disturbs the basic bioregulatory processes could lead to GT of the marrow. Inanition and malnutrition have often been implicated as etiological factors. These factors are instrumental as they mobilize the body fat. The factors other than malnutrition must have a role, as cachexia is not universally seen in these cases. Our case was moderately nourished in which acute febrile state results in the development of GT.

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Received : 10.6.2002; Revised : 26.12.2002; Accepted : 8.8.2003

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Fig. 1 : Photomicrograph of bone marrow aspirate showing amorphous material. Leishman’s stain X 400.