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NEUROLOGICAL COMPLICATIONS OF CHRONIC MYELOID LEUKAEMIA: ANY CURE?

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ABSTRACT
Objective: To attempt to explain the non-reversal, contrary to the widely held view, of the neurological deficits complicating chronic myeloid leukaemia.

Method: Using patients' case folders and haematological malignancy register all cases of chronic myeloid leukaemia seen in Jos University Teaching Hospital between July 1995 and June 2005 were retrospectively studied. All the available literature on the subject was also reviewed.

Results: Thirty-three cases of chronic myeloid leukaemia were seen within the study period. Five (15.15%) of them had one or more sensori-neural defects. Of the five, two (40%) patients presented with bilateral hearing impairment, each beginning with the left ear; one (20%) presented with left ear hearing loss; one (20%) came with severe left ear tinnitus; one (20%) presented with complete bilateral hearing and bilateral visual losses. Fundoscopy showed leukaemic deposits on the retina. Other causes of blindness and deafness, e.g. trauma and foreign body in the ear respectively, were excluded.

Conclusion: While the complications due to hyperleucocytosis-induced stasis recover following the conventional treatment, those due to other pathogenetic mechanisms such as leukaemic deposits do not return to their pre-morbid states following disease control despite the use of the currently available treatment protocols.
For future research, more still needs to be done to elicit other uncommon pathogenetic mechanisms underlying these complications with a view to finding specific treatment measures for worrisome chronic myeloid leukaemia-related sensori-neural deficits.

Key Words: Neurological complications, chronic myeloid leukaemia, cure. *(Accepted 27 July 2007)*

INTRODUCTION

Neurological complications of chronic myeloid leukaemia (CML) are rare[1] but when they occur, their presence is a serious concern for patient and physician. About 15%[2] to 25%[3] of patients present with these complications which include[4]:

CNS- Dizziness, slurred speech, delirium, stupor, intracranial (cerebral) haemorrhage.

SPECIAL SENSORY ORGANS:

Eye- Visual blurring, diplopia,papilloedema, retinal vein distension, retinal haemorrhages, blindness.

Ear- Tinnitus, partial hearing, deafness.

PENIS Priapism

Usually, these neurological deficits are said to respond to rapid cytoreductive measures like leukapheresis and hydroxyurea therapy[2]. In our centre, we use hydroxyurea or busulphan but not leukapheresis for lack of facilities. However, in our experience, neurological complications do not regress with these drugs and we do not think that this is merely due to the absence of leukapheresis alone. This observation prompted a review of the neurological complications seen in CML in our centre in an attempt to explain this unusual finding.

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MATERIALS AND METHODS

In a retrospective study, using patients' case folders and haematological malignancy register all cases of CML seen in Jos University Teaching Hospital (JUTH) between July 1995 and June 2005 were examined. They all had full blood count and bone marrow aspiration done to establish diagnosis. Cytogenetics was not done for lack of facilities. Those who had hearing difficulty had limited ear, nose and throat examination done. The blind patient had fundoscopy done. Detailed hearing tests were not done for lack of personnel and facilities at the time of presentation.
They were all initially admitted for investigations, rehydration and commencement of drug therapy namely hydroxyurea 1 2g daily in divided doses or busulphan 4 10mg daily and allopurinol 300mg

daily. They were all later followed up in haematology out patient clinic.
Available literature on the subject was also reviewed.

RESULTS

Thirty- three cases of CML were seen within the study period. They were made up of 19 males and 14 females giving a ratio of 1.4 to 1 **(Fig. 1)**. Five (15.15%) of them had one or more sensori neural defects. Of the five two (40%) patients presented with bilateral hearing impairment, each beginning with the left ear; one (20%) presented with left ear hearing loss; one (20%) came with severe left ear tinnitus; one (20%) presented with complete bilateral hearing and bilateral visual losses **(Table 1)**. Fundoscopy showed leukaemic deposits on the retina. Other causes of blindness and deafness, e.g. trauma and foreign body in the ear respectively, were excluded. Aural and ocular affectations accounted for 80% and 20% of all the impairments respectively, making the former the commoner affectation **(Table 2)**. **Table 3** shows the laboratory features at presentation and outcome following commencement of treatment. Clinical and haematological disease controls were achieved within 8 weeks of presentation except in case 4 who was never controlled before his death at 4 months after presentation.
Over the various periods of follow up no clinically significant improvement was noticed in any of them (except mild reduction in the tinnitus), not even in those who had haematological control.

Fig. 1: **Year & Sex Distribution of CML in JUTH July 1995 June 2005.**

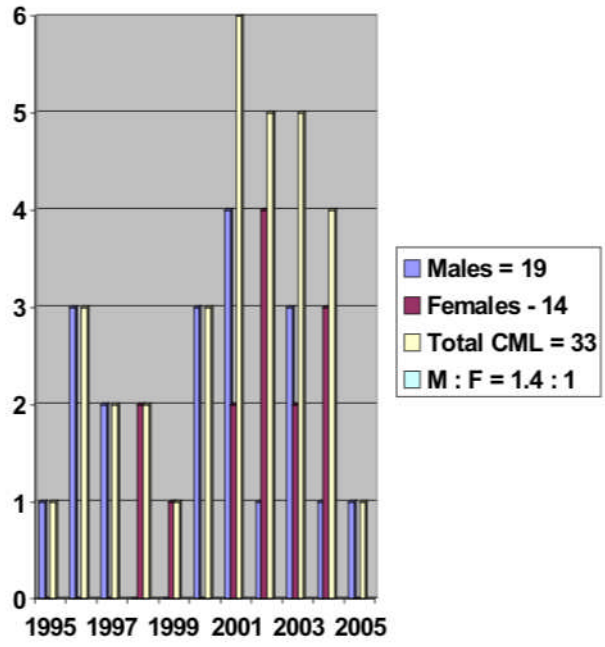

Table 1: **Prevalence Of NeurologicalImpairment In CML Seen In JUTH, July 1995 June 2005**

Neurological impairment	Prevalence (% of 5 patients)
Bilateral Deafness	2 (40%)
Left Ear deafness	1 (20%)
Left Ear Tinnitus	1 (20%)
Bilateral Deafness + Bilateral Blindness	1 (20%)
TOTAL	**5 (15.15%)**

Table 2: **Clinical Features of CML, Chronic Phase at Diagnosis**

CASE S/NO	SEX	AGE (YRS)	ORGAN: LIVER / SPLEEN (CM)	PRESENTING NEUROLOGICAL DEFICIT
1	M	46	7 / 18	Left Ear Deafness only
2	M	45	8 / 20	Severe Left Ear Tinnitus only
3	F	45	15 / 23	Bilateral Partial Deafness (Left worse than Right Ear)
4	M	26	10 / 20	Total Bilateral Deafness & Blindness
5	F	30	8 / 15	Bilateral Partial Deafness (Left worse than Right ear)
MEAN	**M : F 1.5 : 1**	**38.4**	**9.6 / 19.2**	**Aural affectation: 4(80%[1,7]) of all deficits and 12.12% of all CML seen.**
AND				
SUMMARY				**Ocular affectation: 1(20%) of all deficits and 3.03% of all CML seen.**

KEY:
Case serial number (year of presentation):
Case 1(2000); Case 2(2003); Case 3(2004); Case 4(2005); Case 5(2005)

Table 3: **Laboratory Features At Presentation And Outcome Following Commencement Of Treatment**

CASE S/NO	PCV	TOTAL WBC ($X10^9/L$)	PLATELET COUNT ($X10^9/L$)	DRUG TREATMENT GIVEN	FOLLOW UP (months)	OUTCOME
1	0.20	140.0	90.0	Busulphan	>24	-
2	0.19	120.0	190.0	Busulphan	>12	±
3	0.17	105.0	160.0	Busulphan	>12	-
4	0.23	400.0	80.0	Busulphan; Hydroxyurea	4	-
5	0.27	150.0	181.0	Hydroxyurea	6	-
MEAN	**0.21**	**183.0**	**140.2**			

KEY:
CASE S/NO (year of presentation):
Case 1(2000); Case 2(2003); Case 3(2004); Case 4(2005); Case 5(2005)
PCV = Packed Cell volume
TOTAL WBC = Total white blood cell count
OUTCOME: - means no change; ± means little or no change.

DISCUSSION

Neurological complications of CML are rare [1-3] but their occurrence places a serious concern on the patient and physician. Cure, where possible, will therefore bring a great relief to both patient and physician.

More males were affected in our study as opposed to previous study [5]. This suggests that there is no fixed sex pattern of affectation. Aural defects complicating CML are commoner (80%) than ocular defects (20%) as seen in our study (Table 2). This agrees with previous reports [5, 6]. A new finding in our study is the vulnerability of the left ear to neurological complications seen in CML. When the ear was involved, it was either the left ear alone or where the two ears were involved it either started from the left side or worse on the left. Reasons for this are unknown but it is not certain if the lying position of the patients would not be a contributory factor.

Curative treatment of any disease or its complication can best be achieved by removing the cause(s) if known. Among the pathogenetic mechanisms of the neurological defects of CML suggested in literature so far, hyperleucocytosis-induced stasis (hyperviscosity syndrome) appears to be the most predominant [1].This is said to slow down the circulation through small blood vessels in the brainstem and results in deafness [1, 5]. Leucostasis is also known to predispose to a thrombus or plug formation with subsequent occlusion of the internal auditory artery, an end artery, thus producing infarction in the inner ear [5]. This pathogenetic mechanism will respond to the conventional cytoreductive measures [2]. Cochlea lesion is said to be due to haemorrhage in the inner ear, leukaemic infiltration of the endolymphatic space or haemorrhage in the perilymphatic space [5]. Auditory nerve lesion may be due to leukaemic infiltration in the internal auditory meatus or in the auditory nerve [5]. The haemorrhagic mechanism will not respond to cytoreductive measures alone while leukaemic infiltration may do. Haemorrhage into ocular fundus impairs vision [7] while optic nerve infiltration causes permanent blindness [6]. In our case 4 patient, (Table 2), leukaemic deposits on the retina were found. This might be the cause of his blindness and it did not respond to cytoreduction.

All our patients had confirmed CML. However, contrary to previous reports, our patients, except case 4, (Table 3), had relatively lower total white cell count (105 150 X 10^9/L) than what the previous reports suggested (430 620) [5] was associated with neurological deficits. So, lack of improvement in our patients suggests that they might have presented with pathogenetic mechanisms other than the popular hyperviscosity syndrome noted previously. This might as well explain the reason for the post disease control non-reversal of the defects we saw. This is supported by the report of Schocket et al [6]. We believe that case 4 patient had other pathogenetic mechanisms other than hyperviscosity and leukaemic infiltration. Unfortunately, post mortem in him because he died at home within 4 months of presentation and was buried before we were told.

It was also observed that occurrence of more than one neurological complication is a sign of poor prognosis as seen in case 4 who had total bilateral blindness and bilateral deafness and died within 4 months of presentation.

CONCLUSION

Established neurological complications of CML due to pathogenetic mechanisms other than hyperleucocytosis-induced stasis do not return to their pre-morbid states despite adequate treatment. As at now, there does not appear to be any cure for neurological complications resulting from such mechanisms. More still needs to be done to unveil other uncommon pathogenetic mechanisms responsible for the non-reversal of these complications with a view to finding specific curative measures for them.

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