ABSTRACT

An apparent cluster of four aplastic anemia (AA) cases in teenagers residing in a small South Carolina town was further investigated. Incidence of AA in all age groups in a surrounding three county area (TCA) over a 12-year time interval was determined and compared with AA incidence rates in Baltimore, representing the only known population based United States incidence data. The same general age-specific incidence pattern (based on 27 cases in the TCA and 118 in Baltimore) was found in the two areas, both overall and for the four race-sex groups. Although based on small numbers, nonwhite average annual age-adjusted rates for males and females were higher in the TCA (6.8 and 13.7 per million) than in Baltimore (4.7 and 7.3). For whites, TCA rates were 11.7 and 5.4 (for males and females) and Baltimore rates were 7.1 and 5.4. The differences for nonwhites in the two areas may indicate a greater prevalence of risk factors for AA in the TCA than in Baltimore, but the small numbers of cases and the lack of comparable data from other areas of the country, together with the possibility of misdiagnosis of the disease, make definitive conclusions impossible.

INTRODUCTION

Four teenagers, three of whom were white and one nonwhite, out of about 1750 ages 14–17 residing in a small town (total population, 15,000–20,000) in South Carolina (1), were diagnosed as having severe AA over a 7-year period. A previous detailed descriptive epidemiological study of the four cases and survey of high school students in the town showed statistically significant associations between aplastic anemia and both infectious mononucleosis and history of working in the textile industry; suggestive associations were noted for junior high school at (2). The objective of the present population based investigation was to determine whether the apparent excess incidence of aplastic anemia in teenagers in the town also extended to a geographically expanded TCA, and whether the excess was also present in other age groups.

There are very few United States or international data describing incidence of this blood dyscrasia and even fewer analytic studies examining postulated risk factors (3–11). Case fatality rates for AA continue to be high (63% at 1 year and 75% cumulative at 5 years) in case groups without transplantation.

Despite the great improvement in 5-year cumulative survival for AA patients undergoing bone marrow transplantation (12, 13), only a small proportion of such patients is both eligible for and able to afford this expensive procedure. Therefore a second purpose of our investigation was to expand the currently limited United States data relating to incidence of aplastic anemia, since such studies may help to identify ultimately preventable exposures.

MATERIALS AND METHODS

Medical records from all hospitals in the TCA with ICD codes 284 (Ed. 8) 284.0, 284.4, and 284.9 (Ed. 9) for the years 1970–1981 and physicians’ office records of the only two hematologists-oncologists practicing in the TCA during the period were reviewed by a physician epidemiologist (M. S. Linet). In addition, a death certificate search for the TCA was undertaken to identify all individuals with aplastic anemia as an underlying cause of death during this period; these certificates were also reviewed (W. F. Morgan and M. S. Linet).

A case identified from medical records was defined as an individual diagnosed as having aplastic anemia between January 1, 1970 and December 31, 1981, residing in the TCA at the time of diagnosis, and whose disease was characterized by the following criteria based upon a stricter modification of those described by Williams et al. (10): hematocrit, ≤30% or hemoglobin ≤11 g/100 ml; absolute granulocyte count, ≤1,800/mm³; total platelet count, ≤100,000/mm³; reticulocyte count, <2% corrected; and hypoplastic bone marrow aspirate or biopsy compatible with aplastic anemia and free of tumor or other infiltrative disease. All of these clinical and laboratory criteria had to be present on two qualifying examinations at least 1 month apart. In addition there had to be an absence of conditions, diseases, or medications causing secondary marrow aplasia. For all cases identified from medical records, admissions or physician visits subsequent to the initial diagnostic admission were also reviewed to determine whether the natural history of the disease and response to treatment were consistent with aplastic anemia. Potential cases were excluded if they had an apparently congenital form of aplastic anemia, aplastic anemia secondary to radiation therapy or cytotoxic chemotherapeutic agents, transient aplasia, or if they resided outside of the TCA. The time interval chosen for study (1970–1981) was selected because medical records prior to that time were often not available, incomplete, or missing. For hospital or physician office-diagnosed cases, information from the initial hospital admission or physician visit was abstracted.

A case identified from death certificate review was defined as follows: aplastic anemia or pancytopenia had to be listed as the underlying cause of death; no other disease, condition, therapy (therapeutic radiation), or medication known to cause secondary marrow aplasia could be listed as a cause or contributory condition on the death certificate; the case had to be a resident of the TCA. Cases identified from death certificates were excluded if congenital forms of aplastic anemia were listed. A death certificate search was carried out for the period 1970–1982. For cases identified from death certificates only (for which no medical record could be found) we attempted to exclude most cases which could have been diagnosed prior to 1970 by restricting the study period to deaths occur-
ring during 1972-1982. This seemed reasonable because at least 63% of cases diagnosed during 1970 would have died by the beginning of 1972 (12, 13). Because data collection for this study was carried out in the spring of 1983, in order to corroborate the diagnosis possible cases were excluded if death occurred after 1982 and no medical chart could be found for the study period. Thus the results reported here may reflect an underestimate of the actual rate. Age-specific average annual incidence rates for the four race-sex groups were calculated using estimated midpoint (1975) population data for the three counties (1).

These rates were compared with rates determined for the Baltimore metropolitan area for the years 1970-1978, representing the only known population based United States incidence data for aplastic anemia (9). Ninety-five% confidence intervals for these rates were determined using a normal approximation to the Poisson distribution for rarely occurring events (14). Age-adjusted average annual incidence rates, using the indirect method of adjustment, with the Baltimore 1975 estimated population census data as a standard (15), were also calculated for the four race-sex groups. Methods used to estimate incidence rates in the metropolitan Baltimore study involved the same techniques used to systematically search medical records and death certificates and for data analysis as described above for the TCA.

In an indirect attempt to validate ascertainment procedures used for identifying cases of aplastic anemia, age-specific average annual incidence rates for another, probably related disease (acute nonlymphocytic leukemia) were determined, using identical methods to identify cases. These were compared with rates from Baltimore (9) [and with those from the Third National Cancer Survey (16)]. Criteria used for defining a case of acute nonlymphocytic leukemia included the following: a bone marrow aspirate or a biopsy compatible with acute granulocytic leukemia or ANLL with an abnormally increased number of blast cells (greater than 15%); abnormal morphology characteristic of malignant cells (increased number of nuclei, bizarre cell shape, failure to mature, and clustering of cells in groups). If a bone marrow report could not be found, then case identification was based upon the presence of abnormal blasts (greater than 15%) in peripheral blood, with a predominance of myeloblasts containing Auer rods. These criteria were based upon criteria described by Henderson (17, 18) and those of the French-American-British Group (19). Death certificates were included only if the underlying cause of death included one of the following: acute myelocytic leukemia, acute progranulocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, and acute erythroleukemia. Death certificates with the diagnoses acute leukemia (not further specified) or acute undifferentiated leukemia were excluded.

RESULTS

For the study period 1970-1981, 27 cases of aplastic anemia were identified in the TCA. A medical chart and a matching death certificate were located for 20 of the cases, whereas for the remaining 7 cases (25.9%) only a death certificate was found. By comparison 34.7% of cases identified in the Baltimore study were identified by a death certificate only (19). Further examination of the place of death as listed on the death certificates of the TCA cases showed that 2 died in nursing homes, 1 died in an extended care facility, and 4 died at home. Although the numbers were small, cases with both medical chart and death certificate were younger than cases with death certificate only; sex and race distributions were similar between the two groups. These age, sex, and race characteristics for TCA "death certificate only" cases were similar to those for the Baltimore study (9).

Using all cases (those with a medical chart plus matching death certificate and those with death certificate only) rates for persons ages 0-59 and those 60+ in the four race-sex groups were compared between the TCA and Baltimore. More detailed comparison of age-specific rates was also undertaken and very similar patterns were noted between the two areas, but these must be interpreted cautiously because several of the age categories had 2 or fewer cases (Table 1). For white males rates were found to be low under age 60, with an antimode (a minimum frequency or relative minimum) in the age group 20-39, and exponentially rising rates in those 60 and older (Table 1). This suggestive trend for white males is identical to the pattern noted for Baltimore. Because of very small numbers and no cases 60 years of age or older in either nonwhite males or females it is difficult to describe a trend for them. Significance testing showed that age-specific Baltimore rates were easily encompassed within the wide Poisson confidence intervals calculated for the TCA rates (as shown for white males in Chart 1). The age-adjusted average annual incidence rate was highest in nonwhite females (13.7 per million), next highest in white males (11.7), and lowest in nonwhite males (6.8) and white females (5.4).

A comparison of incidence rates for AA in the age group 0-19 between the TCA and Baltimore revealed that rates were higher in the TCA for each race-sex group (varying from just under a 2-fold to a 12-fold difference). In general AA rates in the other age categories were also found to be higher in the TCA than in Baltimore. These rates were compared with rates determined for the Baltimore metropolitan area for the years 1970-1978, representing the only known population based United States incidence data for aplastic anemia (9).

Table 1: Average annual incidence rates* per million for aplastic anemia in three county area, 1970-1981

<table>
<thead>
<tr>
<th>Age group</th>
<th>White males</th>
<th>White females</th>
<th>Nonwhite males</th>
<th>Nonwhite females</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-59</td>
<td>6.7</td>
<td>0.9</td>
<td>6.8</td>
<td>15.1</td>
</tr>
<tr>
<td>0-19</td>
<td>9.7 (4)</td>
<td>2.5 (1)</td>
<td>6.4 (1)</td>
<td>12.4 (2)</td>
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<tr>
<td>20-39</td>
<td>2.8 (1)</td>
<td></td>
<td></td>
<td>9.3 (1)</td>
</tr>
<tr>
<td>40-59</td>
<td>7.4 (2)</td>
<td></td>
<td></td>
<td>20.5 (1)</td>
</tr>
<tr>
<td>60+</td>
<td>43.5 (6)</td>
<td>28.9 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11.7 (13)</td>
<td>5.4 (7)</td>
<td>6.8 (2)</td>
<td>13.7 (5)</td>
</tr>
</tbody>
</table>

* Population census data estimated for 1975 were used as denominators.

Provided with this document is a chart illustrating the average annual incidence rates by age for aplastic anemia in three county area in South Carolina (1970-1981) compared with metropolitan Baltimore (1970-1978) for white males. The chart shows a comparison of age-adjusted average annual incidence rates for three county area rates. Brief description: average annual incidence rates for aplastic anemia are consistently higher for each age group in the three county area in South Carolina than in metropolitan Baltimore, although the difference is not statistically significant.
Baltimore for all race-sex groups (except white females), but analysis was complicated by small numbers and absence of any cases in certain age groups.

Following indirect age adjustment, average annual aplastic anemia incidence rates for both nonwhite males and females in the TCA were found to be higher than those for Baltimore. Rates for white males were 50% higher in the TCA and those for white TCA females were the same as for those in Baltimore (Table 2).

Although numbers were quite small we attempted a preliminary examination of time trends dividing the interval 1970–1981 into two periods: 1970–1975 prior to availability of local hematologists-oncologists in the community, and 1976–1981 following their arrival. No differences in rates were found between the two time periods.

To further examine the reliability of our results, we also determined incidence rates for acute nonlymphocytic leukemia in the TCA during the same time period (1970–1981). Age-adjusted ANLL rates were approximately two times higher for white males and females in Baltimore than in the TCA, whereas rates for both nonwhite males and females although higher, showed less striking differences (Table 2).

**DISCUSSION**

This study was undertaken to determine whether the apparent excess incidence for aplastic anemia in teenagers, 14–17 years old, observed in a small town extended to a larger surrounding geographic area and to other age groups. Comparison of average annual age-specific incidence rates in the TCA with those determined for an overlapping 9-year period in Baltimore showed consistently higher rates in the age group 0–19 in the TCA compared with Baltimore, but nowhere near the pronounced excess noted for the narrower age range, 14–17.

We found no cases occurring in nonwhites over age 60 and residing in the TCA during the entire interval, which could be a random fluctuation given the rarity of this illness, may reflect failure of older nonwhite persons developing aplastic anemia to come to medical attention, or may be caused by misdiagnosis by physicians. Another possibility is that age-specific incidence of this illness in nonwhites in South Carolina differs from that of whites in South Carolina and nonwhites and whites in Baltimore due to differing exposures.

Based upon these findings and results from our earlier survey of teenagers in the small town in the TCA, certain, as yet unidentified, exposures in the textile industry or agricultural industry in this region of South Carolina may be more common among nonwhites or may result in excess occurrence of aplastic anemia among nonwhites due to greater sensitivity of bone marrow. This speculation, however, must be tempered by the small numbers of cases in nonwhites (N = 7) from which race-specific, age-adjusted rates were calculated. Since direct validation of incidence rates for aplastic anemia in the TCA was limited to comparison with Baltimore rates, we also used an indirect method as described above in an attempt to examine the validity of incidence rates. The surprising finding of generally lower age-specific incidence rates for ANLL in the TCA (compared to data from Baltimore) may have several interpretations: underascertainment of cases of ANLL; misclassification of ANLL cases as aplastic anemia (thus accounting for apparently lower rates of the former and higher rates of the latter than was actually the case); or different risk factors for aplastic anemia than those for ANLL in this particular area in South Carolina. The scope of this study did not permit us to examine the possible impact of cases who were residents of the TCA but were initially diagnosed at the many referral centers outside of the TCA, including other institutions in South Carolina, North Carolina, Washington State, Maryland, etc. However, it is likely that such persons would have had a local physician who would have been responsible for referral of suspected cases and medical care in between treatments.

It is also possible that the somewhat arbitrary demarcation of both the three-county geographic area as well as the time interval of 12 years influenced these results. However, there is no obvious reason why the time-space boundaries selected would result in biased or unusual findings.

The rarity of aplastic anemia makes it difficult to obtain stable incidence rates. Nevertheless additional incidence studies and case-control studies carried out in a number of large geographic areas may be helpful in further defining associations between a number of postulated risk factors and aplastic anemia and in identifying preventive measures.

**REFERENCES**


**Table 2**


<table>
<thead>
<tr>
<th>Race-sex group</th>
<th>Aplastic Anemia</th>
<th>ANLL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TCA</td>
<td>Baltimore</td>
</tr>
<tr>
<td>White Male</td>
<td>11.7 (13)</td>
<td>7.1 (49)</td>
</tr>
<tr>
<td>Female</td>
<td>5.4 (7)</td>
<td>5.4 (45)</td>
</tr>
<tr>
<td>Nonwhite Male</td>
<td>6.8 (2)</td>
<td>4.7 (9)</td>
</tr>
<tr>
<td>Female</td>
<td>13.7 (5)</td>
<td>7.3 (15)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, number of cases on which calculation of rate was based.
APLASTIC ANEMIA INCIDENCE


Incidence of Aplastic Anemia in a Three County Area in South Carolina

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