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Otological manifestations of thalassaemia intermedia: evidence of temporal bone involvement and report of a unique cholesteatoma-like lesion

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Abstract

Thalassaemia intermedia should be considered in any chronically anaemic patient presenting from the Middle East with hearing impairment. We report here three Saudi siblings with thalassaemia intermedia and features of severe bone marrow expansion, particularly invading the temporal bone. They were seen first for their otological problems before they had access to proper haematological evaluation. One member was admitted for surgical exploration of a cholesteatoma, which was then found to be marrow expansion of the temporal bone. Screening of the family revealed two more anaemic siblings with thalassaemia intermedia. Audiological examination of all the family members showed that only the two affected members had a high frequency sensori-neural hearing loss.

Bone marrow expansion into the temporal bone is a rare feature of thalassaemia intermedia. Cholesteatoma-like lesion has not been previously described. It has to be considered in all cases of symptomatic thalassaemia intermedia manifesting with cavitation and lytic lesions in the mastoid system. The likelihood that sensorineural hearing loss may complicate the thalassaemias is raised and the possible mechanism for such involvement discussed. The proper management for different otological manifestations of the thalassaemias is suggested. These cases would suggest a more extensive involvement of the temporal bone in the thalassaemias than has been previously recognized. Further large scale studies are required to illuminate the subject.

Introduction

The thalassaemia syndromes constitute one of the most serious public health problems in the Middle East, Mediterranean world and the Far East (Martin and Nathan, 1990). They are hereditary diseases resulting from defective synthesis of the globin-chains of the haemoglobin molecule (Modell and Berdoukas, 1984). There are two main groups of thalassaemias: thalassaemia minor, the well-defined heterozygous carrier state that is characterized by a remarkably homogeneous clinical and haematological picture, and thalassaemia major, which is the transfusion-dependent homozygous form. In thalassaemia minor there is only a mild degree of anaemia; the spleen is not palpable; there is no jaundice; haemoglobin A_2 is elevated but haemoglobin F is normal or only minimally raised. In thalassaemia major, the anaemia is severe and splenomegaly is remarkable; patients are usually jaundiced and their haemoglobin F is quite high. Not all types of thalassaemias fit into one of these categories. With the complex genetic interactions producing different types of thalassaemias, there are forms which are of intermediate severity. They are not the minor form in the sense that patients are quite symptomatic from their anaemia; and they are not the major type because their anaemia is not life threatening. This so called thalassaemia intermedia (Weatherall and Clegg, 1981) is particularly common among Kurds, Cypriots and in Iran and Azerbaidjan (Engelhard *et al.*, 1975; Nasab, 1979; Rustamov *et al.*, 1981). It is characterized by a moderately severe anaemia, splenomegaly and extramedullary haemopoiesis. Somewhat surprisingly, this latter complication is even more common than in the thalassaemia major form. Unfortunately most physicians have only a vague if any idea about this extremely common genetic problem.

We describe here a unique Saudi family whose first member presented to us with a cholesteatoma-like lesion; he was admitted with a hearing impairment from an extramedullary mastoid tumor encroaching on the middle ear. Out of eight siblings, three had thalassaemia intermedia and presented with features of temporal bone involvement. These features would seem to suggest a more severe involvement of the temporal bone in thalassaemia intermedia than has been previously realized.

Subjects and methods

An 18-year-old Saudi boy presented to the Otolar-

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yngology unit of the Asir Central Teaching Hospital with a three year history of hearing impairment in the left ear. Although he had been anaemic all his life, he had never been incapacitated by it or been properly investigated. He had two transfusions in the past and advised to take haematinics in local clinics and dispensaries. The patient denied any history of otorrhoea, pain, tinnitus or vertigo. Clinical examination showed a pale patient with evident thalassaemic facies (Fig. 1). His cephalofacial deformity was scored as grade 2, applying the Logothetis scoring system (Logothetis *et al.*, 1971; Sbyrakis *et al.*, 1987), with evident mongoloid appearance and mild maxillary hypertrophy. The abdomen was soft with moderate splenomegaly at 10 cm below the costal margin and mild hepatomegaly. ENT examination revealed an intact pars tensa with granulation in the pars flaccida above the posterior malleolar fold. X-rays of the mastoids showed an osteolytic area in the left mastoid (Fig. 2a). CT scan also showed an osteolytic 'cavity' in the left mastoid (Fig. 2b). Pure tone audiometry showed a conductive hearing loss of 40 db in the left ear (Fig. 3), with normal hearing in the right. Haemogram showed severe anaemia; the results of the pre-operative anaemia screen are shown in Table I.

A provisional diagnosis of chronic suppurative otitis media with cholesteatoma was made and the patient's left mastoid was explored. At surgery, the mastoid was found to be filled with vascular tissue. Similar tissue was found in the middle ear, surrounding the ossicular chain and filling the meso- and hypotympanum.

Through a posterior tympanotomy approach, the swollen tissue was cleared from the mastoid and middle ear with preservation of the ossicular chain. All the material removed was sent for histopathology which showed haemopoietic tissue. The patient made an uneventful post-operative recovery.

The diagnosis of marrow expansion in the mastoid of the propositus made us undertake a detailed search of his immediate family members for any similar problems. Of eight siblings, two more were found to be severely anaemic and had palpable spleens: a 12-year-old brother and a 29-year-old sister (Table I). The brother of the propositus was totally asymptomatic as regards his ears, nose

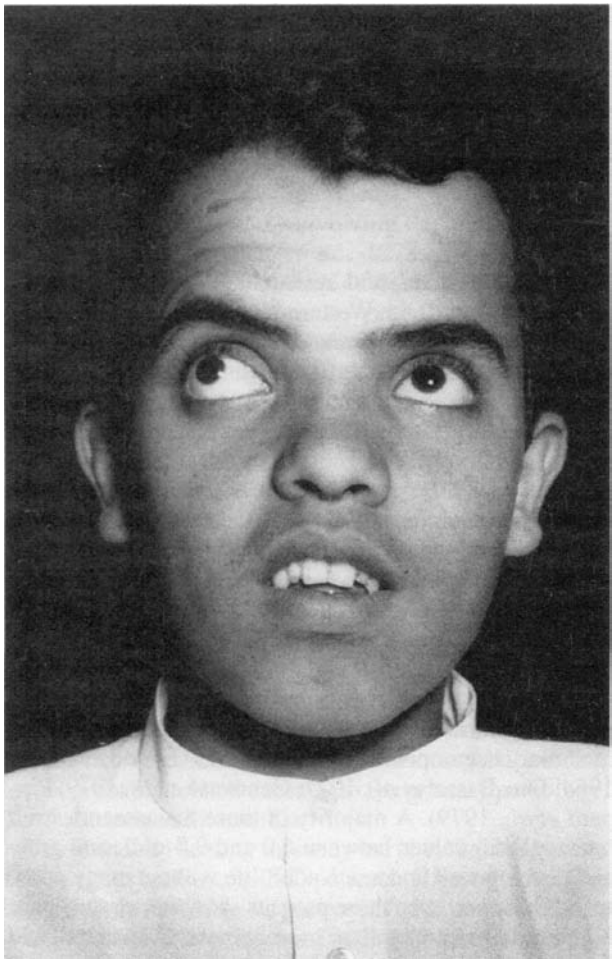

FIG. 1

Photograph of the propositus showing grade 2 cephalofacial deformity (Logothetis *et al.*,1971), with mongoloid features and mild maxillary hypertrophy.

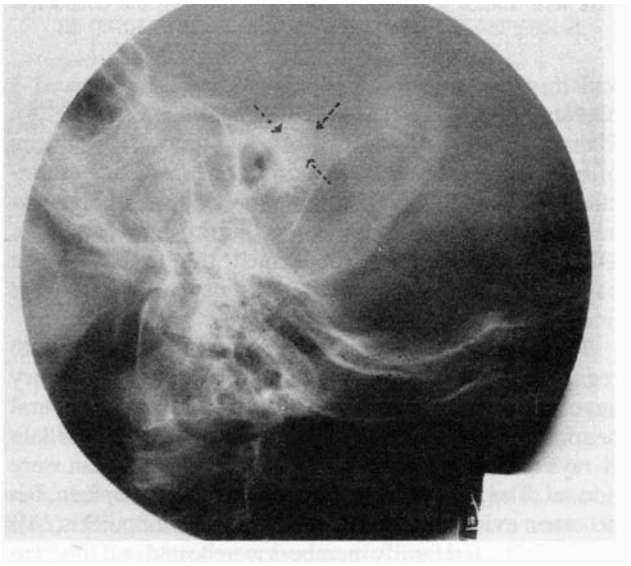

FIG. 2a

Plain X-ray of the left mastoid showing the 'cavity' with a sclerotic margin 'arrows'.

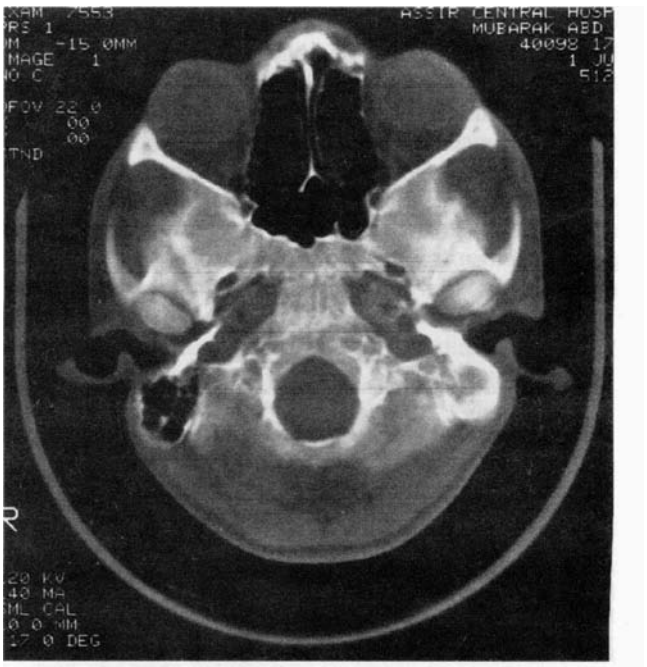

FIG. 2b

CT scan showing the involved left mastoid with a central lucent area.

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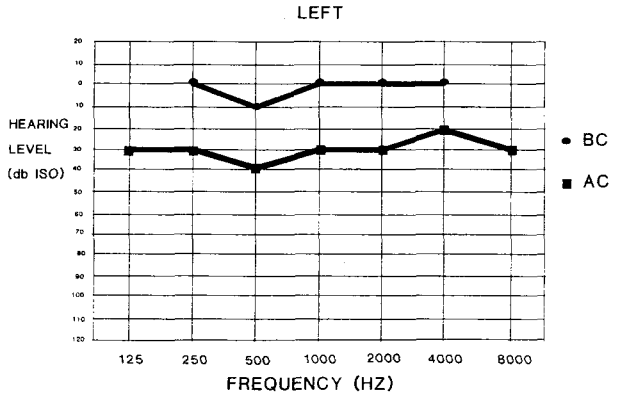

FIG. 3

Pure tone audiogram of the propositus showing the conductive hearing loss in the left ear with an A–B gap of 30–40 dB.

and throat. Pure tone audiometry, however, showed a bilateral high tone sensorineural hearing loss (Fig. 4). Plain X-ray showed sclerosis of both mastoids; a CT scan of both temporal bones was normal. Ultrasound examination of the abdomen revealed a moderate splenomegaly and a paravertebral mass in the thoraco-lumbar region. This was subsequently confirmed by CT scan. The patient's spinal-motor and spinal-sensory systems were normal.

The sister of the propositus was also asymptomatic with regard to her ears, nose and throat. Pure tone audiometry again demonstrated a significant bilateral sensorineural hearing loss in the higher frequencies (Fig. 5). Plain X-rays of both temporal bones as well as a CT scan were normal. The patient had a moderately enlarged spleen, but no other evidence of extramedullary haemopoiesis. All other unaffected family members were tested and found to be normal.

All the affected members showed progressive evidence of hypersplenism as evidenced by remarkable splenomegaly and various degrees of cytopenia. It was felt that this would aggravate their anaemia with more pressure on the bone marrow to expand. With the audiometric evidence of hearing loss in all the affected family members, it appeared that the temporal bone was the main target for bone marrow expansion. To obviate progression of this expected complication, we plan to splenectomize them and start a hypertransfusion regimen with iron chelation, to suppress their own bone marrow. For the time being, patients are on folic acid and allopurinol. It is hoped to report on auditory improvement at a future date.

Results

The propositus and two of his siblings have clinical and haematological stigmata of thalassaemia intermedia (Table I), and all three are now followed up in the haematology clinics for further management. The propositus, in addition, presented with a conductive hearing loss and an X-ray cavity in the mastoid. Both plain X-ray and CT scan suggested the cavity to be cholesteatomatous. At exploration, however, the cavity was found to be filled with vascular haemopoietic tissue. Surgical clearance of the middle ear and mastoid yielded a good hearing improvement. In addition, two of the siblings of our patient showed a bilateral sensorineural hearing loss, while the unaffected members of the family had normal audiometric patterns. Significantly, only those siblings with thalassaemia intermedia demonstrated a high tone hearing loss. They will be followed up in the haematology clinics after more aggressive management has been initiated. The results of their audiometric response will be published after splenectomy and a long course of hypertransfusion regimen. These two patients should act as controls for future management of patients with this sort of haematological problem. A satisfactory audiometric response and improvement in the quality of life should encourage us to manage selective patients with similar haematological disorders comparable to thalassaemia major instead of neglecting them to become victims of unwanted and ineffective bone marrow expansion. The propositus will also be managed on similar lines, but only after a plateau response to surgery is achieved. This should help us to pin-point the degree of his response to proper haematological management rather than surgery. We hope that this well studied family can act as a model for management of patients who do not have access to proper haematological assessment but present with evident hearing defect.

TABLE I

RELEVANT LABORATORY DATA OF THE AFFECTED FAMILY MEMBERS

Patient	Hb (g/dL)	MCV (fL)	MCH (pg)	HbF (%)	LDH (U/L)	Uric Acid (mg/dL)	Bilirubin (mg/dL)
Propositus	7.8	55	21.0	22	990	7.0	2.4
Brother	5.6	47	17.5	16	1123	7.4	2.8
Sister	6.7	54	20.2	21	856	8.5	3.3

Reference values: Haemoglobin 13–18 gm/dL (our Asir region is >7000 feet above the sea level); MCV 76–96 fL; MCH 27–32 pg; Haemoglobin F<1 per cent; Lactate dehydrogenase (LDH) 100–450 U/L; Uric acid <70 mg/dL; Bilirubin 0.3–1.0 mg/dL.

Discussion

While physicians and researchers caring for thalassaemics in most of the Western world far outnumber their patients; in the Mediterranean area, Far and the Middle East, thalassaemia attains the status of a genetic public health problem. Now with easy travelling and the near redistribution of the world population, very few diseases remain local problems. The aim of this study is to orientate others with the possible atypical presentations of this very common problem.

Unfortunately there is no adequate definition of thalassaemia intermedia. It is a disorder with an extraordinarily widespread clinical spectrum. A minority of these children go through a miserable early childhood with relatively low haemoglobin without needing transfusion for their survival; these patients may finally succumb to gross skeletal abnormalities from marrow expansion and extramedullary haemopoietic tumour masses (Erlandson *et al.*, 1964; Ben-Bassat *et al.*, 1977; Genovese *et al.*, 1979; Pippard *et al.*, 1979). A majority of these thalassaemics run haemoglobin values between 6.0 and 9.0 g/dL and grow and develop well and reach adult life without many problems. However, even these patients show an extraordinary high rate of extramedullary haemopoiesis (Weatherall and Clegg, 1981). Spinal cord compression is a well recognized complication of thalassaemia intermedia (Bate and Humphries, 1977; Issaragrisil *et al.*, 1981), and temporal bone involvement is not unknown (Hazell and Modell, 1976; Modell and Berdoukas, 1984). Thus, skeletal defor-

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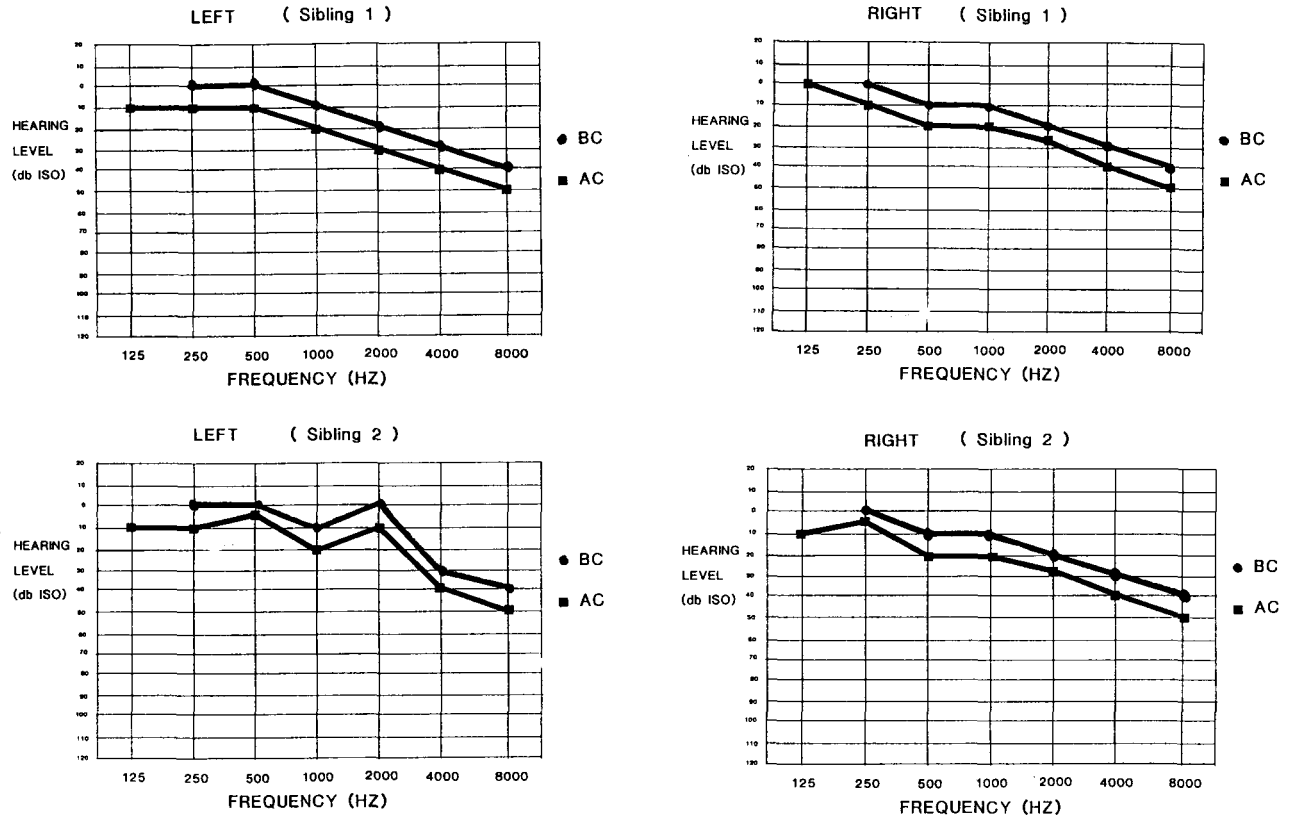

FIGS. 4 & 5
Audiometry of the siblings showing bilateral symmetrical high-tone hearing loss.

mities and bone and joint disease is quite common in patients with thalassaemia intermedia. Osteoarthropathic complications, particularly involving the ankle joint has been reported (Gratwick *et al.*, 1978; Weatherall and Clegg, 1981). Histology of these cases showed osteomalacia and microfractures, besides other findings. These patients will eventually become more anaemic and symptomatic as hypersplenism and folate deficiency develop, or when they become nutritionally deficient or get intercurrent infections. We describe here a young Saudi patient with bone marrow expansion into the temporal bone presenting as a cavity in the mastoid system with involvement of the middle ear. Two of his siblings, who suffered from the same disease, also showed high tone loss of hearing. It may be argued that the occurrence of sensorineural hearing loss in these two siblings may represent some other unrelated familial cause of deafness; the fact that this occurred only in the two siblings suffering from thalassaemia intermedia, whilst the other siblings were totally unaffected audiometerically is, in our opinion, very strong circumstantial evidence that the sensorineural hearing loss is probably related causally to the primary pathology, *viz.* thalassaemia intermedia.

Sensorineural hearing loss may occur in the steady state homozygous sickle cell (SS) patients. High tone hearing loss being described in 12 per cent of children (Friedman *et al.*, 1980) and 22 per cent of adults (Todd *et al.*, 1973). Compression of the auditory nerve in the internal auditory canal by the expanded bone marrow in the petrous temporal bone (Morgenstein and Manace, 1969) could contribute to hearing loss but radiological measurement of the internal auditory canal did not differ between patients with and without abnormal audiograms (Serjeant *et al.*, 1975). This SS disease hearing impairment is variously attributed to infarctive episodes, sickling and sludging of the cochlear venous system with consequent cochlear hypoxaemia (Koide *et al.*, 1964). Currently the most tenable hypothesis for the sensorineural hearing loss in SS disease appears to be a sickling impaired blood flow in the cochlear venous system (Serjeant, 1985).

These features do not occur in the thalassaemias. Although both sickle cell disease and thalassaemia are hereditary haemoglobinopathies, their pathophysiological consequences are quite different. Thalassaemics are basically hypoxic with resultant marrow expansion, while sicklers are usually not symptomatic from their anaemia but succumb to the painful vaso-occlusive and infarctive crises of sickling. The possibility that sensorineural hearing loss in sickle cell disease may result from marrow expansion leading to narrowing of the internal auditory canal with compression of the eighth cranial nerve could not be confirmed (Sergeant *et al.*, 1975). As thalassaemics show more tendency for bone marrow expansion and extramedullary haemopoiesis, we assume that this possibility should be seriously considered in these patients. Certainly cavitation of the mastoid system and marrow invasion of the middle ear would suggest a more severe involvement of the temporal bone in thalassaemia. The possibility that sensorineural hearing loss in this condition may result from narrowing of the internal auditory canal needs to be investigated.

With the wide distribution of sickle and thalassaemia genes in many parts of the world, it is not uncommon for a patient to inherit a sickle-cell gene from one parent and a

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thalassaemia gene from the other. This interaction can create a remarkably heterogeneous group of haemoglobinopathies called sickle-cell thalassaemias (S-thal). If the thalassaemia gene is of the kind that is non-existent or totally dysfunctional, then the clinical picture is that of severe sickle-cell disease with all of the above mentioned possible otological manifestations. However, variable expression of the beta gene leads to production of increasing amounts of haemoglobins A and F. This will certainly affect the clinical course of the condition and to certain extent ameliorates the severity of the sickling process. Otological features similar to that of Ménière's disease has been described in these patients (Marcus and Lee, 1976). These authors described two S-thal members of a family who presented with hearing impairment and vertigo after strenuous exercise. They thought that it was due to sickle cell auditory crises.

The right management of patients with thalassaemia intermedia is quite controversial. Although the majority of them can live without much medical intervention, the sporadic occurrence of these audiological manifestations is quite alarming in specific clinical situations. Whether to adopt a prophylactic policy to avoid progression of these otological manifestations or to resort to surgical and other invasive procedures only when a real problem arises, needs clarification. The fact that three siblings with similar haematological conditions have had otological manifestations suggests that more than a 'wait and watch' policy is needed. We are going to be more aggressive with our patients and advocate splenectomy with possible hypertransfusion and iron chelation regimen to reverse the audiological impairment.

The fact that one of them developed cavitation of the mastoid bone with a cholesteatoma-like lesion is in our opinion a warning for more action. When one is faced with the real problem of hearing impairment from marrow expansion, then low dose radiotherapy can be tried. This approach has been found to be quite effective in the control of spinal cord compression from paraspinal masses (Issaragrisil *et al.*, 1981). Surgical exploration should not be needed, except in exceptional situations such as ours when the diagnosis is not established, if proper diagnosis and early medical management could be made. Management of these selected patients along the same lines as thalassaemia major should reduce the risk of extramedullary complications.

Conclusion

Thalassaemia intermedia is a common but vaguely understood haemoglobinopathy. It is not uncommon for these anaemic children, especially in the less prosperous parts of the world, to remain undiagnosed, simply because their anaemia is not life threatening like the major forms of thalassaemia. These patients can then present with complications resulting from the compensatory but ineffective pathophysiological events leading to bone marrow expansion and extramedullary haemopoiesis. We conclude here that when chronically anaemic patients present with hearing impairments, thalassaemia intermedia should be considered in the differential diagnosis. When thalassaemic patients present with conductive or sensorineural hearing loss and if this is accompanied by osteolytic areas in the temporal bone, the possibility of invasion of the area by bone marrow will have to be entertained seriously. Although hearing impairment and cholesteatoma can occur in thalassaemic patients, bone marrow expansion will have to be excluded. We recommend that such patients should be given the benefit of more aggressive medical management with splenectomy and/or hypertransfusion regimen, and surgery be reserved for symptomatic or diagnostically difficult cases. We hope to publish our data on the hearing improvements in this family after embarking on a planned medical management to suppress their own bone marrow. As they are hypersplenic now, splenectomy should relieve some pressure on the ineffective marrow. Regular hypertransfusion should suppress their bone marrow and possibly reverse, or at least halt, progression of their audiological impairment.

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