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Epidemiology of children with epilepsy at a tertiary referral centre in South Africa

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ABSTRACT

Purpose: This retrospective observational hospital-based study assessed the characteristics of children with epilepsy in a sub-Saharan African tertiary service over a 10-year period.

Methods: Children with a primary or secondary diagnosis of epilepsy seen during the study period were identified from the departmental database. Demographic and clinical data were collected from the database and available medical records.

Results: Of 4701 children managed in the neurology service, 2407 children (51%) had epilepsy. The 2017 International League Against Epilepsy Classification of the Epilepsies was used to ascribe seizure and epilepsy type, epilepsy syndrome diagnosis and aetiologic categories. Forty-three percent of children had seizure onset before age one year. Focal Epilepsy occurred in 48% of the cohort (n = 1145). Twenty-five percent had an epilepsy syndrome diagnosis. Most children (54%) had epilepsy of unknown aetiology. Among those with underlying non-genetic aetiologies (33%), sequelae of intracranial infections, perinatal insults and structural brain malformations were most prevalent. Motor disability was present in 24% of children. Seventy-four percent had at least one associated motor disability, intellectual or learning disability, developmental delay or psychiatric comorbidity.

Conclusion: Epilepsy is common in sub-Saharan Africa. Many affected children have avoidable aetiologies. Compared to data from similar hospital-based studies in poorly resourced and resource-equipped settings, our cohort had a higher proportion of seizure onset below the age of one year and a greater number of infectious aetiologies, which is similar to population-based studies reported in sub-Saharan Africa. The presence of co-morbidities is significant and demands greater advocacy for services for these children.

1. Introduction

Epilepsy is a common neurological disorder globally affecting 70 million people [1,2]. Up to 90% live in low-income and lower-middle-income countries (L&LMICs) and over half of these are children [1,2]. Epilepsy presenting in childhood is heterogeneous, with diverse underlying aetiologies, clinical presentations, severity and prognosis. Neurobehavioural and psychiatric comorbidities occur in up to 80% of children and are frequently under-recognized [3].

Classification and Terminology of the epilepsies were reorganised in 2010 to reflect neuropathological and aetiological mechanisms, largely enabled by technological advances in neuroimaging techniques and molecular genetics [4]. In 2017 the International League Against Epilepsy (ILAE) published the first position papers on the classification of seizures and the epilepsies since 1989 [5–7].

In Africa, significant challenges to both diagnosis and management remain despite these advances. Population-based studies have examined prevalence, causes and risk factors for epilepsy, as well as associated comorbidities [8,9]. However, in sub-Saharan Africa data remain limited for distribution of seizure and epilepsy types, and description of epilepsy syndromes is poor [10]. This hospital-based study describes characteristics of epilepsy across ages in children attending a tertiary epilepsy service over a 10 year period, in accordance with the new ILAE classification system, and compares findings with similar studies from other regions.

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2. Materials and methods

2.1. Context

This retrospective observational study was conducted within the paediatric neurology service of the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa. RCWMCH is a government funded tertiary facility for children located in Cape Town, Western Cape, South Africa, affiliated to the University of Cape Town. The hospital serves a provincial population of over 1.4 million children below the age of 14 years [11]. Population distribution data for the Western Cape province in 2011 include 50% mixed race (comprising 49% mixed ancestry and 1% Indian/Asian), 33% indigenous African, 16% European ancestry and 1% 'other' [11,12]. The neurology service is unique compared to international units in that it cares for children aged 0–12 completed years at first consultation across all levels of care, primary to quaternary. Children may remain in the service until 16 years of age or older, prior to transfer to adult services. Capacity to manage children with epilepsy at primary level within the Western Cape is very limited and prior to 2010 secondary level support was similarly affected. Direct referral to the neurology service from primary care centres is common. As a result the service delivers care for a wider community than would normally occur in a resource-equipped setting with adequate primary and secondary facilities.

In addition, the department serves as a quaternary epilepsy service for other provinces in South Africa. It is the only government-funded facility providing long-term video electroencephalography (VEEG) monitoring for children. Electroencephalography (EEG) is routinely performed in all children referred to the neurology clinic with unprovoked seizures and for specific indications such as suspected subclinical status epilepticus and localization of seizure onset. Neuroimaging, using either computed tomography (CT) or magnetic resonance imaging (MRI), metabolic investigations and karyotyping are performed when indicated for diagnosis or management. Prior to 2002 MRI was not readily available. Due to resource constraints CT is performed where there is a clear history of an underlying insult or in the emergency setting. MRI is routinely performed in children without an obvious underlying cause, as part of a metabolic assessment and in those refractory to anti-seizure medications (ASM). Neuropsychology assessments are limited to children assessed for epilepsy surgery or for complex patients. Genetic services for children with epilepsy are largely restricted to karyotyping or targeted syndromic diagnoses; testing for specific mutations such as *SCN1A* is not available in the government sector but accessible for a small proportion through a collaborative research project [13,22]. ASM levels are not routinely tested except where either toxicity or non-adherence is suspected.

2.2. Data collection

All children with a primary or secondary diagnosis of epilepsy seen between January 2000–December 2010 were identified from the neurology service confidential clinical database. Additional data was collected from the medical records: demographic data, primary residence, history of neonatal and febrile seizures, family history of epilepsy, age at onset of epilepsy, causative factors, seizure types, syndromic classification, additional neurological impairments, intellectual or developmental status, EEG and neuroradiology findings, positive metabolic or genetic findings, number of ASMs prescribed, drug resistance, use of the ketogenic diet, vagus nerve stimulation (VNS) or epilepsy surgery procedures.

2.3. Criteria and definitions used

Epilepsy was defined as two or more unprovoked seizures at least 24 h apart or where a single seizure occurred in the presence of a well-defined electroclinical syndrome [14]. Children with neonatal onset seizures were included only if seizures continued beyond the neonatal period or recurred without provocation. Children with only simple febrile seizures or acute symptomatic seizures were excluded. Patients were also excluded if their medical records were unavailable or inadequate.

Seizure onset was defined as the age at first unprovoked seizure. Epilepsy was classified according to seizure type, epilepsy type, epilepsy syndrome and aetiology in accordance with the 2017 ILAE Classification of the Epilepsies [5–7].

Drug resistant epilepsy was defined in accordance with the consensus proposal by the ILAE Commission task force [15]. Developmental delay (in children <5 years old) was recorded where documented according to the Molteno Adapted Development Scale as per standard practice in our Neurodevelopmental clinic [16]. Intellectual disability (children >5 years old) was based on the Molteno Adapted Development Scale assessment (if appropriate), an Educational or Neuropsychology assessment (where available) or best clinical judgement based on school placement if not specifically recorded. Children with an intellectual quotient (IQ) or developmental quotient (DQ) below 70 were classified as cognitively impaired or significantly developmentally delayed [mildly delayed/impaired (50–70), moderately delayed/impaired (35–50) or severely delayed/impaired (<35)].

2.4. Ethics statements

The research was granted ethical approval by the Human Research Ethics Committee of the University of Cape Town, in accordance with the Declaration of Helsinki (HREC/Ref 275/2010).

2.5. Statistical data analysis

Standard statistical approaches were used for data exploration. Measures of central tendency for continuous variables were reported as median (range). Relationships between child and seizure characteristics were assessed overall and in sub-groups of age at seizure onset, using Pearson's chi^2 tests. All analyses used Stata 14.0 (Statacorp, College Station TX).

3. Results

A total of 4701 children attended the neurology service during the study period, 2407 (51%) of whom were diagnosed with epilepsy, including 56% (1349/2407) males. Sixty percent of the cohort were of mixed ancestry (n = 1441/2407), 37% were indigenous African (n = 896/2407) and 3% were of European ancestry (n = 70/2407). Seventy-five percent were resident within the City of Cape Town Metropole and 17% were resident outside of Cape Town but within the Western Cape province. Six percent of the cohort were resident outside of the Western Cape Province, of these, approximately one quarter were residing in rural areas. Fewer than 1% of patients were resident elsewhere in Africa.

After combining data collected from available medical records and the database, all study modalities were available for 71% (1699/2407) of children, whilst one or more modalities were lacking on 708 children. The commonest reason for missing data was unavailability of medical records (either untraceable or archived, n = 823 children). There was no systematic reason for missing or incomplete data, indicating minimal risk of selection bias.

The median age of onset of epilepsy was 22 months (range 1 day to 143 months) based on data available for 1716/2407 patients (71% of the cohort). Seizure onset occurred before the age of one year in 43% (n = 743/1716), between one and five years in 36% (n = 621/1716) and between five and 12 years in 21% (n = 352/1716). Over half of the total cohort experienced their first seizure before age two years (n = 952/1716).

A family history of epilepsy was identified in 13% (167/1288) of

Table 1
Seizure Types and Epilepsy characteristics by age of onset.

All epilepsies	<1 year n = 743 (%)	1–5 years n = 621 (%)	5–12yrs n = 352 (%)	No data n = 691 (%)	Total cohort[d] n = 2407 (%)
Seizure Type[a]					
Generalised onset[b]	382 (51)	346 (56)	133 (38)	195 (28)	1056 (52)
Multiple semiologies	81 (21)	159 (26)	25 (7)	15 (2)	280 (12)
Focal onset[b]	325 (44)	353 (57)	227 (64)	404 (58)	1309 (54)
Multiple semiologies	4 (<1)	9 (1)	7 (<1)	0	20 (<1)
Unknown onset	122 (16)	16 (3)	5 (1)	101 (15)	244 (10)
Seizure Types detailed[c]					
Generalised					
Motor onset					
Tonic-clonic	171 (23)	161 (26)	90 (26)	97 (14)	519 (22)
Tonic	56 (8)	92 (15)	6 (2)	13 (2)	167 (7)
Myoclonic	80 (11)	82 (13)	19 (5)	18 (3)	199 (8)
Atonic	43 (6)	134 (22)	8 (2)	12 (2)	197 (8)
Epileptic spasms	136 (18)	3 (<1)	0	0	139 (6)
Non-motor onset					
Typical absence	6 (<1)	30 (5)	30 (9)	40 (6)	106 (4)
Atypical absence	39 (5)	108 (17)	19 (5)	30 (4)	196 (8)
Myoclonic absence	0	3 (<1)	1 (<1)	0	4 (<1)
Focal					
Aware					
Motor onset - clonic	0	7 (1)	33 (9)	42 (6)	82 (3)
Aware					
Non motor onset	0	0	0	0	0
Impaired awareness					
Motor onset					
Clonic	299 (40)	320 (52)	157 (45)	310 (45)	1086 (45)
Tonic	12 (2)	3 (<1)	4 (<1)	8 (1)	27 (1)
Epileptic spasms	22 (3)	0	0	0	22 (<1)
Non motor onset	3 (<1)	6 (1)	11 (3)	28 (4)	48 (2)
Focal to bilateral TC	19 (3)	22 (4)	24 (7)	13 (2)	78 (3)
Epilepsy Type[a]					
Generalised	329 (44)	254 (42)	123 (35)	186 (27)	892 (37)
Focal	272 (36)	261 (43)	217 (62)	395 (57)	1145 (48)
Combined Generalised and Focal	53 (7)	92 (15)	10 (3)	9 (1)	164 (7)
Unknown	122 (16)	16 (3)	5 (1)	101 (15)	244 (10)
Epilepsy Syndrome					
Focal	36 (5)	15 (2)	43 (12)	31 (4)	125 (5)
Generalised	171 (23)	100 (16)	37 (11)	60 (9)	368 (15)
Combined Generalised and Focal	38 (5)	79 (13)	1 (<1)	4 (<1)	122 (5)
Aetiology[e]					
Genetic[f]	61 (8)	62 (10)	49 (14)	76 (12)	248 (11)
Structural[f]	250 (34)	93 (15)	55 (16)	162 (26)	560(24)
Metabolic	9 (1)	7 (1)	3 (<1)	7 (1)	25 (<1)
Infectious	71 (10)	78 (13)	58 (16)	48 (8)	255 (11)
Immune	0	3 (<1)	3 (<1)	0	6 (<1)
Unknown	360 (49)	391 (63)	182 (52)	330 (53)	1263 (54)
Insufficient data to assign	7 (1)	1 (<1)	0	73 (11)	81 (3)
Unknown cause and no Syndrome diagnosis	260 (35)	238 (38)	148 (42)	289 (42)	935 (39)

[a] Figures in parentheses expressed as a percentage of the individual age category. Totals may exceed patient numbers where mode of onset evolved over time.
[b] Includes focal or generalised seizures occurring in isolation, or evolving over time, or in combination (e.g. occurring as part of Combined Generalised and Focal Epilepsy).
[c] Figures in parentheses expressed as a percentage of the individual age category. Totals may exceed patient numbers where multiple seizure types were present in a single patient (e.g. tonic-clonic and absence seizures).
[d] Figures in parentheses expressed as a percentage of the total cohort.
[e] Figures in parentheses expressed as a percentage of the total in each category, excluding those with insufficient data to assign a cause (e.g. for structural aetiology 560/2326, 24%).
[f] Totals include 31 children with combined genetic and structural aetiology (tuberous sclerosis).

patients with data available.

Seizure types are summarized in Table 1 and Supplemental Fig. 1.

In those children without a specific electroclinical syndrome diagnosis (n = 1804), focal motor seizures were the predominant seizure type (n = 879). A third of children with myoclonus had their first seizure before the age of 12 months and half of these had isolated myoclonus.

Seven percent of the cohort had epileptic spasms (n = 161). Fifty percent (n = 80) of these children subsequently developed other seizure types; 23% (n = 37) generalized onset, 19% (n = 30) focal onset and 8% (n = 13) evolving to Combined Generalised and Focal Epilepsy, 9 of whom had Lennox-Gastaut syndrome. Twenty-nine children (19%) with epileptic spasms had a prior history of neonatal seizures and 4 children had a prior history of seizures outside of the neonatal period

Table 2
Aetiological categories by age of onset.

AETIOLOGY	<1 year (n = 743)	1–5 years (n = 621)	5–12 years (n = 352)	Unknown onset (n = 691)	Total (n = 2407)
GENETIC[a] (%)	**61 (8)**	**62 (10)**	**49 (14)**	**76 (11)**	**248 (10)**
Chromosomal abnormalities/gene mutation syndromes	8	6	0	19	33
Rett syndrome	1	1	3	6	11
Other	47	42	62	55	206
STRUCTURAL (%)	**250 (34)**	**93 (15)**	**55 (16)**	**162 (23)**	**560 (23)**
Perinatal insult[b]	134	45	20	23	204
Hypoxic/vascular insults[c]	132	28	12	20	192
Term HIE	105	10	2	6	122
Preterm PVL	13	6	6	3	25
Hypoglycaemia	3	1	0	2	6
Postnatal hypoxic injury[d]	7	4	4	7	22
Cerebral malformations	56	14	5	30	105
Malformations of cortical development	48	12	4	22	86
Cortical dysplasia	8	3	1	6	18
Lissencephaly	7	0	0	0	7
Polymicrogyria	1	0	0	1	2
Heterotopia	1	1	2	3	7
Hemimegalencephaly	6	0	0	3	9
Schizencephaly	9	1	0	4	14
Other	16	7	1	5	29
Other cerebral malformations[e]	8	2	1	8	19
Trauma	6	10	13	30	59
Neurocutaneous disorders	22	11	4	18	55
Tuberous sclerosis	15	8	3	5	31
Sturge Weber syndrome	1	2	0	8	12
Neurofibromatosis	3	0	0	1	2
Other	5	1	0	4	10
Tumour[f]	3	7	6	6	22
Stroke	13	9	2	19	43
Congenital	8	6	2	4	19
Postnatal	5	2	0	14	22
Moya Moya syndrome	0	1	0	1	2
METABOLIC (%)	**9 (1)**	**7 (1)**	**2 (<1)**	**7 (1)**	**25 (1)**
Betaketothiolase deficiency	2	1	0	0	3
Biotinidase deficiency	2	0	0	0	2
Nonketotic hyperglycinemia	1	0	0	0	1
MMA	1	0	0	0	1
DHPR deficiency	0	0	0	1	1
Mucopolysaccharidosis	1	0	0	1	2
FIGLU	1	0	0	0	1
Fahr Disease	0	0	0	1	1
Glutaric aciduria type 1	1	0	0	0	1
Smith-Lemli-Opitz	0	0	0	1	1
GLUT1 deficiency	0	0	0	0	0
Mitochondrial	2	1	2	3	8
Neuronal ceroid lipofuscinosis	1	0	0	0	1
Alexander disease	0	0	1	0	1
INFECTIOUS (%)	**71 (10)**	**77 (12)**	**59 (17)**	**48 (7)**	**255 (11)**
Meningoencephalitis	50	43	18	14	125
Neonatal	12	4	5	2	22
Pneumococcal	3	2	0	0	5
Meningococcal	4	2	1	0	7
Haemophilus	4	2	0	1	7
Viral	5	1	2	0	8
Tuberculous	9	19	4	4	36
Unknown	13	14	6	7	40
PML	0	0	1	0	1
Congenital infections	7	5	1	5	18
CMV	7	3	0	2	12
Toxoplasmosis	0	1	1	2	4
Rubella	0	1	0	0	1
Granuloma	3	28	39	24	94
Neurocysticercosis	2	15	28	10	55
Tuberculous	0	3	4	3	10
NOS	1	10	7	11	29
HIV encephalopathy	1	2	1	5	9
IMMUNE (%)	**0**	**2 (<1)**	**4 (1)**	**0**	**6 (<1)**
Rasmussen syndrome	0	2	4	0	6

(*continued on next page*)

Table 2 (*continued*)

AETIOLOGY	< 1 year (n = 743)	1–5 years (n = 621)	5–12 years (n = 352)	Unknown onset (n = 691)	Total (n = 2407)
Anti-NMDA receptor encephalitis	0	0	0	0	0

HIE, hypoxic-ischaemic encephalopathy; PVL, periventricular leukomalacia; MMA, methylmalonic aciduria; DHPR deficiency, dihydropteridine reductase deficiency; FIGLU, formiminoglutamic acidaemia; GLUT1, glucose transporter type 1; PML, progressive multifocal leukoencephalopathy; CMV, cytomegalovirus; NOS, not otherwise specified.

[a]Tuberous sclerosis complex included in both the structural and genetic groups.

[b]Excludes perinatal CNS infections.

[c]Includes antenatal, perinatal hypoxic insults, porencephaly, congenital stroke, hypoxic-ischaemic encephalopathy, periventricular leukomalacia.

[d]Includes near-drowning, brain injury post shock, brain injury post toxin.

[f]A single patient with a subependymal giant cell astrocytoma (tuberous sclerosis) with seizure onset at age 4 years is included in the structural and genetic groups.

but preceding spasm onset. Sixty percent (n = 96) of children with epileptic spasms had an identifiable cause, mostly term or preterm perinatal insults (n = 51) or disorders of neuronal migration (n = 17). Four infants had underlying tuberous sclerosis.

Table 1 summarises the epilepsy characteristics and aetiologies across individual age groups and the total cohort. The presence of Focal Epilepsy was more common with increasing age at seizure onset (60% of children with onset between age five to 12 years) ($p < 0.0001$). Combined Generalised and Focal Epilepsy was significantly more common in the one to five year onset age group ($p < 0.0001$).

Table 2 and Supplemental Fig. 2 outline the distribution of specific aetiologies within each category and across different ages of onset. The majority of epilepsies (54%) were of unknown aetiology (n = 1263). Structural, metabolic, infectious and immune causes were identified in 36% of the cohort (n = 846). Intracranial infections (n = 255), perinatal insults (n = 204) and structural brain malformations (n = 107) were most prevalent. Metabolic disorders were rarely identified. Almost 40% of children (n = 935) could not be assigned a specific Epilepsy Syndrome diagnosis or underlying aetiology.

Table 3 shows the distribution of Epilepsy Syndromes. A specific diagnosis could be made in 25% of the cohort (n = 603/2407). West syndrome was the most common syndrome diagnosis (n = 161).

The distribution of specific disabilities by age of onset is detailed in supplementary online material (see Supplementary Table 1). A full data set for all disabilities was available for 82% of the cohort (n = 1970/2407). Among those with disability data, 62% of children (n = 1323/2139) had one or more associated motor, intellectual or developmental disability and/or psychiatric comorbidity. The proportion of children with any disability increased to 74% (n = 1590/2139) when those with borderline IQ/DQ (70–85) and/or specific learning disabilities such as dyslexia were included. One or more developmental, learning and/or psychiatric disability was detected in 59% of the cohort (n = 1260/2139), including 32% with intellectual disability (n = 698). Boys were substantially more likely to be diagnosed with any neurobehavioural or psychiatric disability than girls (boys with disability versus girls with disability: 21% vs. 15%, $p < 0.0001$) or with a specific learning disability or borderline IQ/DQ (boys versus girls 12% vs. 7.5%). Age of onset was significantly associated with the presence of any disability; 80% (576/718) of children presenting under age 1 year had some form of motor, cognitive or psychiatric disability, either at presentation or at a later age, versus 54% (322/599) of children presenting between ages 1 and 5 years and 29% (97/337) of children presenting after the age of 5 years ($p < 0.0001$). As expected, a diagnosis of epileptic spasms was strongly associated with disability, present in 94% (152/161) of children, as was Combined Generalised and Focal Epilepsy [85% associated disability (138/163 with known data) versus 53% for Generalized Epilepsy (430/810 with known data) and 60% for Focal Epilepsy (589/987 with known data), $p < 0.0001$].

Motor disability was present in 24% of children across all age groups and varied significantly by age of onset, underlying aetiology and ancestry. Children presenting under the age of 1 year were more likely to have motor disability (327/728,45%) compared to children presenting at any other age [14% (88/612) in the 1–5 year age group and 7% (24/350) in the >5 year age group, $p < 0.0001$]. The majority of these children had an underlying structural or infectious cause (181/327,55%). A significant proportion had no identifiable aetiology

Table 3
Distribution of Epilepsy Syndromes.

Epilepsy Syndrome Diagnosis[a]	Boys	Girls	Total
Neonatal			
Self-limited Familial Neonatal Epilepsy	0	0	0
EME	3	2	5
Ohtahara syndrome	1	1	2
Infancy (< 2 years)			
Epilepsy of infancy with migrating focal seizures	3	0	3
West syndrome	85	76	161
Myoclonic epilepsy in infancy	1	8	9
Self-limited Infantile Epilepsy	4	4	8
Self-limited Familial Infantile Epilepsy	0	0	0
Dravet syndrome	4	8	12
Myoclonic encephalopathy in non-progressive disorders	1	0	1
FFEVF	0	1	1
Febrile seizures plus	13	4	17
Genetic epilepsy with febrile seizures plus	15	6	21
Childhood			
Febrile seizures plus	13	8	21
Genetic epilepsy with febrile seizures plus	5	5	10
Early onset childhood occipital epilepsy[b]	0	0	0
Late onset childhood occipital epilepsy[c]	4	1	5
Epilepsy with myoclonic atonic seizures	35	7	42
ECTS	28	27	55
ADNFLE	5	2	7
Epilepsy with myoclonic absences	0	0	0
LGS	65	45	110
Epileptic encephalopathy with CSWS	0	2	2
Landau Kleffner syndrome	4	1	5
Childhood absence epilepsy	41	44	85
GTCA	2	3	5
Adolescence			
Juvenile absence epilepsy	1	1	2
Juvenile myoclonic epilepsy	1	9	10
Progressive myoclonic epilepsy	0	0	0
Constellations			
Rasmussen syndrome	3	3	6
MTS	5	2	7
IHHE	0	0	0
Gelastic seizures with hypothalamic hamartoma	1	2	3
All syndromes	343	272	615

EME, early myoclonic encephalopathy; FFEVF, familial focal epilepsy with variable foci; ECTS, self-limited epilepsy with centrotemporal spikes; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; LGS, Lennox-Gastaut syndrome; CSWS, continuous spike-and-wave during sleep (also known as Electrical Status Epilepticus during slow wave sleep/ESES); GTCA, Epilepsy with generalised tonic-clonic seizures alone; MTS, mesial temporal sclerosis; IHHE, idiopathic hemiconvulsion-hemiplegia-epilepsy.

[a] Totals exceed the number of children as some evolved over time.

[b] Panayiotopoulos type.

[c] Gastaut type.

despite the presence of motor disability (133/327,41%). Motor disability was more common among children with African ancestry (280/851,33%) than those with European (11/69,16%) or mixed ancestry (253/1384,18%), ($p < 0.0001$). Structural (n = 243/496,49%) and immune (n = 6/6,100%) causes were associated with a greater risk of motor disability than other aetiologies ($p < 0.0001$). Cognitive disability (IQ < 70) or developmental delay (DQ < 70) was also strongly associated with aetiology, with the highest risk seen among children with structural abnormalities (n = 345/503, 69%) and inborn errors of metabolism (n = 17/23, 74%), ($p < 0.0001$).

Twenty-three percent (n = 484/2105) of the cohort had drug resistant epilepsy, 34 children (1%) initiated the ketogenic diet, 4 patients (<1%) had a vagus nerve stimulation device (VNS) implanted and 23 (1%) underwent epilepsy surgery.

Data regarding ASMs was available for 1895 children. At the time of data collection 60% (1137/1895) were on a single ASM, 23% (440/1895) were on two ASMs and 17% (318/1895) were on 3 or more ASMs.

4. Discussion

This is the first study from sub-Saharan Africa describing a hospital-based paediatric epilepsy cohort and the largest published paediatric hospital cohort in the literature to date. It provides a retrospective overview of 2407 children with epilepsy. Our cohort is unique in that it represents children with epilepsy across multiple levels of care providing insight into the full spectrum and burden of paediatric epilepsy in our setting.

Our study was limited by difficulties accessing medical records. The unit has since implemented a standardized data collection tool for all children with epilepsy. In addition, there remain an undefined number of children accessing treatment within the provincial secondary healthcare services, private healthcare services and the general medical out-patient department within our own hospital. The government service numbers are likely to be relatively small as most children with epilepsy were referred to our service for review during the study period. From 2010 the general medical out-patient service extended their role and capacity to manage children with less complex epilepsy.

An important strength of our study is the size of the cohort compared to similar hospital-based studies from L&L-MICs (see Supplemental Table 2) [17–21], the largest of which, from a tertiary hospital in Turkey, includes 533 children over a 5 year period [18]. The authors report seizure onset below the age of 1 year in 30.6%, compared to 43% in our cohort. Our figure is considerably higher despite a similar proportion of structural abnormalities and infectious aetiologies (32% versus 36%). Infectious causes were more frequent in our cohort in comparison (10% versus 4%), but we identified a lower number of structural abnormalities (24% versus 32%). It is difficult to draw aetiologic comparisons with other similar hospital-based studies given their smaller cohort size and limited reporting of specific aetiologies [17–21]. The high percentage of infectious causes in our cohort is inline with population-based figures from sub-Saharan Africa [22]. This may relate to the unique range of patients in our clinic, including those with primary through to quarternary level of care needs, suggesting our findings may be more representative of our local paediatric population as a whole, rather than a tertiary hospital-based cohort.

The proportion of children with epileptic spasms (7%) is similar to those found in other L&L-MIC cohorts (4.8–8.2%) [17–21] and to those reported in hospital-based studies from high-income countries (HICs) (5.2–9%) [23–25]. Figures are also comparable to the Turkish cohort for Lennox-Gastaut syndrome (5% in our study versus 3.7%), but substantially higher than figures reported from HIC cohorts (0.5–1.5%) [23–25]. This discrepancy may be influenced by the higher number of acquired aetiologies seen in L&L-MIC settings.

Only one population-based study, carried out in a high income setting, has attempted to classify the causes of epilepsy in children according to the latest ILAE Classification of the Epilepsies [7,26]. They report 50% of children with unknown aetiology, 22% with genetic causes and 28% with structural/metabolic causes [26]. The vast majority of the latter group were due to structural causes; 50% perinatal brain injury and only two reported infectious causes. Although direct comparisons are limited due to different methodologies, our cohort faired similarly for those with unknown aetiology (57%), but had a much higher proportion of infectious causes (10% versus 2%) and less than half the number of identified genetic causes (10%).

This is likely to be influenced by access to genetic testing, neuroimaging and more extensive metabolic testing together with the well described higher prevalence of infectious insults found in resource-limited countries. We did not identify any cases of anti-NMDA receptor encephalitis during the study period, but with increased awareness we have diagnosed cases subsequent to this study. Similarly, we identified no cases of GLUT1 transporter deficiency; though rare, one might expect more cases given the size of the cohort. By introducing a more structured approach to epilepsy work-up, and with recent access to research based genetic testing in our service, we expect this yield to increase. Data from the first study investigating the genetic causes of Dravet syndrome in South Africa identified 10 children with genetic mutations (9 of these with *SCN1A* mutations*)* [13]. The majority of these were children managed in our service. A high proportion of children in our cohort with onset prior to age 1 year had disability despite no known aetiology or syndrome diagnosis. We postulate that a number of this children have undiagnosed genetic or metabolic causes. Similarly, our cohort of children with epileptic spasms had a higher than reported number of unknown aetiologies (40% versus 60% with structural, post infectious or metabolic causes), some of these are presumed to have undiagnosed genetic and/or metabolic aetiologies.

Only 15 children with fetal alcohol spectrum disorder (FASD) were identified in our cohort; the majority had no other identifiable underlying aetiology. Based on the high prevalence of FASD in the Western Cape Province of South Africa and the higher prevalence of epilepsy in individuals with a diagnosis of FASD, this figure is less than expected and some children may not have been identified [27].

Prevalence studies from sub-Saharan Africa report varying frequency of focal versus generalised onset seizure types [10]. Overall, generalized seizures predominate, presumed related to methodological difficulties and reporting bias [10]. Incidence studies from both HICs and L&L-MIC, report focal seizures as more common than generalised seizures [28]. There is a lack of consistency across hospital-based studies regarding seizure types from both HICs and L&L-MICs with focal seizures reported in 9.5% to 56% of individual cohorts (see Supplemental Table 2 [17–21,23–25]. This could be due to variations in amongst others, cohort size, clinical recognition of focal onset or access to EEG. Studies from both Turkey and China report focal seizure predominance (56.5 and 48.5% respectively) which is similar to our figure of 48% focal seizures [17,18]. Breakdown of focal seizure types in our study was limited in a large proportion due to incorrect use of the term 'complex partial seizure', used to describe both focal motor (clonic) seizures and non-motor seizures with impaired awareness.

A quarter of our cohort could be assigned a specific electroclinical syndrome diagnosis compared to about a third reported by Wirrell et al in their population-based study using the most recent proposals for classification [26]. In our study electroclinical syndrome diagnoses were underestimated due to limited application of specific syndromic diagnoses and clinical data documentation. Myoclonus occurred with unexpected frequency in children without a syndrome diagnosis. Approximately one third of this group had seizure onset before the age of one year with associated disability, a number of these children may have had undiagnosed Early Myoclonic Encephalopathy.

Comparison of aetiological data with similar studies is limited by a paucity of studies using the new ILAE Classification system [26]. Compared to data from resource-equipped settings our cohort had a greater number of children without a defined aetiology or

electroclinical syndrome diagnosis (37% in the under 2 year group compared to 26% in children under age 2 years reported in the North London infantile onset study) [29]. Despite this difference, considering our limited access to high quality imaging and genetic testing at the time of this study, and the comparatively lower number of children with structural causes (31% versus 51% in the North London cohort), aetiological and electroclinical syndromic diagnoses were defined in a significant percentage of the cohort with seizure onset under 1 year of age [29]. Wirrell et al report 41% of their 359 cases, ages 1 month to 17 years, as having an unknown cause and no clear syndrome identified [26]. Interestingly, despite the limitations of our service and the different resource setting, our figure of 40% is in line with their findings. Since completion of the study the neurology service has been restructured, implementing comprehensive approaches to care that encompass co-morbidities in a proactive rather than reactive manner and a methodical approach to diagnosis in line with the new classification system. In addition the service now has improved access to MRI, metabolic testing and research-based genetic panel testing for children with epileptic encephalopathies. This will improve the ratio of known to unknown aetiologies [13,22].

The majority of the cohort had a full set of disability data (82%), including information about motor function, cognition, developmental and psychiatric comorbidities. Only 1% of the cohort had no disability data for any of the three categories; the remaining 17% had information about at least one comorbidity. The reported rates of learning disabilities and/or intellectual impairment vary widely depending on case definitions used and the population studied (25–55%) [3,30]. Comparative HIC hospital-based studies do not specify associated motor and cognitive disability [23–25]. Hospital studies from L&L-MICs report between 6–57% motor disability and between 19–72% associated cognitive disability but with few specifying whether this was considered mild, moderate or severe [17–21]. Unver et al report normal cognition in 44% of their Turkish cohort, lower than 51% of the current study [18]. Data from a population-based Norwegian patient registry identified developmental and psychiatric comorbidities in 43% of children age 0–17 years with epilepsy, including 17% with intellectual disability [31]. Fourteen percent had cerebral palsy [31]. Other population-based studies report IQ < 70 in 40% of children [3]. Figures are assumed to be higher in resource-limited settings. However, a recent population-based study in school going children with epilepsy in Kenya in which formal neuropsychological testing was performed found comparatively lower rates of cognitive (3.7%) and motor disability (5.6%) but a higher proportion of ADHD (33.3%) and ASD (13%) [9]. Overall, neuropsychological comorbidities occurred in 54% [9]. Our finding of 32% intellectual disability is significantly higher even considering the different study cohort. The proportion of children with cognitive and/or psychiatric disability is likely to be underestimated at 59% as not all children underwent formal neuropsychological testing and screening for neurobehavioural and psychiatric comorbidities. The proportion of children with associated motor disability is higher than expected for the number of children with defined structural and infectious underlying aetiologies. This may reflect the limited availability of special investigations during the study period.

In resource-limited countries, including South Africa, health care systems are often poorly equipped to meet the needs of chronically ill patients, in particular patients with limited access to regular care [32,33]. Contributing factors include unaffordable costs, poor availability of services across all levels of health care and poor acceptability of epilepsy [33]. Children with epilepsy, and in particular those with additional disabilities, face further barriers to both initial access to care and continuity of care, including stigmatisation, cultural beliefs and practical issues such as the availability of transport for the physically disabled child. Inevitably, these barriers may greatly impact on both the quality of life and long term outcomes of children with epilepsy in our setting.

5. Conclusion

There is considerable inconsistency in findings across hospital-based studies from L&L-MICs [17–21]. Only one study from Turkey paralleled some our findings [18]. Our data highlights the need for improved data capturing and structured epilepsy work-up and seizure classification in children. The expanded classification is less open to interpretation thereby facilitating continuity, standardisation and quality of care in a busy clinic service. This study provides unique insight into aetiologies common in sub-Saharan African countries which, in general, are significantly resource-limited. The current ILAE classification remains useful in practice across different resource settings but limits direct comparisons of data where diagnostic resources are lacking with the risk that proportionally more patients will be categorized under “unknown” and “unclassified” where resources are limited. Our centre has access to a wider range of diagnostic tools than most African countries which has enabled classification of seizure and epilepsy types and causes. The burden of care in our cohort mandates improvements in provision of, and access to, chronic care services including therapy services and education for learners with special needs. This study highlights the importance of further research to establish prevalence and incidence data specific for our setting. This, in addition to data examining the risk factors and causes of epilepsy and improved detection of comorbidities, will improve advocacy for services for these children.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2019.06.018.

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