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Non-Chemotherapy Medullary Aplasia in the Pediatric Oncology Unit of the Gabriel Touré Teaching Hospital, Bamako

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Abstract

Objectives: The main objective was to study the epidemiological, diagnostic and therapeutic aspects of medullary aplasia (MA). **Methods:** This was a prospective and descriptive retro study conducted from January 1, 2008 to December 31, 2018 in the pediatric oncology unit of the pediatrics department of the Gabriel Touré teaching Hospital in Bamako. **Results:** We collected 29 children's cases out of 1632 admissions during the study period, representing a frequency of 1.8% and an incidence of 2.6 cases per year. The sex ratio was 2.6. The 11 - 15 age group accounted for 45%, with an average age of 8.93 years. The majority of fathers (55.2%) and mothers (62.1%) had received no education; they were mainly farmers (62.1%) and housewives (86.2%). The average consultation time was 92.21 days. Anemia was the reason for consultation in 69% of cases. Pallor was present on admission in 96.5%; infectious syndrome accounted for 79.3%, anemic syndrome for 51.7% and hemorrhagic syndrome for 27.6%; the three syndromes were associated in 27.6%. Malaria was associated with bone marrow aplasia in 58.6%. Anemia was present in 93.1%, neutropenia in 65.5% and thrombocytopenia in 86.2%. All had received a labile blood product (LBP) transfusion, and 24 (83%) had received antibiotics. Patients were treated with corticosteroids (58.6%), androgens (20.7%) and immunosuppressants (20.7%). The death rate was 34.6%.

At last count, 15 (83%) had discontinued treatment, 2 (11%) were undergoing treatment and 1 (6%) was in remission. **Conclusion:** Effective treatment of MA requires improved technical facilities and better economic conditions for parents.

Keywords

Medullar Aplasia, Children, Bamako

1. Introduction

Medullar aplasia (MA) is defined as a deficit in blood cell production due to a quantitative insufficiency of hematopoiesis, resulting in pancytopenia with poor bone marrow [1] [2]. This deficiency, according to current concepts of pathophysiology and treatment of MA, may be constitutional (familial); related to occupational or drug-induced toxic agents, ionizing radiation, viral infection or other causes [3]. The majority of acquired MA is idiopathic, *i.e.* without apparent cause. The pathophysiological mechanism invoked is that of inhibition of hematopoiesis by dysregulation of the immune system [4]. MA is a rare disease with an incidence of less than ten cases per million per year, which is 20 times less than multiple myeloma and ten times less than acute leukemia. According to the main incidence rates from prospective studies, the disease is more widespread in Asia than in Europe and America. Incidence is currently around two cases per million per year in Europe. It reaches six in Thailand and 7.4 in China. The incidence of MA follows a bimodal curve, with a first peak in younger subjects and a second peak after the age of 50 [5]. In Africa, its incidence is 0.2 new cases per year in Algeria, according to a 4-year paediatric hospital study [6]. Its hospital incidence is 4.2% in Morocco [7] and 17.6% in children aged 0 to 15 in Ivory Coast [8]. Although overall mortality is clearly declining, it remains high, especially during the first months of the disease. Death usually follows severe hemorrhage or infection. There is a risk of myelodysplasia or acute leukemia [9]. In severe acquired MA, the combination of anti-lymphocytic serum (ALS) and cyclosporine is the treatment of choice in the absence of an HLA-identical donor in the siblings. This treatment improves survival [10]. Hematopoietic stem cell transplantation is the only treatment for constitutional forms [5]. Few studies had been carried out on bone marrow aplasia in Mali, and particularly in children, which motivated us to initiate this work, the aim of which is to study bone marrow aplasia in paediatrics.

2. Material and Methods

2.1. Study Setting

Our study took place in the pediatric oncology unit of the pediatric department of the Gabriel Touré teaching hospital in Bamako.

2.2. Patient Management

MA was diagnosed on the basis of blood count (BC), myelogram and blood smear results. Cytology slides of MA were read by the two pediatric oncologists trained in cytology, then confirmation was requested from the biological hematology laboratory at Robert-Debré Hospital in Paris if there was any diagnostic doubt. The chemotherapy protocols used in the unit were those of Franco-African Pediatric Oncology Group (FAPOG), which donated the drugs free of charge. Bone marrow aplasia is not one of the pathologies targeted by FAPOG, which is why there is no protocol for bone marrow aplasia, and the drugs are paid for by the family. Treatment is based on protocols taken from the literature.

Different protocols are used, depending on availability and feasibility:

- High-dose corticosteroid therapy: Methylprednisolone 1 g/m^2/d IVL for three (3) days;
- Immunosuppressive treatment: Cyclophosphamide 5 mg/kg/d per os for 10 days;
- Synthetic androgen: Norethandrolone (Nilevar®) at 1 mg/kg/d).

Results are assessed after 3 to 6 months of treatment.

2.3. Type and Period of Study

This is a descriptive retro-prospective study conducted from January 1, 2008 to December 31, 2018, *i.e.* 11 years.

2.3.1. Inclusion Criteria

All children aged 0 - 15 years treated and followed up for bone marrow aplasia during the study period had been included.

2.3.2. Non-Inclusion Criteria

Excluded from our study were all children with bone marrow aplasia secondary to chemotherapy for malignant pathology or with unexploitable medical records.

2.3.3. Variables Studied

The following variables were analyzed on the basis of individual survey forms:

- Parents' socio-demographic data,
- Patients' socio-demographic data,
- Patients' clinical data,
- Patients' biological data,
- Patients' therapeutic and evolutionary data.

2.3.4. Operational Definitions

We adopted the following definitions: according to WHO [11].

- Moderate acute malnutrition: if the weight/height ratio is between −2 and −3 z score.
- Severe acute malnutrition: if weight/height ratio is <−3 z score
- Marginal malnutrition: if BMI is between 17 - 18.4
- Moderate thinness: if BMI is between 16 - 16.9

- Severe thinness: if BMI < 16.0

2.4. Ethical Considerations

For this work we had obtained the authorization of the administrative authorities of CHU Gabriel Touré for the exploitation of the files and the verbal agreement of the children's parents or guardians. The information gathered from the files was kept confidential.

3. Results

3.1. Frequency

During our study period (2008-2018), 1632 patients had been admitted to the pediatric oncology unit, 29 of whom had bone marrow aplasia, a frequency of 1.8%.

3.2. Socio-Administrative Characteristics

72% of patients were male, with a sex ratio of 2.6. The 11 - 15 age group accounted for 45%, with an average age of 8.93 years. The majority of the children's fathers (55.2%) and mothers (62.1%) had received no education; they were mainly farmers (62.1%) and housewives (86.2%) (Table 1).

3.3. Clinical Characteristics

69% of patients were referred by a health facility; consanguinity was the only risk factor found (34.4%). The average consultation time was 92.21 days, with extremes of 24 and 365 days. Anemia was the reason for consultation in 69%; fever was the inaugural sign in 58.7%; severe thinness was present in 65.5% and general condition was altered in 76%. Pallor was present on admission in 96.5% and was marked in 86.2%. The infectious syndrome accounted for 79.3%, the anemic syndrome for 51.7% and the hemorrhagic syndrome for 27.6%; the three syndromes were associated in 27.6%. Malaria was associated with bone marrow aplasia in 58.6%. Anemia was present in 93.1% of cases, 34.5% of which were very severe (<5 g/dl); neutropenia in 65.5%, 51.7% of which were very severe (<500); and thrombocytopenia in 86.2%, 48.3% of which were very severe (<20,000/mm^3).

Table 1. Sociodemographic characteristics.

Characteristics	Number	Percentage
Age groups (year)		
0 - 5	6	21
6 - 10	10	34
11 - 15	**13**	**45**
Sex		
Male	**21**	**72**
Female	8	28

Hepatitis A, B and C serology in 34% of patients was negative; Ag Hbs was positive in 10%; CMV serology in 34.5% of patients was negative; EBV and parvovirus B19 serology in 8 patients was positive in 1; HIV serology in 79% of patients was negative; the Intra Dermo Tuberculin Reaction performed on 69% of patients was negative. All patients had received a LBP transfusion, and 24 (83%) had received antibiotics. Patients were treated with corticosteroids (58.6%), androgens (20.7%) and immunosuppressants (20.7%). The death rate was 34.6%. At last count, 15 (83%) had discontinued treatment, 2 (11%) were undergoing treatment and 1 (6%) was in remission (Table 2).

Table 2. Clinical characteristics.

Characteristics	Number	Percentage
Consanguinity of parents		
Yes	10	34
No	8	28
Not specified	**11**	**38**
Reason for consultation		
Anemia	**20**	**69**
Deterioration of general condition	3	10.3
Epistaxis	3	10.3
Suspected leukemia	2	7
Abdominal pain	1	3.4
Syndromes found		
Infectious syndrome	**23**	**79**
anemic syndrome	15	52
Hemorrhagic Syndrome	8	28
The three associated syndromes	8	28
Blood count abnormalities		
Anemia	**27**	**93.1**
Thrombocytopenia	25	86.2
Leukopenia	20	69
Neutropenia	19	65.5
Lymphopenia	8	27.6
Monocytopenia	7	24.1
Specific treatment		
Corticosteroid	**17**	**58.6**
Androgen	6	20.7
Immunosuppressive	6	20.7
becoming		
alive	**18**	**62**
deceased	10	35
lost view	1	3

4. Discussion

4.1. Limitations of Our Study

Like any retrospective study, our study had its limitations, notably the lack of completeness of certain medical records, the parents' lack of resources, the inadequacy of the technical platform and the difficulties in managing and regularly monitoring patients. Molecular biology, cytogenetics, immunohistochemistry and bone marrow biopsy are not performed in Mali due to a lack of technical facilities. A positive diagnosis of MA is made in the presence of pancytopenia with poor bone marrow. It is then confirmed by osteo-medullary biopsy, which was not feasible in our context. Histological examination of bone marrow obtained by biopsy of the posterior iliac crest is of vital importance for the diagnosis and prognosis of MA. It enables accurate study of bone marrow richness, alterations in bone marrow structure, and assessment of the extent of fatty marrow, which is important to evaluate.

All these difficulties prevented us from including all patients, but also from analyzing certain important clinical aspects of diagnosis and management.

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All these difficulties prevented us from including all patients, but also from analyzing certain important clinical aspects of diagnosis and management, thus underestimating our frequency.

4.2. Socio-Demographic Characteristics

The mean age was 8.9 years, with extremes of 1 and 15 years. This result is close to that of Sanae in Fes, where the mean age was 8.5 years, with extremes of 1 and 14 years [12].

The 11 to 15 age group accounted for 44.8%, with an earlier age of onset (2 to 10 years) found by Benmehdi S and Bensoltane A in Tlemcen [13].

The sex ratio was 2.6, higher than that of Benmehdi S and Bensoltane A (1.4) [13]. Other authors found an equal sex ratio, notably Riyat *et al.* in Kenya [14] and Sanae B in Morocco [12]. The majority of fathers (55%) and mothers (62.1%) had no formal education, and the majority (62.1%) were farmers and housewives (86.2). According to several series, MA is most often observed in the

lower socioeconomic classes, including Tolo-Diebkilé in Ivory Coast [8], Riyat in Kenya [14], Elira in Congo [15] and Issaragrisil in Thailand [16].

Clinical features

Consanguinity was found in 10 patients (34.5%), including 7 of 1st degree and 3 of 2nd degree. We found no clinical signs of Fanconi anemia, dyskeratosis or other congenital anomalies, and no evidence of drug or toxic intoxication.

The average consultation time was 90.21 days. This delay in diagnosis could be explained by our patients' primary recourse to traditional treatment. The majority of our patients' parents had low purchasing power and socio-cultural considerations such as witchcraft, the devil, etc. pushed them towards traditional treatment. Our results are similar to those reported by Mary in France [17] and Sadiki H *et al.* in Casablanca, Morocco [18], who found an average delay of 90 days. Hind EY found a shorter mean delay of 41.45 days in Fes, Morocco [19].

The infectious syndrome was (79.3%) the most common, followed by the anemic syndrome (51.7%). These results were similar to those of Tolo-Diebkilé at Yopougon teaching hospital [8] and Elira in Congo [15]. On the other hand, Sanae B in Fes [12] and Yao in Ivory Coast [20] found a predominance of the anemic syndrome in 100% of cases, followed by the hemorrhagic syndrome in 75% of cases. Infectious syndrome came last.

4.3. Biological Characteristics

We found anemia in 27 patients (93.1%) and hemoglobin levels below 5 g/dl in 10 patients (34.5%). Our results concur with those of Sanae B in Fes [12] and Tolo-Diebkilé in Yopougon [8], who found hemoglobin levels below 7 g/dl (62.5%) and 6 g/dl (62%) respectively. Platelet count was below 20,000/mm^3 in 48.3% of cases, much higher than the 18% found by Sanae B in Fes [12]. Neutropenia was present in 65.5%, significantly lower than that of Sanae B [12], who found neutropenia in 75% of cases, but higher than that of Rennes University Hospital [21], where only 50% had neutropenia.

The myelogram was deserted with no visible morphological abnormalities in all our patients. In the series by Tolo-Diebkilé in Yopougon [8], the myelogram was desert-like in 55.9%, and poor in 44.1%.

It has been established that the majority of AM remain without apparent cause [2] [10] [22]. As only a few patients were investigated for etiology, we cannot draw any reliable conclusions. Nevertheless, we found idiopathic MA in 93.2% of cases and infectious MA in 6.8%. Our results concur with those of Khoubila [23], RM. Hamladji [24] and Mary [17], who found a high frequency of idiopathic MA.

All patients had received at least one LBP transfusion, and almost 83% had received antibiotics. Seventeen (17) patients (58.6%) had received corticoids, 6 androgens (20.7%) and 6 immunosuppressants (20.7%). Corticosteroids were the most prescribed specific treatment (61.8%) in the Tolo-Diebkilé study in Yopougon [8]. No patient benefited from a bone marrow transplant, which is not available in Mali.

The death rate was 34.6%, higher than those of Sanae B [12] in Morocco and Benmehdi S and Bensoltane A in Tlemcen [13], who found 12 and 25% respectively, but lower than Riyat (52.4%) in Kenya [14]. Parents' low socio-economic status, the difficulty of obtaining LBP, the unit's inadequate technical facilities and insufficient social security coverage could explain this high mortality rate.

5. Conclusion

MA is a rare condition in our unit. Improved technical facilities will enable accurate diagnosis, appropriate treatment and a reduction in MA-related mortality.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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