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Comparative Study of Neurosurgical Complications of Thalassemia and Sickle Cell Disease

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Abstract

Introduction: Sickle cell disease and thalassemia are the most frequent hemoglobinopathies. During their evolution, they present certain complications, among which are two neurosurgical emergencies, namely spontaneous cranial epidural hematoma and non traumatic radiculo-medullary compression, with some particularities for each. **Method:** In order to highlight these particularities, we compared the characteristics of these two complications, from a number of publications reported between 2000 and 2021. **Results:** Sickle cell disease was complicated by spontaneous cranial epidural hematoma. Forty-two cases were reported, the mean age was 14.7 years (2 - 21 years) and the sex ratio was 6.4. The clinical presentation combined, in a non-traumatic context, signs of intracranial hypertension with those of neurological focalization. Neuroimaging showed epidural-type collection, often frontal and parietal in location. The incriminating mechanisms were ischemia, hemorrhage and extra medullary hematopoiesis. The treatment was surgical. Non traumatic radiculo-medullary was the complication of thalassemia. Of the 77 cases reported, the mean age was 27.5 years (9 - 66 years) and the sex ratio was 4.1. The lesions were epidural with a clear thoracic predominance and resulted from extra marrow hematopoiesis. Treatment included: hypertransfusion, radiotherapy, hydroxyurea and surgery. Vital and functional prognosis were globally satisfactory when the management was rapid. **Conclusion:** Cranial and spinal epidural lesions, respective complications of sickle cell disease and thalassemia, result from similar mechanisms. Their prognosis depends on the rapidity of management.

Keywords

Hemoglobinopathy, Sickle Cell Disease, Thalassemia, Spontaneous Epidural Hematoma, Extra Marrow Hematopoiesis, Slow Marrow Compression

1. Introduction

Sickle cell disease and thalassemia, initially described in Africa and the Mediterranean basin respectively [1], now represent major medical challenges worldwide. These conditions are caused by mutations in the beta-globin gene for sickle cell disease and in the synthesis of the alpha or beta chains of hemoglobin for thalassemia.

Due to the disruption of hemoglobin production, patients suffer from chronic anemia, to which the body responds with chronic stimulation of erythropoiesis, which has its drawbacks. Indeed, this reactive erythropoiesis occurs not only in the organs usually involved in this process but also in those that have lost this function after embryonic life, as well as in unusual spaces [2] [3]. This latter situation involves "abnormal" or "ectopic" hematopoiesis, which, depending on its location, can be termed juxta-medullary or extramedullary. Often asymptomatic, it can lead to certain complications [4]. Among these are two neurosurgical emergencies: spontaneous cranial epidural hematoma (SCEDH) and Non-traumatic radiculo-medullary compression (NTRMC), which add to stroke, a common neurological complication of these hemoglobinopathies. These conditions, whose diagnoses have been refined thanks to new medical imaging techniques, are increasingly reported in the medical literature.

Despite their common origin, these neurosurgical emergencies display certain differences in their clinical and paraclinical expressions. Understanding these complications is necessary to improve their management within the group of these complex hemoglobinopathies.

It is with this aim that we sought to report these particularities, comparing the epidemiological, diagnostic, therapeutic, and evolutionary characteristics of these two complications, based on cases published in the literature and our own.

2. Methodology

In order to compare the neurosurgical complications of these two haemoglobinopathies, we searched, over a period of 21 years (January 2000 to December 2021), using search engines (Pub Med, Google, Google Scholar), for articles published, in French or English, on this subject. The search terms were: complications of haemoglobinopathies, extramedullary haematopoiesis, juxtamedullary haematopoiesis, epidural haematoma, extradural haematoma, thalassaemia, sickle cell anaemia, non-traumatic spinal cord compression, cauda equina compression. To avoid duplication, we analysed each article carefully, looking at the parameters of age, sex, year and place of publication, location of the lesion,

treatment carried out and outcome. When all these elements were identical between two cases, they were counted once. Other locations of ectopic haematopoiesis were excluded, as were cases discovered at autopsy.

We added to this number those of our team who had not yet been published. From these publications, we extracted and recorded in an Excel table, the epidemiological, clinical and paraclinical, therapeutic and evolutionary data for each of these two haemoglobinopathies (Table 1). As not all publications contained the same information, the number of patients found per parameter studied was noted. As this was not a meta-analysis or a review of the literature on the neurosurgical complications of thalassemia or sickle cell disease, we compared the complications of these two haemoglobinopathies on each parameter.

Table 1. Comparative table of neurosurgical complications in sickle cell disease and thalassaemia.

Items	Sickle cell disease	Thalassaemia
Type of haemoglobinopathy	SS, FS	Minor, Major
Sex ratio	6,4	4,1
Mean Age (Year)	14.7 [2 - 21]	27.5 [9 - 66]
Type of complication	SCEDH	NTCRM
Investigation	TDM/IRM	IRM
Mechanism	Ischaemia Coagulopathy Ectopic haematopoiesis	Ectopic haematopoiesis
Treatment	Transfusion Surgery	Transfusion Radiotherapy Chemotherapy Surgery
Evolution (letality)	16,2%	None

3. Results

Over the 21 years that constitute our study period, 95 publications were identified with a total of 118 cases. Spontaneous cranial epidural hematomas (SCEDH) were reported in 31 articles for a total of 40 cases. This number increases to 41 cases, when we add the last case observed in our department. Concerning the second complication, we counted 64 articles in which 77 cases of Non-traumatic radiculo-medullary compression (NTRMC) were published.

Spontaneous cranial epidural haematoma [4]-[34]

Spontaneous cranial epidural haematomas (41 cases) were exclusively a complication of sickle cell disease in its SS (97.3%) and FS (26.7%) forms. The patients had a mean age of 14.7 years [2 - 21 years] and were predominantly male (sex ratio: 6.4). They were seen in consultation within a mean time of 55.6 h or 2.3 days with extremes ranging from 4 h to 168 h. The clinical picture was made, in a non-traumatic context, of headaches that were considered as part of the dif-

fuse algic picture of vaso-occlusive crises. They were associated with neurological focal signs in 80% of cases. Neuroimaging, including computed tomography (CT) and/or magnetic resonance imaging (MRI), was reported in 34 cases. This not only showed the haematoma and its location, but also allowed us to suspect the mechanism behind its formation. The location was unilateral in 70.3% of cases (47.6% on the right, 21.7% on the left) and bilateral in 29.7%. They were frontal in 42.4%, parietal in 36.7%, fronto-parietal in 15.5% and occipital and posterior cerebral fossa in 2.7% each. The mechanism of occurrence of these hematomas, reported in 15 cases, was ischemia in 73.4%, coagulopathy and extra medullary hematopoiesis in 13.3% each. The treatment performed in all patients was transfusion (conservative) alone in 25.9% or associated with surgery in 74.1%. The latter resulted in a good outcome in 83.8% of cases and a lethal outcome in 16.2%.

Non-traumatic radiculo-medullary compression [1] [3] [35]-[94]

Non-traumatic radiculo-medullary compression (NTRMC) (77 cases) complicated thalassemia. These were intermediate thalassemias in 17 cases (including 5 cases of E thalassemia), thalassemias major in 11 cases. Associations of thalassemia and Lepore hemoglobin in 2 cases and thalassemia and sickle cell disease in one case had been reported. The average age of the patients was 27.5 years [9 - 45 years] with again, a male predominance (sex ratio = 4.1). They were seen in consultation with a mean delay of 93.2 days [3 - 360 days] for a spinal cord compression syndrome. They had all undergone an MRI, the results of which were reported in 72 patients. The compressive lesion was epidural, localized to a single spinal region in 83.3% of cases and to more than one region in 16.7% of cases. The lesions localized to a single region were mostly in the thoracic portion (76.4%). This same thoracic segment was often involved in multi-regional localizations with the cervical, lumbar and/or sacral segments.

At the end of this assessment, several therapeutic modalities were used. These were radiotherapy for which the doses and number of sessions were not always reported, hypertransfusion, surgery (laminectomy + removal of compressive epidural tissue), and hydroxyurea chemotherapy (drug treatment). Treatment using one or more of these procedures was reported in 62 patients. Regarding single treatments (50% of cases), radiotherapy alone, with its 17.6% of cases, was the most used. It was followed by hypertransfusion (13% patients), surgery (11.3%) and chemotherapy (8.1%). As for combinations, transfusion + radiotherapy and transfusion + surgery were used in 8 cases each. The combinations of drug treatment + radiotherapy and drug treatment + transfusion were reported in 3 cases each. Transfusion, surgery and radiotherapy were combined in 4 cases. Other combinations were also used (4 cases). Spontaneous recovery was also reported. The clinical evolution, apart from some neurological sequelae reported, was good in all cases.

4. Comments

This study is not a meta-analysis or a review of the literature on the neurosur-

gical complications of thalassemia or sickle cell disease. It compares the epidemiolgic, clinical, therapeutic and evolutionary aspects of two neurosurgical complications of these two most frequent hemoglobinopathies. This explains the non-exhaustive nature of the publications made on these subjects. Nevertheless, the numbers obtained allowed us to make this comparison. The period of this study was chosen somewhat because it corresponds to that of the generalization of new medical imaging techniques (CT scan and nuclear magnetic resonance imaging) in African countries south of the Sahara.

Thus, during the period from 2000 to 2021 (21 years), we found 95 articles published on the neurosurgical complications of these two hemoglobinopathies, namely sickle cell disease and thalassemia. These were SCEDH for sickle cell disease and NTRMC for thalassemia. These publications were mainly case reports. The largest series, for sickle cell disease complications, was 6 cases and for thalassemia 5 cases.

SCEDH were described in SS homozygous sickle cell patients and very rarely in the FS form. Intermediate forms (including E-Thalassemia) and major forms of thalassemia were the ones most complicated by NTRMC, but they were also encountered during the associations thalassemia + hemoglobin Lepore and thalassemia + sickle cell disease. They mainly affected young adult boys for thalassemia and adolescent boys for sickle cell disease.

The consultation time was shorter (2.3 days on average) for SCEDH and longer for NTRMC (93.2 days on average). These are, in fact, two neurosurgical emergencies with different immediate consequences. SCEDH remains an acute condition with a rapid clinical course and a risk of lethal evolution, whereas spinal cord compression is often slow to develop. It is more likely to be a functional disease.

The clinical signs for these non-traumatic or SCEDH combined those of intracranial hypertension (frequent) with signs of neurological focalization. In some cases a disturbance of consciousness was noted. The headache, sometimes the only sign of this intracranial hypertension, was often considered as part of the vaso-occlusive manifestations. In the absence of other neurological signs, this isolated headache probably explains the delay in diagnosis in some patients. The spinal cord compression syndrome was the classic clinical picture of this complication of thalassemia and was sometimes the revealing manifestation of this thalassemia [92].

The lesions were located in the epidural space in both cases. At the cranial level, the EDH presented as a peri-cerebral effusion in the form of a biconvex lens, like those of traumatic origin. The density or signal of the effusion depended on the duration of the lesion's evolution. Unilateral localizations were the most frequent with a predominance in frontal and parietal regions. MRI remains, even in this context, the paraclinical examination of choice in radiculo-medullary compressions. It showed dorsal epidural lesions that were hypo- or iso-signal with enhancement after injection of gadolinium [92] or iso or discretely hypersignal on T1 and T2 weighted sequences [75]. The thoracic spinal

location, alone or associated with other locations, was the most frequent. The predominance of thoracic spinal location is thought to result either from extension of hematopoietic tissue through the proximal costal tubercles or adjacent vertebral bodies, or from development of hematopoietic tissue from branches of the intercostal veins, or from both mechanisms [89]. Root compression may also be observed, due to the same mechanisms [91]. Extramedullary hematopoiesis may involve the vertebral body, the epidural space, or both structures, resulting in radiculo-medullary compression. This lesion of ectopic hematopoiesis was found in one or more spinal segments but also in other organs which, for the circumstance, remembered their hematopoietic activity during embryonic life [2].

The MRI also gives arguments in favor of the mechanisms that were multiple in the occurrence of SEDH, namely: ischemic, hemorrhagic or by extramedullary hematopoiesis [28]. The latter was the only mechanism incriminated in NTRMC. These mechanisms also explain the epidural location of these lesions, this space being the first one that separates the bone from the cranial or spinal contents.

Therapeutically, SCEDH is a condition that responds to surgical treatment, when arguments based on thickness, mass effect and involvement indicate it. In cases of low thickness, absence of mass effect and non-existence of involvement, conservative treatment can be chosen. This was the case with our last patient. In the case of NTRMC, several therapeutic modalities were reported. They ranged from hypertransfusion regimen to radiotherapy, surgery and chemotherapy. In spite of the decision tree proposed by Haïdar [15] in this therapeutic management, the indications seemed to depend on the habits of the teams or on the decision of the multidisciplinary consultation. For patients who were seen in the neurosurgery department as a first line treatment and whose thalassemia was not known [92], or for those who had presented a rapid clinical deterioration, surgical treatment was indicated immediately, because of the functional emergency constituted by the spinal cord compression. This treatment has the advantage of providing operative material whose pathological examination makes it possible to make a definite diagnosis of this ectopic hematopoiesis by showing a polymorphic cellular infiltrate containing erythroblastic myeloid cells, lymphocytes, plasma cells, megakaryocytes and megakaryoblasts [1] [92].

This treatment had allowed to observe, in SHED, a cure in 83.8% and a mortality of 16.2%. For NTRMC, all cases had a good evolution, sometimes with neurological sequelae.

5. Conclusion

SHED and NTRMC are rare but serious complications of sickle cell disease and thalassaemia respectively. Ectopic haematopoiesis, which is the consequence of the physiological response to chronic anaemia, when it gives rise to a neurosurgical complication, is expressed differently in sickle cell disease and thalassaemia. It is therefore necessary to take this into account when monitoring patients

with these haemoglobinopathies, as these are complications whose course is well known and does not take into account the context in which they occur.

Conflicts of Interest

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

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