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Diagnosis of CAH in a Sub Saharan Country: Visible Part of Iceberg

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Abstract

Introduction: Congenital adrenal hyperplasia (CAH) is the most common cause of primary adrenal insufficiency. It is a rare monogenic recessive disorder. In African setting in absence of neonatal screening, the diagnosis is still late, based on a clinical approach. During this clinical enquiry, information from past history or pedigree of the patient is of a huge importance and may revealed surprises. **Patients and Methods:** In this observational study, we retrospectively included all patients with a diagnosis of CAH. The diagnosis of CAH was retained based on a high 17 hydroxyprogesterone level in addition to clinical and morphological findings. From patients' files, we extracted data on family history of disease, pedigree, clinical findings and genetics when available of 39 patients from two endocrinopeadiatric centers. **Results:** In 13 (30%) families, we found 20 reported deaths of infant less than 12 months. In these 13 families, half of the patients followed had 21 hydroxylase deficiencies and had 11 hydroxylase deficiencies. Unsurprisingly, we suspected adrenal insufficiency in these patients at verbal autopsy even in families with a patient with 11 hydroxylase deficiency. Other non DSD malformations or genetic disorders with apparently no link with CAH were reported in 3 families. The father of a patient reported to have hypospadias. **Conclusion:** Each diagnosis of CAH made in our context is visible part of an iceberg. Behind a diagnosis of CAH made in our setting, is a long course of care, a dramatic past history revealing access to appropriate care disparity. Neonatal screening should thus be considered as an emergency.

Keywords

Congenital Adrenal Hyperplasia

1. Introduction

Congenital adrenal hyperplasia is the most common causes of primary adrenal insufficiency [1] [2] [3]. It is a rare monogenic recessive disorder. The most common genetic lesion is on CYP21A2 gene mutation and CYP11B1 gene mutation [1]. The latter seems to be more frequent in some African setting in absence of studies on incidence [5]. In absence of neonatal screening, diagnosis is still late in this context [4] [5]. Therefore, each patient diagnosed, revealed a history of long course of care and misdiagnosis for both the patient and family. This past history draws our attention and our aim was to describe family journey to appropriate care.

2. Patients and Methods

In this observational study, we included all patients followed in two paediatric endocrinology and diabetology services of Cameroon: Laquintinie Hospital of Douala, Mother and child centre of the Chantal Biya Foundation in Yaounde. Both teaching hospitals with a paediatric endocrinology and diabetology service, managed by a senior paediatric endocrinologist.

We consecutively included all patients aged less than 21 years with diagnosis of CAH based on clinical (abniormal genitalia, premature pubarche) and hormonal basis (elevated 17 OH progesterone), from May 2013 to December 2022. The complete diagnosis process of our patients is described elsewhere [5].

From patients' records, we extracted data on pedigree: consanguinity, history of child death, history of abnormal genitalia or other malformations reported in the family. In case of history of child death, a verbal autopsy was done using elements of the WHO standards [6]. This questionnaire was addressed to the child's mother at first consultation and stored in patient files. Information on age at death, context of death, symptoms leading to death to establish a presumptive diagnosis. The presumptive diagnosis was discussed by the 2 senior pediatric endocrinologist. Adrenal failure was suspected if the following were reported: failure to thrive, dehydration without diarrhoae, with or without abnormal genitalia.

The genetic aetiology of CAH was noted when available. We excluded files with lack information on family history (patient brought by a relative without proper information). The Data were noted on a Microsoft excel file also used for descriptive analysis. Qualitative data are expressed as counts or proportions and quantitative data as percentage.

3. Results and Discussion

From 41 files found, we retained 39 patients from which 5 from Laquintinie hos-

pital. Two files were excluded due to missing information. Despite that consanguinity was not declared, patients were from the same close tribal environment in 74.3% of cases. This specificity of close ethnic origin is already described [5].

A contributively past history was found in 15 families (37.5%). Hence, we found 20 reported deaths of infant less than 12 months in 13 families, (**Figure 1**) with two women who had each 3 children died (patient 7, patient 10, **Table 1** and **Figure 2**). Verbal autopsy revealed a notion of dehydration and fever without diarrhoea in 6 cases (30% of death), neonatal death in 4 cases (20%). Reported malformation was found in 4 cases in which 3 was abnormal genitalia. In 6 cases, we had no clear information on death circumstances. In 3 cases, the patient was the first child of the mother with a reported history of DSD or early death in relatives. Two patients were the first alive child of 2 women (Patient 11, 12).

Five cases (33.3%) of DSD was reported in relatives of 4 patients. One of the reported case was a woman with primary infertility and abnormal genitalia (patient 15). The father of one patient reported to have hypospadias (Patient 1).

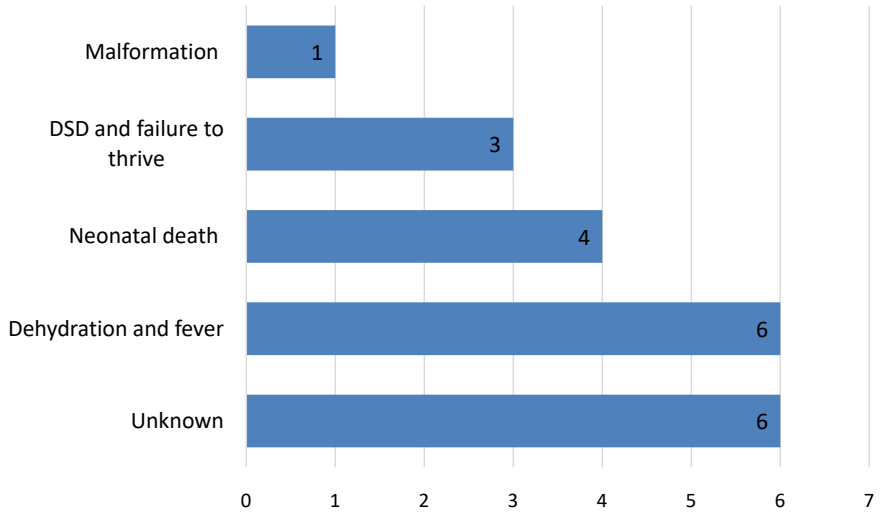

Figure 1. Circumstances of death of relatives aged <12 months.

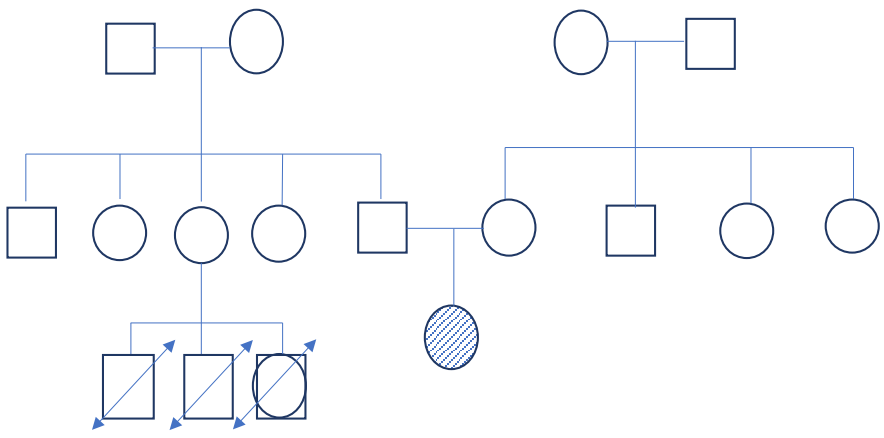

Figure 2. Pedigree of patient 10.

Table 1. Summary of findings of children with a particular past history.

Patient Number	Same tribes	Family history	Biomol
1	Yes	Infant death at 3 months: failure to thrive and DSD Father with hypospadias	CYP 21
2	Yes	Male infant death at 4 months: dehydration	CYP 21
3	No	Anovaginal fistula elder sister	CYP 21
4	No	Neonatal death of a cousin with unknown malformation	NA
5	No	Sickle cell (mum's cousin), epilepsy (father's cousin)	CYP 11
6	No	Infant death: dehydration and sepsis	CYP 21
7	Yes	3 infants' death (<12 months) in sister of grandmother, A cousin of grandmother with DSD dead (aged?), Severe hypospadias in father's cousin	CYP 11
8	Yes	Brother with DSD dead	CYP 11
9	Yes	Brother with DSD dead	CYP 11
10	No	3 neonatal death of cousin (father's sister children)	CYP 11
11	Yes	Elder brother died before a year (dehydration?)	CYP 11
12	Yes	Elder brother died at 2 months Junior affected	CYP 21
13	Yes	2 uncles died in neonatal period (mum's brothers)	NA
14	Yes clan	1 neonatal death with malformation in father's family	CYP 21
15	Yes	DSD and infertility in sister grand mother	CYP 11
16	Yes clan	1 elder brother died in neonatal period, 2 deaths (mum's brothers, fever and dehydration?)	NA

NA, not available.

Other non DSD malformations was reported in siblings or close relatives of three patients: one with anovaginal fistula (patient 3), a cousin with an unknown malformation (patient 4) a cousin with sickle cell and another one with epilepsy (patient 4, 5).

The genetic diagnosis was available in 13 of these families: 7 had 11 hydroxylase deficiency and 6 had 21 hydroxylase deficiency. Eight reported death occurred in family of patients with 11 hydroxylase deficiency, 4 in relatives of those with 21 hydroxylase deficiency and the other in family without a genetic testing.

4. Discussion

The present analysis of past history of patients with CAH in our context was motivated by an interesting discussion with a reviewer on a previous study on CAH in Cameroonian setting, asking for a more complete description of patients in a context of low access to care [5]. The limit of this paper is the few number of cases. Another limit is reliability of verbal autopsy which is less than 80% in our context [6].

However, information provided is reproducible in various settings and can be used for discussion and advocacy.

In absence of neonatal screening, the misdiagnosis of adrenal failure is common and unfortunately dramatic. In our study population, a history of infant death was found in more than half of families with affected child. Unsurprisingly, the context of death is coherent with adrenal failure [1] [7]. Unfortunately, this was not either suspected in this situation. This revealed the insufficient level of training of health care personnel regarding this issue and the pressure of infectious diseases in this context. Because of the later, almost every acute emergency in neonate and infant are considered as an infectious disease and probably, this is true but not always. The insufficient level of awareness of the health personnel is also a key point of discussion. This might be due at least to insufficient training, to limited access to diagnosis tools. Proper training and vulgarisation of an adequate diagnosis algorithm might be helpful without replacing neonatal screening [8]. Behind two diagnoses of CAH, at least one child death is related and a long course of care and misdiagnosis. Behind our cohort of 39 patients, there are potential 20 or more undiagnosed among which 20 deaths. Hence, neonatal screening appears to be an emergency to save that lives in our setting [9] [10].

In our study population, we found suspicion of death related to adrenal insufficiency in 7 patients with proven 11 hydroxylase deficiency and 6 with 21 hydroxylase deficiency. Although 11 hydroxylase deficiency is the most common anomaly found in our setting, the high amount of early death was unexpected despite late age at diagnosis [8]. This severity of adrenal function failure in 11 hydroxylase population needs to be explored.

Other malformations or genetic anomaly was reported in 4 patients' families variable form epilepsy to sickle cell and other anovaginal anomaly. A father was reported to have hypospadias. Despite that the relation CAH with these anomalies is not clear, there are possibilities of cross related genetic abnomalies [11] [12] [13].

5. Conclusion

Each diagnosis of CAH made in our context is visible part of an iceberg. Behind a diagnosis of CAH made in our setting, is a long course of care, a dramatic past history revealing access to appropriate care disparity. Neonatal screening should thus be considered as an emergency.

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Statement

The present study has been partially presented to the 2022 annual ESPE congress as e poster.

Conflicts of Interest

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

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