Serum ferritin and mean corpuscular volume as predictors of bone marrow iron stores

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Summary

The prognostic value of serum ferritin (SF) as a predictor of bone marrow iron stores (BMS) was evaluated in an attempt to use SF and other readily available clinical and laboratory parameters in the more accurate prediction of BMS without bone marrow aspiration. The results of routine haematological studies of 1 000 patients referred for a bone marrow examination as part of their diagnostic evaluation at Tygerberg Hospital were statistically analysed. Significant associations were found. The CHAID programme of automatic interaction detection as developed by Kass was used to determine the optimum classification.

A statistical model in the form of a dendrogram has been computed for this hospital population and this laboratory for future predictions of BMS using only the values for SF and mean corpuscular volume. The predictions were statistically very highly significant, especially in patients with iron deficiencies.

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Assessment of bone marrow iron store (BMS) status is important in the management of an anaemic patient. Until recently bone marrow aspiration and testing for stainable iron was accepted as the only reliable test for iron stores.[1] Serum iron values and iron binding capacity can also be used, but it has been demonstrated that these are unreliable.[2] The serum ferritin (SF) value correlates well with BMS and is the best predictor of iron store levels[3] in the peripheral blood, but even with this test there can be unacceptable discrepancies.[4] In disease states SF is not the only indicator of BMS.[5] By statistical analysis it has been found that other variables interacting with SF can play an important role in more reliable prediction of BMS. In this study an attempt has been made to use SF and other readily available clinical and laboratory parameters to predict BMS with greater confidence without necessitating a bone marrow aspiration.

Patients and methods

SF determinations and Coulter Model S examinations were done on 1 000 patients (285 White males, 227 White females, 260

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non-White males and 228 non-White females) referred to Tygerberg Hospital for bone marrow examination as part of the diagnostic evaluation of their disease, between July 1978 and January 1981. The initial clinical diagnosis was obtained either from the hospital records or from the Haematology Clinic records at Tygerberg Hospital.

Smears of the bone marrow aspirates were evaluated with a Prussian blue reaction, according to the method of Dacie.[6] SF was evaluated with a Gamma Dab (^{125}I) ferritin radio-immunoassay kit (Travenol Laboratories) by the method of Miles *et al.*[7] The upper cut-off point of the test is 500 μg/l. Statistical analyses of the date of examination, the race, age and sex of the patient, the BMS values (0 - 6), the Coulter S, platelet count (Coulter F) values, as well as the initial clinical diagnosis and the diagnostic findings in the bone marrow were carried out on an IBM 370/158 computer.

After logarithmic and other suitable transformations of some of the variables to obtain a more normal distribution where necessary, the sample means and standard deviations were determined. Multivariant regression analyses were done on the variables and the significant associations ascertained.

The SF values were compared with the other variables, with special interest in the association of BMS and the initial clinical diagnosis of the patient.

The BMS and SF values were graphically represented for the four race/sex groups (White men, White women, non-White men and non-White women) separately, but no clustering or graphical associations were observed. With the iterative fitting of a log-linear model, a statistical model was generated in tabular form whereby the four race/sex groups were separately analysed. We were disappointed to find that this form of statistical analysis did not lead us to a practical all-embracing working model for future predictions of BMS with a known degree of statistical assurance. Lastly, the CHAID programme of automatic interaction detection as developed by Kass[8] was used to determine the optimum classification. Briefly, the technique known as CHAID partitions a large data set into mutually exclusive, exhaustive subsets of vectors that best describe a dependent variable. The large data set is parsimoniously treated, and CHAID proceeds in steps. The following parameters were considered as possible predictors of BMS: SF, mean corpuscular volume (MCV), haematocrit, red cell count, race and sex, haemoglobin value, age of patient and total white blood cell count, in order of significance.

First the best partition with SF, as the most highly significant predictor, was found. The set was thus divided into more homogeneous groups, the numbers of patients being separated according to SF values into four groups as follows: (*i*) $\leqslant 99$ μg/l; (*ii*) 100 - 199 μg/l; (*iii*) 200 - 499 μg/l; (*iv*) $\geqslant 500$ μg/l.

Secondly, with MCV as the most significant predictor, when the effect of SF was excluded, the data set was further subdivided into three previously chosen MCV categories as follows: (*i*) $\leqslant 80,9$ fl; (*ii*) 81 - 96,9 fl; and (*iii*) $\geqslant 97$ fl.

The introduction of continual significance testing at each stage of the analysis with the chi-square method provided a practical criterion for assessing multiway subdivisions of the data. It was stipulated that the dendrogram or prediction table would be

complete when no further partitions were significant at least at the 5% level. The cut-off points to classify the SF and MCV values into discrete classes were selectively allocated in an attempt to subdivide the different categories into fairly equally sized groups. This was done in order to predict the BMS in a larger number of cases with a higher degree of certainty.

Results and discussion

When the 1 000 patients were divided into four main groups according to the initial clinical diagnosis: (*i*) anaemic states, (*ii*) malignant lesions, (*iii*) infective conditions, and (*iv*) general systemic disorders, statistically highly significant associations were found with the BMS ($P = 1,76$ x 10^{-36}). The association between SF and BMS was highly significant ($P = 3,81$ x 10^{-84}). The other most highly significant predictors of BMS were found to be MCV ($P = 1,35$ x 10^{-31}), race and sex, red blood cell count ($P = 1,5$ x 10^{-6}), haemoglobin, haematocrit and total white blood cell count. The age of the patient, platelet count and date of examination were not statistically significant. The best prediction of BMS was the SF value ($P = 2$ x 10^{-62}). The data were subdivided into four groups with the CHAID programme according to this chosen predictor, as shown in Fig. 1. MCV provided the next most significant predictor and led to further subdivisions of the data. This provided us with a dendrogram or prediction table which could be used for future estimations of BMS with a known statistical significance. All the other variables — haemoglobin value, red cell count, and race and sex — were

also considered for inclusion into the model but did not make any significant additional contribution to its fit.

The initial clinical diagnosis was not included in the CHAID programme as it was not considered an objective parameter.

This model demonstrates that with the use of readily available clinical information and SF values it is frequently unnecessary to perform bone marrow aspiration for the assessment of BMS only. The prediction of absence of BMS can be made with an extreme degree of statistical assurance when the SF level is below 99 µg/l, and even more so when MCV is less than 81 fl ($P = 5,1$ x 10^{-18}). The other levels of statistical significance for higher SF and MCV values are shown in Fig. 1.

To illustrate the use of the model, consider those patients with SF values below 99 µg/l and MCV below 80,9 fl. In our series 81% of these patients had no BMS, 14% had BMS = 1, and only 5% had BMS > 1. The probability that the statistical distribution found in our series could have resulted by chance is infinitesimally small (multiply the 2 *P* values shown in Fig. 1 to find this possibility).

In patients with macrocytosis (MCV > 97 fl) and SF values below 99 µg/l the chances are about 6% that BMS will be 5 or 6 and 19% that BMS will be absent.

In a similar way, the rest of the table can be analysed or used.

In the proposed model it appears that BMS rises in a corresponding manner as SF increases, but with values higher than 400 µg/l the BMS is lower than expected. This high SF value is especially important in patients with a diagnosis of chronic liver disease, chronic infection, malignant tumour or septicaemia. In these cases it is accepted that high SF values can
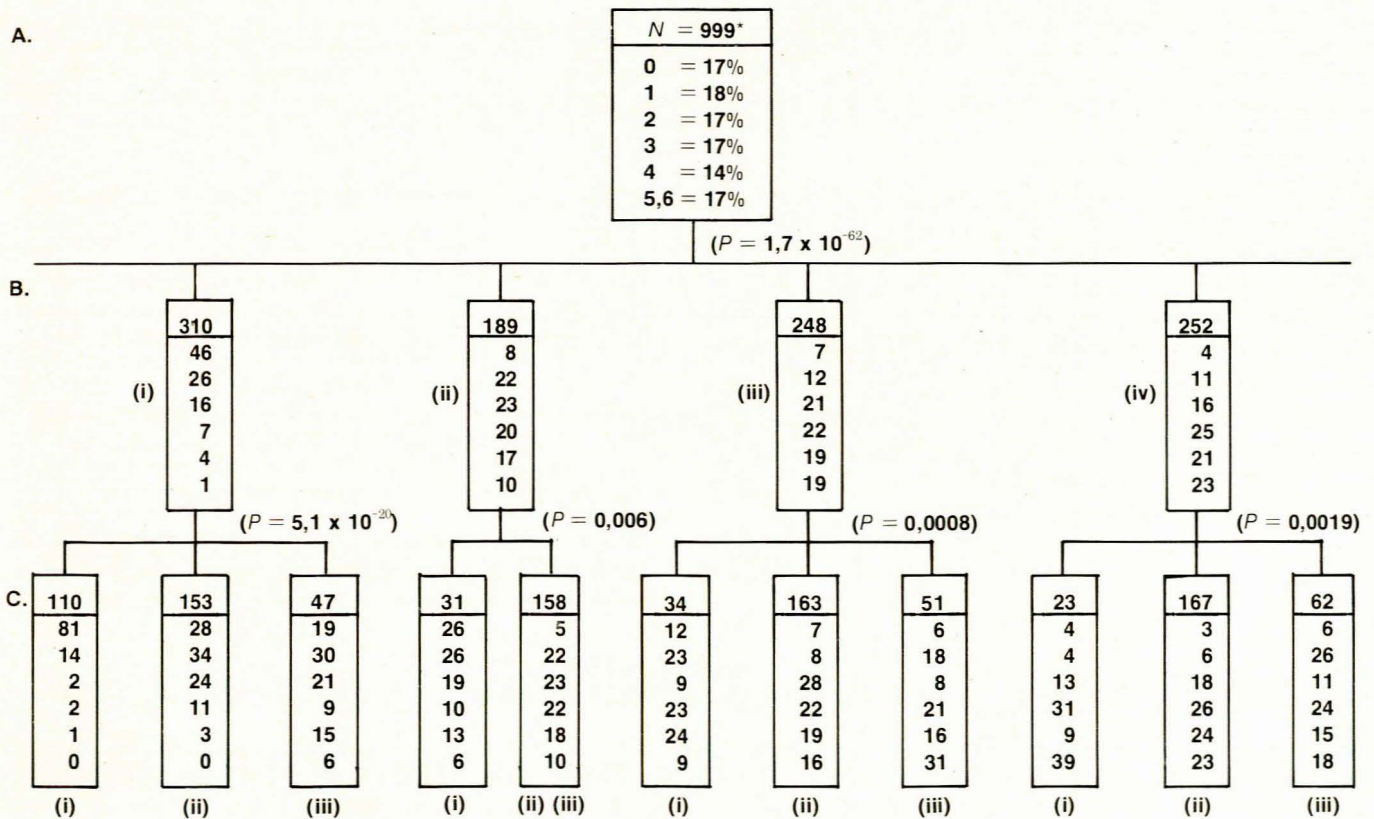

Fig. 1. A. Total group of 999 patients with percentage of patients in each BMS level.
B. Patients divided according to SF with *P* value as given; (*i*) ⩽ 99 µg/l; (*ii*) 100 - 199 µg/l; (*iii*) 200 - 499 µg/l; (*iv*) ⩾ 500 µg/l, with number of patients and percentage of patients at each BMS level in each of the 4 subdivisions.
C. Patients classified by MCV with *P* values for each group: (*i*) MCV ⩽ 80,9 fl; (*ii*) 81 - 96,9 fl; (*iii*) ⩾ 97 fl, with number and percentage of patients at each BMS level in each of the 2 or 3 subdivisions.
* The Coulter value for 1 patient was not available.

be found independently of the BMS values,[9,10] and this was reaffirmed in our series.

Conclusions

With computer processing of the routine data in a large general hospital, the various statistical associations between BMS, SF, race, age and sex of the patients, initial clinical diagnosis, the Coulter data and the date of examination were investigated retrospectively. When the ability of SF to predict BMS values was tested statistically, it was found that a good estimate could often be made, especially in iron deficiency. Independently of SF, it has been demonstrated that MCV values contribute significantly to a better prediction of BMS.[4] A statistical model, represented in dendrogram form, has been computed for this hospital population and this laboratory, but the results would not necessarily be comparable if a population of patients from a different hospital was investigated by a different laboratory.

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Congenital defects of the breast — an autosomal dominant trait

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Summary

A family is reported in which the father and 2 of his 3 daughters have hypoplasia or absence of the nipples with varying degrees of breast hypoplasia. The mode of inheritance of this combination of defects is autosomal dominant.

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Congenital abnormalities of the breast involving hypoplasia are rare, although polymastia is quite common. Reports in the literature before the 1960s did not always give full details of amastia or its less severe manifestations. In 1965, Trier[1] reported on complete breast absence and reviewed the literature. He divided the 43 cases on which data were available into 3 types: (*i*) bilateral absence of breast with congenital ectodermal defect (7

cases); (*ii*) unilateral absence (20 cases); and (*iii*) bilateral absence of the breast (16 cases) with variable associated defects. Three years after this review, Tawil and Najjar[2] reported an additional case of congenital absence of breasts and nipples in a girl with abnormal ears and macrostomia who had chronic glomerulonephritis. A mother and daughter with identical phenotypes were reported by Goldenring and Crelin[3] in 1961. A pair of siblings reported in 1968 had no other stigmata.[4] Since then, the topic does not seem to have been raised in the medical literature.

We wish to report a family in which the father and 2 of his 3 daughters were found to have bilateral absence or hypoplasia of the nipples associated with other minor defects (Fig. 1, Table I).

Case reports

Father (Figs 2 and 3)

This man was found to have hypoplastic nipples with absence of the areolas and no palpable breast tissue. Hair growth on his body was normal, but on the chest it extended over what would be the areolas, leaving only the hypoplastic nipples free of hair. His teeth and sweating pattern were normal. His scalp hair had an unusual number of whorls — 2 on each side anteriorly and posteriorly and 3 in the midline over the site of the posterior fontanelle. He had mild webbing of the interspace between the middle and ring fingers bilaterally and his 2nd and 3rd toes were webbed as far as the distal interphalangeal joint on the right foot.

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