

## Differences between males and females in adult sickle cell pain crisis in eastern Saudi Arabia

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**Background:** Sickle cell disease (SCD) is highly prevalent in the Al-Hasa area of eastern Saudi Arabia. We analyzed our patient data to try and find an explanation for the unexpected observation that more males than females with SCD were transferred to the hospital after a stay in the stabilization unit.

**Patients and Methods:** We compared differences between males and females in demographics, pattern of response to treatment for pain, and discharge records for SCD patients admitted to the stabilization unit during the years 2000 to 2002.

**Results:** Approximately 20% of patients were transferred to the hospital and the remainder were discharged home. Males were admitted more often to the stabilization unit for pain control. Males were also over-represented among those whose pain persisted for over 47 hours and needed hospitalization. Female patients were distributed more evenly over the age groups; there were fewer males in the older age groups.

**Conclusion:** These preliminary observations point to the need for further studies into gender differences in pain crisis in patients with SCD.

**Key words:** Sickle cell disease, pain, gender differences

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Sickle cell disease (SCD) occurs in the form of several haplotypes around the world, and is highly variable in its clinical presentation, even within the same haplotype.<sup>1</sup> Saudi Arabia has a high prevalence of the disorder, with differences in haplotype, prevalence rate, and clinical presentation between the eastern and western provinces of the Kingdom. Physicians therefore need to know and understand the characteristics of the disease in their area of practice in order to give their patients the most appropriate treatment and advice.

The stabilization unit (SU) is an observation ward of six beds attached to the emergency room (ER) of Saudi Aramco Al-Hasa Health Center, where patients with short-term illnesses can be treated for up to 47 hours. SCD pain crisis is the most common disorder treated, making up 20% to 50% of cases, due to the prevalence of the disorder in the region.<sup>2</sup> Internal medicine physicians look after patients, and nursing staff are provided as needed, from the ER.

ER physicians initially treat SCD patients, aged 14 years or older, who present to the ER in painful crisis. Treatment consists of intravenous rehydration, oxygen, and parenteral analgesics, including opiates, depending on pain severity. Those patients who respond adequately are discharged home on oral analgesics, while those with significant persisting pain are referred to the Internal Medicine Service for further evaluation. Most of these patients are admitted to the SU for further care, together with a few patients from the Internal Medicine Sickle Cell Disease clinic.

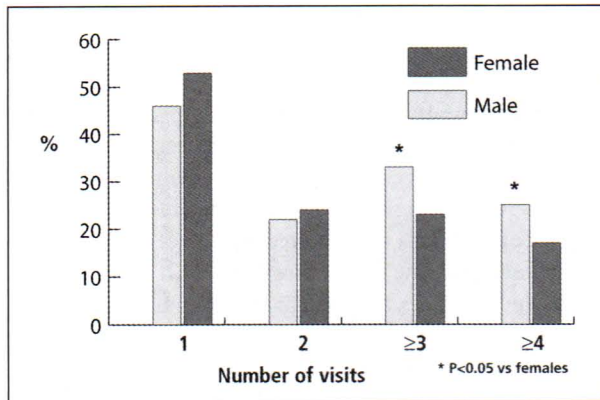
We manage over 300 cases of acute SCD pain crisis in adults annually; about 80% of these are discharged home and the rest are hospitalized. A review of SU data showed that male patients were proportionally over-represented in those transferred to the hospital.<sup>3</sup> We have analyzed our patient data in more detail to further understand this unexpected finding. This paper describes the gender differences observed in our SCD patients treated in the SU.

### Patients And Methods

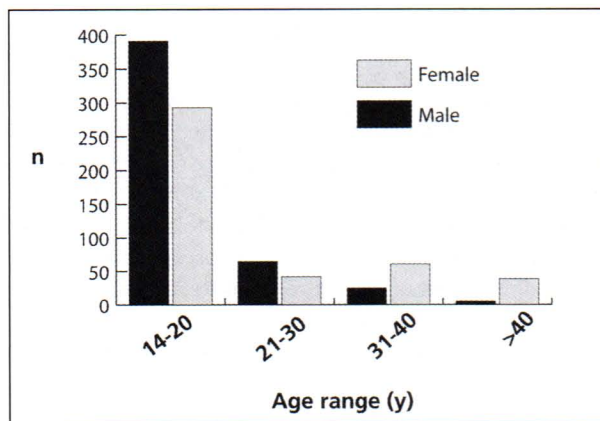
All patient data have been maintained in retrievable computer system (Microsoft Access) since the opening of the SU in 1993. Pertinent patient information was retrieved from the database for the three years of 2000 to 2002. Clinical management of the patients has been described elsewhere.<sup>2</sup> The null hypothesis was applied to differences between males and females in means and percentages, to determine statistical significance, by testing the standard error of differences between percentages.

### Results

A total of 2184 patients were admitted to the SU during the years 2000 to 2002. Twenty percent were transferred to the hospital, and the remainder were discharged home. Of 391 patients with SCD, 193 were males (49%) and 198 were females (51%), who together had 919 painful episodes (cases in Table 1). Males constituted 53% of the SU admissions. The females were slightly older than the males. There



**Figure 1.** Distribution of number of visits to the stabilization unit by sickle-cell disease patients by sex.



**Figure 2.** Sickle-cell disease cases by age and sex.

were 192 transfers to hospital among the SCD patients, including 127 males and 65 females. Although the number of males and females in the SU were almost equal (47% vs 53%), males constituted 66% of transfers to the hospital, a clinically and statistically significant difference ( $P<0.001$ ).

Males were also proportionally over-represented among those admitted to the SU three or more times per year (Figure 1). Sixty-three of 193 males (33%) visited three or more times per year, compared with 46 of 198 females (23%) ( $P<0.05$ ). The data for four or more painful crises per year show the same trend at 25.4% and 16.7%, respectively, for males and females ( $P<0.05$ ). Only 5 male SCD patients were over the age of 40 years, compared with 39 females (Figure 2). There was no difference in the gender distribution of some indicators of SCD severity, including risk of early death,<sup>3</sup> haemoglobin level, fetal haemoglobin (HbF) concentration and occurrence of acute chest syndrome (Table 2).

## Discussion

Our results suggest that females do better than males in acute SCD pain crisis. The female patients consisted of

both unmarried adolescent girls and older women who had borne children, with a majority of the former, who were thus familiar with menstrual and labor pains. It could be that experience with these gender-specific pains or some as yet unknown female hormone characteristic had somehow increased their pain threshold.

Pharmacokinetic differences have been observed in the metabolism of morphine and other opiates between men and women, with a slower clearance in the latter.<sup>11-13</sup> This would result in accumulation in females with repeated doses, resulting in a longer duration of analgesic action and earlier discharge from the SU. However, more adverse events would be expected in females, but we did not observe this, suggesting that the doses used might have been adequate for the females but not the males. Men may require up to 40% more dosage than women for the same analgesic effect.<sup>14,15</sup>

In Saudi Arabia, males are more exposed to the outdoors and physical activity, like sports, and other known triggers of pain crises.<sup>5,6</sup> This may be partly responsible for the increased frequency of pain crisis in males, but not longer pain persistence, as shown by more males needing hospitalization. Other investigators from Qatif, also in Eastern Saudi Arabia, also observed indirectly an increased frequency of pain crisis in males.<sup>7</sup> In a trial of hydroxyurea efficacy in preventing SCD crisis, Al-Jam'a et al recruited 36 patients with four or more crises per year. Among these patients, 23 (64%) were males and 13 (36%) were females.

Pain response, perception and communication by patients have socio-cultural aspects.<sup>8</sup> For example, in the

**Table 1.** Treatment of sickle-cell disease (SCD) patients in the Stabilization Unit of Saudi Aramco Al-Hasa Health Center, years 2000 to 2002.

|  | Males      | Females     |
|--|------------|-------------|
| Number (%) of SCD cases*                     | 486 (53)   | 433 (47)    |
| Mean (SD) age (y)                            | 22.2 (8.3) | 27.9 (13.8) |
| Number (%) of hospital transfers             | 127 (66)†  | 65 (34)     |
| Percentage of gender transferred to hospital | 26         | 15          |

\*Cases (painful episodes) rather than patients because some patients were admitted several times.

†  $P<0.001$  vs. females.

**Table 2.** Values for some predictors of early mortality in male and female sickle-cell disease patients.

|                                | Male (n=44) | Female (n=51) |
|--------------------------------|-------------|---------------|
| Mean Hb (g/dL)                 | 9.5         | 9.0           |
| Mean HbF as % of total Hb (SD) | 27.6 (10.4) | 20.0 (4.4)    |
| Acute chest syndrome (n)       | 6           | 4             |

HbF, fetal haemoglobin.



USA, most SCD crisis pain is treated in the community rather than in hospital.<sup>9</sup> This aspect was not studied in our patients, but if applicable, raises the possibility that males may actually tolerate pain better than females. If so, then the male patients we saw represented the very severe cases, which take more time to resolve. That would then explain their need for more hospitalization for persisting pain.

However, this hypothesis is not borne out by other experience with this disease. A study in the USA and Canada<sup>4</sup> found a higher mortality for males, whose mean age at death was 42 years compared with 48 years, for females in homozygous (HbSS) disease, and 60 and 68 years, respectively, for sickle-haemoglobin C disease (HbSC). The data showed that frequent crises of 3 or more per year predicted earlier death, although there was no specific information that this was more common among the males. More frequent crises in males have also been documented from Jamaica, where episodes of crises are presumably driven by the surge of the male hormone testosterone following puberty.<sup>10</sup> Interestingly, 391 of 486 (more than 80%) of our cases belong to the 14- to 20-year age group, where the pubertal testosterone surge would be highest.

The similarity in the gender distribution of some haemotological indices known to be associated with early mortality in SCD implies that these factors did not contribute significantly to the differences we observed in our patients. For instance, fetal haemoglobin did not differ significantly between genders, although the mean values were higher for males than females, contrary to findings in some other studies.<sup>16</sup> The concentration of fetal haemoglobin is normally stable over life,<sup>17</sup> and is generally raised in SCD patients from eastern Saudi Arabia, because of the common co-occurrence of hereditary persistence of HbF and thalassaemias.<sup>18</sup> The generally elevated HbF level is partly responsible for the relatively less clinical severity of Eastern Arabian SCD when compared with SCD in western Saudi Arabia or West Africa.<sup>19-22</sup> Thus the non-relevance of the HbF level in the observed gender differences among our patients may be because their mean HbF of over 20 g/dL exceeds both the laboratory proven beneficial level of 15% to 20%,<sup>23</sup> and the clinically applicable 4% level.<sup>24,25</sup>

Similarly, steady-state mean haemoglobin concentration, another indicator of early mortality, at 9 to 10g/dL in our patients, exceeded the critical level of 7g/dL, below which

mortality increases.<sup>4</sup> Although raised baseline WBC has been considered another predictor of early mortality in SCD,<sup>4</sup> it has also been associated with earlier mortality in the normal population<sup>26</sup> making it less specific for SCD, except in the context of acute chest syndrome.<sup>27</sup> There were too few cases of this condition in our patients for statistical comparison, but physicians from Hofuf, also in the Al Hasa area of Saudi Arabia, have noted an increased prevalence of increased baseline WBC, together with chronic renal failure, among males.<sup>28,29</sup> Both conditions are indicators of early mortality.<sup>4</sup>

The markedly fewer number of male patients above the age of 40 years in our study is striking, especially considering the increased mortality associated with child-bearing for SCD females and the high parity common in Saudi Arabia. Theoretically, the older males were not coming to the health center because their pain was not as bad as younger males, but the reduced number of older males probably represents earlier death of male patients, as found in mortality studies elsewhere.<sup>4</sup> Recent studies suggest that the decreased bioavailability of nitric oxide in the vascular endothelium of males with SCD may be partly responsible for this difference.<sup>30</sup> Nitric oxide is crucial in both vascular vasodilatation following vasoconstriction, and in the adhesiveness of sickled red cells to the vascular wall. Both factors are important in the pathogenesis of sickle cell vaso-occlusive crisis. Community studies of survival of SCD patients would clarify this point.

There may be no simple explanation for the gender differences observed among the patients in our study. Current evidence, including that from our study, points toward a multi-factorial aetiology. Since the factors involved may have important implications for patient management, they warrant further investigation, if confirmed. Community studies of life expectancy and prospective studies on analgesic dose requirements with measurable pain assessment in both sexes would further our knowledge in this area.

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