Clinical Profile of Children with Autism Spectrum Disorder in a Developmental Clinic in Western Cape

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1 Declaration

I, *Louisa Rudo Mudawarima MDWLOU001*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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2 Abstract

Clinical profile of children with Autism Spectrum Disorder in a developmental clinic in Western Cape

Abstract

Introduction

Autism Spectrum Disorder (ASD) is increasingly being recognised as a significant neurodevelopmental condition in African countries. There is some evidence to suggest that the children who present with ASD in Africa may be diagnosed late and have a more severe clinical picture. The purpose of this study was to describe the clinical profile of children with ASD in the neurodevelopmental clinic at Red Cross War Memorial Children's Hospital in Western Cape Province South Africa.

Methods

We sampled patients with a previous or new diagnosis who attended our clinic during the period January to July 2017. Consenting participants were administered a questionnaire with sociodemographic and clinical questions, clinical details of medical and developmental diagnosis were extracted from medical records and children. were further assessed using the Autism Diagnostic Observation Schedule version 2 (ADOS-2).

Results

A total of 32 patients were recruited into the study with 26 out of 32 (81%) being boys. On assessment as part of the study, all participants met DSM 5 criteria for the diagnosis of ASD. Most participants (94%) had not experienced general developmental regression but a substantial proportion (39%) had reported early regression of language milestones. Almost half of participants (48%) had self-injurious behaviour reported, 25% had associated motor

difficulty and 10% comorbid epilepsy. More than half of participants (53%) required substantial support in day-to-day activities. Most participants (81%) were administered module 1 of the ADOS-2 reflecting the high proportion of children in the sample who were either preverbal or using only single words.

Conclusions

Children seen in this clinical sample reflected the more severe end of the autism spectrum with a significant proportion having associated comorbidities such as epilepsy, and motor difficulties. The phenotypic profile on the ADOS 2 in this study correlated well with clinical assessments.

3 Acknowledgements

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- The African paediatric fellowship program that enabled me to study developmental paediatrics and who are giving opportunities to health care workers across Africa in order to make a difference in the lives of children
- The research committee of the University of Cape Town School of Child and Adolescent Health for the research support funding that made the conducting of this research possible.
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6 Abbreviations

ADOS	Autism Diagnostic Observation Schedule
ASD	Autism Spectrum Disorder
CDC	Centres for Disease Control and Prevention
DCAP	Department of Child and Adolescent Psychiatry
DRC	Democratic Republic of Congo
DSM-5	Diagnostic Statistical Manual 5th edition
PDDNOS or PDD	Pervasive Developmental Disorder Not Otherwise Specified
RRB	Restricted repetitive behaviours, interest and sensory problems
RXWMCH	Red Cross War Memorial Children's Hospital
SCAH	School of Child and Adolescent Health
UK	United Kingdom of Great Britain

7 Chapter 1: introduction and literature review

7.1 Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterised by persistent deficits in social communication and social interaction and restricted repetitive patterns of behaviour, interest and activity (Association, 2013). It manifests early in life and the symptoms should not be better explained by some other condition such as intellectual disability. This diagnosis now encompasses all of those with previously described diagnoses of Pervasive Developmental Disorder Not Otherwise Specified (PDDNOS or PDD), Childhood Autistic Disorder and Asperger's syndrome (Association, 2013). Mild forms of ASD may go undiagnosed even into adulthood (Ritvo et al., 1994), however if the symptoms have been present from childhood a diagnosis may still be made. (Association, 2013).

The recognised prevalence of ASD has been increasing. In the 1960s Lotter estimated the prevalence of ASD to be 0.2 to 0.4 cases per 1000 children (Lotter, 1966). Recently, the Centre for Disease Control and Prevention (CDC) has reported a steady increase in the prevalence in the United States from the period extending from 2000 to 2010 but remaining the same between 2010 and 2012 at 14.6 per 1000 children in the reported cohort (CDC). There has been an increase in the number of individuals diagnosed with or accessing services for ASD worldwide (Boat et al., 2015).

In Israel although previous studies had estimated the prevalence of ASD to be much lower in Arab communities, they found similar prevalence in Jewish and Arab communities of 4.3 per 1000 and 3.8 per 1000 population respectively (Mahajnah et al., 2015). A recent systematic review of the prevalence of ASD and PDD pooling data from several countries estimated the median prevalence of ASD to be 1.7 per 1000 and PDD at 6.7 per 1000 (Elsabbagh et al., 2012). There is no estimate of the prevalence of ASD in Africa and little from other developing countries in this review (Elsabbagh et al., 2012). The studies that are available do suggest ASD

is a significant problem in Africa. A study of Arab countries showed that 11.5% of Tunisian children and 33.6% of Egyptian children diagnosed with developmental disabilities had ASD (Seif Eldin et al., 2008). A review of ASD literature from African populations includes estimated prevalence in people of African ethnicity who had emigrated to Europe (Bakare and Munir, 2011a). It is not clear if emigration has an effect on incidence of autism. In Somali immigrants in Sweden, the population prevalence of Autistic Disorder or PDDNOS was 7 per 1000 population which is markedly higher than that of the overall population in the area which is 1.9 per 1000 (Barnevik–Olsson et al., 2008). The only recent study on a sub-Saharan African population that gave an estimate of prevalence of ASD was a study set in a community in Uganda to validate a screening tool for local use. In this study 12 to 13 per 1000 children in the population screened had ASD confirmed (Kakooza-Mwesige et al., 2014). This is similar to the figures from the CDC suggesting that the burden of ASD may be similar in Africa and other contexts.

7.2 The Clinical Profile of Autism

In his original account of "autistic disturbances", Kanner described eleven children who had features of ASD. In this account there were more boys than girls (8 boys and 3 girls) with a ratio of 2.6:1. The children had normal motor development but different verbal ability levels, abnormal social interaction and many repetitive behaviours (Kanner, 1943). Many parents had symptoms suggesting they were also part of the broader autism phenotype with descriptions of serious, introspective, socially withdrawn behaviour and hyperactive potentially manic behaviour by some parents despite being highly successful driven individuals (Kanner, 1943). This has been frequently reported elsewhere in the context of mild autism diagnosed in later childhood and adulthood (Ritvo et al., 1994).

Several studies have given a clinical description of children with ASD in a number of settings outside Africa including the United Kingdom, Israel, Saudi Arabia, Mexico and India (Fombonne et al., 2004, Juneja et al., 2005, Al-Salehi et al., 2009, Mahajnah et al., 2015). There have also been studies looking at ASD in Africa but initially not looking at the clinical phenotype of ASD in sub-Saharan Africa. Most of these studies are set in tertiary psychiatric units that are often associated with stigma in local communities (Bakare and Munir, 2011a, Mpaka et al., 2016). A systematic review of literature studies from Africa (Bakare and Munir, 2011b), included a case series of three children from Kenya in the 1980s (Dhadphale et al., 1982). A case series from Tanzania suggested malaria as a contributing causative agent of ASD (Mankoski et al., 2006). There are also cases described in the literature of ASD in those with oculo-cutaneous albinism, though visual impairment associated with albinism makes ASD a difficult diagnosis to make in this population(Mankoski et al., 2006, Bakare and Munir, 2011b). Elsewhere in Africa, a case series of 63 participants at a tertiary clinic from Tunisia in North Africa (Belhadj et al., 2006) and more recently, from the Democratic Republic of Congo (DRC), a study involving participants from three outpatient clinics described 120 participants enrolled over a two year period (Mpaka et al., 2016). Another study from a unit in South Africa retrospectively examined clinical records of children from a specialised neurodevelopmental clinic and described their clinical findings(Springer et al., 2013). A Swedish study and follow up looked at families with at least one parent who originally came from Somalia (Barnevik–Olsson et al., 2008, BARNEVIK-OLSSON et al., 2010). The findings of these studies are described below.

7.2.1 Gender, age at diagnosis and family history

The male predominance in ASD clinical populations has been well described from the earliest reports. In a study from the United Kingdom, 81% of children with a diagnosis of ASD were male with similar percentages in Israel (88%), Saudi Arabia (76%), USA (84%) and India

(69%) (Fombonne et al., 2004, Juneja et al., 2005, Al-Salehi et al., 2009, Jones and Campbell, 2010, Mahajnah et al., 2015). A case series from Tunisia in North Africa found that 75% of participants were male (Belhadj et al., 2006). This is also consistent with findings from the DRC and South Africa (Springer et al., 2013, Mpaka et al., 2016), suggesting that this is a very stable feature of ASD across all environments.

In Kanner's initial case report and description of autism, the ages of children was from 3 to 11 years (Kanner, 1943). In a recent UK review of general practitioner records, the median age at ASD diagnosis was 6.25 years with a standard deviation of 4.52 years despite the median age at first parental concern being 1.4 years (Fombonne et al., 2004). In an Indian hospital-based report, the mean age of diagnosis was 3.28 years with none of the participants having a significant family history for autism (Juneja et al., 2005). In North-western Israel, a study looking at ASD in children from two developmental clinics in different sectors the median age at first diagnosis was just over 3 years of age. Children of Arab ancestry were more likely to be the result of a consanguineous union. Parents were most likely to be the first ones to identify symptoms of ASD in their children (Mahajnah et al., 2015). In Saudi Arabia, the median age of participants at the time of referral into a hospital-based service was 6.3 years with a standard deviation of 2.6 years. Females were more likely to be older at presentation, which the authors attributed to societal differences in the health seeking behaviours for male compared to female children. Many families were reported as consanguineous and most of their cases were self-referred (Al-Salehi et al., 2009). In a review of African literature the age at presentation was over 8 years in most studies (Bakare and Munir, 2011b). The average age of participants in a study from Tunisia was 8 years old with a standard deviation of 3 years (Belhadj et al., 2006). In DRC, the median age in their clinic-based study was 6.91 years (Mpaka et al., 2016). In a previously reported South African hospital based study the median age at diagnosis was only 42 months (Springer et al., 2013). Overall, there is a wide range of reported age at diagnosis in

the studies from African contexts, suggesting the need for further research to explore this phenomenon.

7.2.2 Language ability and intellectual functioning.

Studies have shown low language ability in many children with ASD. Despite the fact that the in the evaluation of children with clinical findings of ASD these symptoms should not be better explained by intellectual disability (ID) or intellectual developmental disorder (IDD), these conditions may coexist with ASD (Association, 2013). Even verbally fluent children with ASD frequently have pragmatic language difficulties and may have difficulty with elements of non-verbal communication including eye contact (Philofsky et al., 2007). There may also be variability in the trajectory of language development in children with ASD. Described patterns in children referred for diagnostic evaluation of ASD, include children with language regression, language plateauing at a specific age or consistently delayed development (Jones and Campbell, 2010).

In terms of overall level of expressive language, a UK study reported that 17% of their participants were non-verbal, 19.5% had single words, 18.7% had a few phrases and the remainder, 44.9%, had phrase speech (Fombonne et al., 2004). In Israel, 35.5% of children with ASD referred to a major referral centre had some form of language delay. Regression of language milestones preceded development of autistic symptoms in 30.5% of these children (Mahajnah et al., 2015). In Saudi Arabia 70% of children referred to a tertiary service with ASD had communication impairment as the reason for referral. Of these, 10% did not have any expressive language and 10% had reported language regression (Al-Salehi et al., 2009). In India, in a tertiary centre 94% of children with ASD did not have meaningful speech (Juneja et al., 2005). There is a high proportion of non-verbal cases of ASD reported in the African literature to date (Bakare and Munir, 2011b). All three cases included in a case series in Kenya had speech difficulties (Dhadphale et al., 1982). In a case series from Tanzania, reporting on

14 cases, 71% of the participants were nonverbal (Mankoski et al., 2006). In Tunisia, 51.2% of participants in a referral clinic-based study had no expressive language. Nine percent had a relative reported on the autism spectrum (Belhadj et al., 2006). It is unclear if the proportion of children who are non-verbal in Africa is higher than in other settings.

As with expressive language, there is variability in the reported proportion of children with ASD having comorbid intellectual disability. In the general practitioner study from the UK high prevalence of intellectual disability (ID) was reported in their sample, with 38.4% being mild, 19% being moderate and eight percent with severe impairment. Normal intelligence was found in 34.5%. There were 19% who had experienced developmental regression (Fombonne et al., 2004). In the Israeli report, 10.5% were reported as having ID (Mahajnah et al., 2015). In Saudi Arabia more than half of the ASD sample had intellectual disability (Al-Salehi et al., 2009). In the Indian hospital study, 96% of children with ASD in their cohort were referred with concerns of global developmental delay, however other concerns included speech delay, "mental retardation" and attention deficit and hyperactivity (Juneja et al., 2005). Another further study from India looking at the profiles of children with ASD, with and without a history of developmental regression, and found no difference in the abilities of these participants and no difference between the developmental profile of these two groups (Malhi and Singhi, 2012). In a Swedish study of immigrants of Somali origin, most of the Somali children had experienced developmental arrest at the age of 12 to 24 months. Sixteen of the 17 children who were described had either developmental delay on the Griffiths Mental Development Scales or had clinical suspicion of learning disability. Motor difficulties were not a major feature of participants in this study (Barnevik–Olsson et al., 2008). A repeat of the study in a younger generation of the same population in the same area had similar findings (BARNEVIK-OLSSON et al., 2010). A study on African immigrants in Australia also showed greater impairment of cognition in comparison to those of an Irish immigrant population who were

used as controls (Bolton et al., 2014). In the DRC hospital based study, 75% of study participants with ASD had either developmental or intellectual disability defined as DQ or IQ of less than 70 (Mpaka et al., 2016), while Springer and colleagues in South Africa described global developmental delay in almost all of their clinic cohort ranging from mild impairment (DQ 51 – 70) in 21%, moderate (DQ 31 – 50) in 43% and severe impairment (DQ less than 30) in 31% (Springer et al., 2013), suggesting children in Africa presenting to hospital based services, may be more severely impaired. These studies however are not in the general population but of children in referral units suggesting that although there is some evidence for children presenting to clinical services in Africa being more severely affected, there remain gaps in the understanding of these phenotypic patterns and there are insufficient data on the language and prevalence of comorbid intellectual disabilities in children with ASD in Africa to fully inform provision of services to these children.

7.2.3 Comorbid factors

The clinical diagnosis of ASD should include several associated described difficulties in order to give a full picture of a child's needs. In Israel, seven-point five percent of children with ASD had epilepsy. Sleep disturbance was found in 40.5%, almost a third (29.5%) had anxiety symptoms and a quarter (24%) had behavioural difficulties (Mahajnah et al., 2015). This is compared to 16% who had comorbid epilepsy in a UK cohort. This study did not look at other comorbidities (Fombonne et al., 2004). In Saudi Arabia, 22 out of the 49 participants (45%) were on medication for behaviour problems (Al-Salehi et al., 2009). In the Indian cohort, 31% of study participants had associated epileptic seizures. Other associated described problems in the group included toilet training difficulty, impaired joint attention, abnormal play and disinterest in play or inappropriate play with toys (Juneja et al., 2005). The level of associated problems in ASD in Africa is unclear. In Tanzania almost a third of children in a case series had epilepsy. However the sample size of this study was 14 cases (Mankoski et al., 2006). In

DRC 72.5% of participants had epilepsy (Mpaka et al., 2016). Springer and colleagues in South Africa (Springer et al., 2013) found epilepsy in 10% of their clinic sample of 58 children with ASD. The presence of comorbid conditions has been reported inconsistently across these clinical reports making it difficult to suggest how this compares to children with ASD living elsewhere in the world.

7.2.4 Justification

Available evidence suggests that the prevalence of ASD in Africa is the same as in other settings and there is need to provide services for these families (Kakooza-Mwesige et al., 2014). There may also be evidence to suggest that a higher number of children with ASD in Africa are non-verbal and present at a late age however these reports are based on isolated reports or involve people no longer resident in Africa (Barnevik–Olsson et al., 2008, BARNEVIK-OLSSON et al., 2010, Bakare and Munir, 2011b, Bakare and Munir, 2011a). There may be a higher proportion of children in Africa with ASD who have associated epilepsy but larger studies are needed to confirm this (Mankoski et al., 2006). There is little information about the intellectual functioning and development of children with ASD in African populations and this is skewed by the more severe phenotype described overall(Barnevik–Olsson et al., 2008, BARNEVIK-OLSSON et al., 2010).

While the literature that is available on ASD in Africans on the continent and in the diaspora has suggested the clinical phenotype of children with ASD (at least those presenting to clinical services) is more severe, there is currently little published data that reports on currently resident, local African population focusing on the detailed clinical profile of children with ASD using a gold standard assessment tool.

Knowing the description of children with ASD in this setting will benefit planning for health and educational services for these children. It will also inform planning for future research in this area that is becoming increasingly important from a public health perspective.

7.3 Ethical considerations

The study was approved by the Health Research Ethics Committee of the University of Cape Town (REF: 702/2016) and consent to conduct the study was obtained from Red Cross War Memorial Children's Hospital (RXWMCH). After identifying potential participants, informed written consent was obtained from parents or guardians. Interpreters from the hospital were available to assist with the consent process when required. Individuals who declined to give consent for the study still received standard care and where needed were referred for ADOS-2 assessment via the normal channels either within the Developmental Clinic at RXWMCH or at the adjacent Department of Child and Adolescent Psychiatry (DCAP). Participants were compensated for their time if they were seen as part of their routine clinic visit and additionally travel costs were reimbursed.

7.4 Author guidelines

The manuscript presented below is prepared for submission to the journal Acta Neuropsychiatrica. This is an international peer reviewed journal focusing on translational neuropsychiatry according. They also have focus on healthcare and a thrust on global health and clinical application. This journal has been chosen as it also looks at research from different contexts that may be disadvantaged and require a different approach to patient care.

Author guidelines are appended in appendix 7.

7.5 References

Al-Salehi SM, Al-Hifthy EH and Ghaziuddin M (2009) Autism in Saudi Arabia: presentation, clinical correlates and comorbidity. *Transcult Psychiatry,* **46,** 340-7.

Association AP (2013) *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*, American Psychiatric Pub.

Bakare MO and Munir KM (2011a) Autism spectrum disorders (ASD) in Africa: a perspective. *African journal of psychiatry,* **14,** 208-210.

Bakare MO and Munir KM (2011b) Excess of non-verbal cases of autism spectrum disorders presenting to orthodox clinical practice in Africa - a trend possibly resulting from late diagnosis and intervention. *S Afr J Psychiatr,* **17,** 118-120.

Barnevik-Olsson M, Gillberg C and Fernell E (2010) Prevalence of autism in children of Somali origin living in Stockholm: brief report of an at-risk population. *Developmental Medicine & Child Neurology,* **52,** 1167-1168.

Barnevik–Olsson M, Gillberg C and Fernell E (2008) Prevalence of autism in children born to Somali parents living in Sweden: a brief report. *Developmental Medicine & Child Neurology,* **50,** 598-601.

Belhadj A, Mrad R and Halayem MB (2006) [A clinic and a paraclinic study of Tunisian population of children with autism. About 63 cases]. *Tunis Med,* **84,** 763-7.

Boat TF, Wu JT, On Children B, Of Medicine I, Of Behavioral D, Sciences S and Of Sciences TNA (2015) Prevalence of Autism Spectrum Disorder.

Bolton S, Mcdonald D, Curtis E, Kelly S and Gallagher L (2014) Autism in a recently arrived immigrant population. *European Journal of Pediatrics,* **173,** 337-343.

Cdc. *CDC | Data and Statistics | Autism Spectrum Disorder (ASD) | NCBDDD* [Online]. Available: http://www.cdc.gov/ncbddd/autism/data.html [Accessed 16 February 2016].

Dhadphale M, Lukwago M and Gajjar M (1982) Infantile autism in Kenya. *The Indian Journal of Pediatrics,* **49,** 145-148.

Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcín C, Montiel-Nava C, Patel V, Paula CS and Wang C (2012) Global prevalence of autism and other pervasive developmental disorders. *Autism Research,* **5,** 160-179.

Fombonne E, Heavey L, Smeeth L, Rodrigues LC, Cook C, Smith PG, Meng L and Hall AJ (2004) Validation of the diagnosis of autism in general practitioner records. *BMC Public Health,* **4,** 5.

Jones LA and Campbell JM (2010) Clinical characteristics associated with language regression for children with autism spectrum disorders. *J Autism Dev Disord,* **40,** 54-62.

Juneja M, Mukherjee SB and Sharma S (2005) A descriptive hospital based study of children with autism. *Indian Pediatrics,* **42,** 453-458.

Kakooza-Mwesige A, Ssebyala K, Karamagi C, Kiguli S, Smith K, Anderson MC, Croen LA, Trevathan E, Hansen R and Smith D (2014) Adaptation of the "ten questions" to screen for autism and other neurodevelopmental disorders in Uganda. *Autism,* **18,** 447-457.

Kanner L (1943) *Autistic disturbances of affective contact*, publisher not identified.

Lotter V (1966) Epidemiology of autistic conditions in young children. *Social psychiatry,* **1,** 124-135.

Mahajnah M, Sharkia R, Shalabe H, Terkel-Dawer R, Akawi A and Zelnik N (2015) Clinical characteristics of autism spectrum disorder in Israel: impact of ethnic and social diversities. *Biomed Res Int,* **2015,** 962093.

Malhi P and Singhi P (2012) Regression in children with autism spectrum disorders. *Indian Journal Of Pediatrics,* **79,** 1333-1337.

Mankoski RE, Collins M, Ndosi NK, Mgalla EH, Sarwatt VV and Folstein SE (2006) Etiologies of autism in a case-series from Tanzania. *Journal of autism and developmental disorders,* **36,** 1039-1051.

Mpaka DM, Okitundu DLEA, Ndjukendi AO, N'situ AM, Kinsala SY, Mukau JE, Ngoma VM, Kashala-Abotnes E, Ma-Miezi-Mampunza S, Vogels A and Steyaert J (2016) Prevalence and comorbidities of autism among children referred to the outpatient clinics for neurodevelopmental disorders. *Pan Afr Med J,* **25,** 82.

Philofsky A, Fidler DJ and Hepburn S (2007) Pragmatic language profiles of school-age children with autism spectrum disorders and Williams syndrome. *Am J Speech Lang Pathol,* **16,** 368-80.

Ritvo ER, Ritvo R, Freeman BJ and Mason-Brothers A (1994) Clinical characteristics of mild autism in adults. *Compr Psychiatry,* **35,** 149-56.

Seif Eldin A, Habib D, Noufal A, Farrag S, Bazaid K, Al-Sharbati M, Badr H, Moussa S, Essali A and Gaddour N (2008) Use of M-CHAT for a multinational screening of young children with autism in the Arab countries. *International Review of Psychiatry,* **20,** 281-289.

Springer PE, Van Toorn R, Laughton B and Kidd M (2013) Characteristics of children with pervasive developmental disorders attending a developmental clinic in the Western Cape Province, South Africa. *South African Journal of Child Health,* **7,** 95-99.

8 Chapter 2: Publication-ready Manuscript

Journal title	Acta Neuropsychiatrica
Journal scope	"Acta Neuropsychiatrica, the official Journal of Scandinavian College of Neuropsychopharmacology, is an international journal focusing on translational neuropsychiatry. It publishes high-quality original research papers and reviews. The Journal's scope specifically highlights the pathway from discovery to clinical applications, healthcare and global health that can be viewed broadly as the spectrum of work that marks the pathway from discovery to global health. The steps of translation that are within the scope include: 1) fundamental discovery, 2) bench to bedside, 3) clinical trials, 4) translation to clinical guidelines, 5) health policy and usage, and 6) global health. Research covering molecular biology, genetics, pharmacology, imaging and epidemiology is welcome as it contributes to enhancing the field."
Article word count	3951
Word count limit	6500
Abstract word count	236
Abstract limit	250
Title word count	15
Title limit	15
Key words	Autism Spectrum disorder

	Autistic disorder
	Developmental disabilities
	Language development disorder
Number of figures	0
Number of tables	2
Tables and figures limit	7
Referencing style	author, date (Harvard)
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This publication ready paper has been formatted for the thesis. Author instructions are to be applied to the paper that is ready for submission.

Title page

Clinical profile of childhood Autism Spectrum Disorder in a South African tertiary hospital developmental clinic

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Running title: Clinical profile of children with Autism Spectrum Disorder in a developmental clinic in Western Cape, South Africa

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Abstract

Introduction

Autism Spectrum Disorder (ASD) is increasingly being recognised as a significant neurodevelopmental condition in African countries. There is some evidence to suggest that the children who present with ASD in Africa may be diagnosed late and have a more severe clinical picture. The purpose of this study was to describe the clinical profile of children with ASD in the neurodevelopmental clinic at Red Cross War Memorial Children's Hospital in Western Cape Province.

Methods

We sampled patients with a previous or new diagnosis who attended our clinic during the period January to July 2017. Consenting participants were administered a questionnaire with sociodemographic and clinical questions, clinical details of medical and developmental diagnosis were extracted from medical records and children. were further assessed using the Autism Diagnostic Observation Schedule version 2 (ADOS-2).

Results

A total of 32 patients were recruited into the study with 26 out of 32 (81%) being boys. On assessment as part of the study, all participants met DSM 5 criteria for the diagnosis of ASD. Most participants (94%) had not experienced general developmental regression but a substantial proportion (39%) had reported early regression of language milestones. Almost half of participants (48%) had self-injurious behaviour reported, 25% had associated motor difficulty and 10% comorbid epilepsy. More than half of participants (53%) required substantial support in day-to-day activities. Most participants (81%) were administered module 1 of the ADOS-2 reflecting the high proportion of children in the sample who were either preverbal or using only single words.

Conclusions

Children seen in this clinical sample reflected the more severe end of the autism spectrum with a significant proportion having associated comorbidities such as epilepsy, and motor difficulties. The phenotypic profile on the ADOS 2 in this study correlated well with clinical assessments.

Key words

Autism Spectrum Disorder

Autistic disorder

Developmental disabilities

Language development disorder

Background

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterised by persistent deficits in social communication and social interaction and restricted repetitive patterns of behaviour, interest and activity (1). There has been an increase in the number of individuals diagnosed with or accessing services for ASD worldwide, with average estimates of one in 100 persons having the condition, and a recognition that this disorder is a global public health concern, including on the African continent (Boat et al., 2015). One of the only population-based prevalence studies conducted in Africa to date is a study set in a community in Uganda that gave an estimated prevalence of ASD of 12 to 13 per 1000 children in the population (11). In the Democratic Republic of Congo, an outpatient neurodevelopmental clinic-based study found that a significant proportion of children referred for neurodevelopmental assessment had ASD with 29% meeting diagnostic criteria indicating that ASD constitutes an important clinical burden(Mpaka et al., 2016).

Available evidence suggests that the prevalence of ASD in Africa is the same as in other settings and there is need to provide services for this (Kakooza-Mwesige et al., 2014). There may also be evidence to suggest that a higher number of children with ASD in Africa are non-verbal and present at a late age however most of these reports are based on isolated reports or involve people no longer resident in Africa (Barnevik–Olsson et al., 2008, BARNEVIK-OLSSON et al., 2010, Bakare and Munir, 2011b, Bakare and Munir, 2011a). In South Africa, a clinic record review of 58 children showed that 72% of participants were non-verbal, 19% experienced sleep disorders and 25% were hyperactive (Springer et al., 2013). There may be a higher proportion of children in Africa with ASD who have associated epilepsy but larger studies are needed to confirm this (Mankoski et al., 2006). There is little information about the intellectual and developmental functioning of children with ASD in African populations, and

this is likely to be skewed by the more severe phenotype described overall(Barnevik–Olsson et al., 2008, BARNEVIK-OLSSON et al., 2010).

While the literature that is available on ASD in Africans on the continent and in the diaspora has suggested the clinical phenotype of children with ASD (at least those presenting to clinical services) is more severe, there is currently little published data that reports on currently resident, local African population focusing on the detailed clinical profile of children with ASD. (Barnevik–Olsson et al., 2008, BARNEVIK-OLSSON et al., 2010). Understanding the phenotype of children with ASD in this setting will be valuable in planning for health and educational services for children with these disorders as well as their families.

Aims of the study

In order to add to the body of knowledge on the clinical profile of children diagnosed with ASD in our context, we set out to prospectively describe the detailed clinical features of children with a new or previous diagnosis of ASD in a neurodevelopmental Clinic at Red Cross War Memorial Children's Hospital (RCWMCH) a quaternary hospital in the Western Cape Province of South Africa.

Materials and Methods

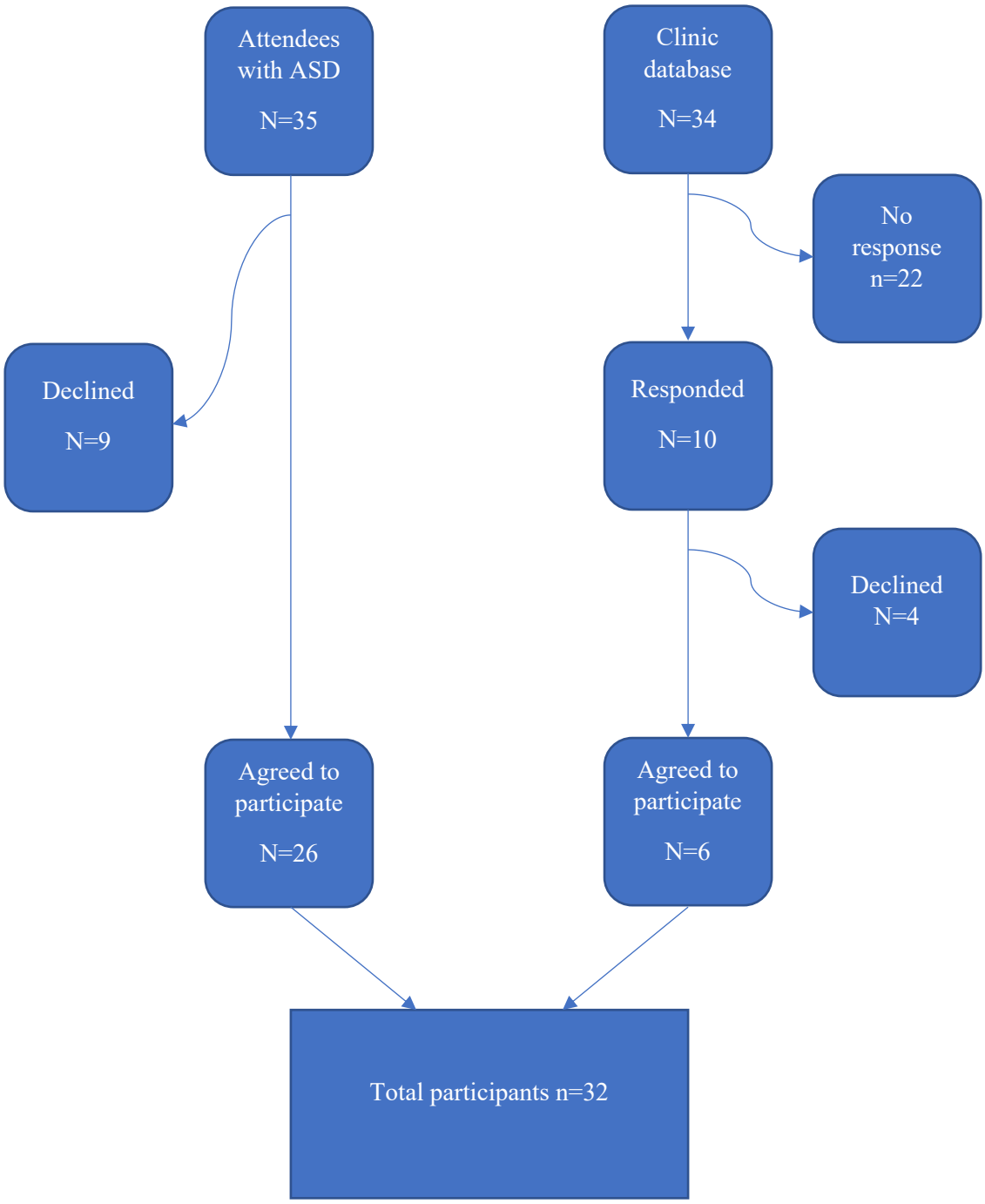
Environment

We conducted a cross sectional descriptive study of children diagnosed with an ASD in the neurodevelopmental clinic at Red Cross War Memorial Children's Hospital. This state-funded hospital is situated in the Western Cape which is in the South-West of South Africa. The population is heterogeneous with the largest proportion of the population being of mixed ancestry (50.2%), followed by black African ancestry (30.1%), European ancestry (18.4%) and

Asian ancestry (1.3%) (Anonymous). The neurodevelopmental clinic at the hospital which serves more than 4000 clients a year with a variety of developmental disabilities of which ASD is an important proportion.

Study population

Figure 1: participant recruitment diagram



Children with a clinical diagnosis of ASD and their families, attending RCWMCH between January and July 2017, were invited to take part in this study. This was a convenience sample based on children attending the clinic (both newly and previously diagnosed children) invited sequentially in person at the clinic. We approached 35 patients seen in the clinic who had a diagnosis of ASD. Nine client's caregivers declined to participate in the study while 26 consented. In addition, we also invited families of children with ASD who had been diagnosed over the course of the previous six months (July to December 2016) who were in the clinic database by telephone call. Of the 34 children invited off the database only ten responded to the telephone call and of these six agreed to attend for the purposes of data collection. All children with a clinically confirmed diagnosis of ASD (meeting DSM 5 criteria for ASD) attending the clinic were eligible to participate if their parents gave consent and were prepared to attend the study assessment visit. Recruitment is illustrated in figure 1.

Sample size

Sample size was calculated using the Dobson formula based on the following parameters. Over a sixteen-month period from January 2013 to April 2014 there were 518 new entries of patients in the database of the developmental service at the Red Cross Children's Hospital. Of these 68 had ASD. Of the ones with ASD, 21% had moderate to severe global developmental delay. Using a confidence limit of 5% and a confidence level of 95% the calculated sample size to determine level of impairment was 54 participants.

Data collection method and tools

From January 2017 until July 2017 participants who fulfilled the DSM 5 criteria for ASD (Association, 2013) during clinical assessment or from their previous records were invited to participate in the study. Written informed consent was obtained from participant caregivers. Although provision for assent made for older children, this was not required . The index child's caregiver was engaged using the English language unless they indicated a preference for a different language such as IsiXhosa in which case a formally trained interpreter was engaged. There were no requests to use Afrikaans as a language medium.

Participants had a baseline clinical assessment and examination as well as developmental assessment conducted by a paediatrician (LM) in one of the clinic rooms at RCWMCH. Development was assessed using a locally developed tool (the Molteno scales). The tool uses simple locally manufactured and available toys as tools to assess development and has been found to be reliable and accurate in the local context (Laughton, 2011, Honeth et al., 2019). Problems and developmental level were derived from this assessment and the participants development classed as no delay or mild, moderate and severe developmental delay as per the assessment manual.

A standardised data collection record form was used to collect information from the medical records, family and assessment visit. In addition, the family and child were invited for an Autism Diagnostic Observation Schedule version 2 (ADOS-2) which was administered on all participants and documented on standard forms. The ADOS-2 is based on the assessor's observations and not dependent on a parent or caregiver providing information. It uses a hierarchy of social presses to elicit social communication/interaction problems. It also documents the participant's behaviour during the assessment. Standard approach to administration of the ADOS was used (Lord et al., 2008). Choice of module used was based

on the expressive language ability of the individual. Module 1 is used for those children who are preverbal or only use single words, module 2 for participants with phrase speech but are not verbally fluent, module 3 for children and young adolescents with fluent speech and module 4 for verbally fluent older adolescents and adults. All the ADOS-2 assessments were administered by the same assessor (LM) who had received formal clinical and research administration training in the ADOS-2 and additionally had participated in monthly ADOS-2 supervision group sessions with ADOS-2 trainers and research-trained administrators. In this context of this study's aims, the ADOS-2 was used as a descriptive phenotyping instrument.

Data analysis.

Data was entered into Epi Info 7 database ©CDC 2014 and exported into SPSS version 27 for analysis. Descriptive statistics were used.

Ethical approval

The study was approved by the Health Research Ethics Committee of the University of Cape Town (REF: 702/2016) and further approval to conduct the study was obtained from Red Cross War Memorial Children's Hospital administration. Written informed consent was obtained from parents of children with ASD included in the study.

Results

Between January and June 2017, 32 children who had a clinical diagnosis of ASD took part in the study. Basic characteristics and risk factor information for the participants is shown in Table 1. As expected, there was a greater proportion of boys than girls. Most children were South African with English as their home language. Those four children who were not native South

African were from the Democratic Republic of Congo, Zimbabwe, Rwanda and Nigeria. There were no participants who were the product of a consanguineous union and none of the participants in this study had a history of diagnosed syndromic genetic disorder such as fragile X syndrome or tuberous sclerosis. Three participants (9%) had a history of preterm delivery. Birth asphyxia was reported in one (3%) participant. The median birthweight was 3430g with a minimum of 1280g and a maximum of 4360g.

Table 1: Participant characteristis and risk factors

Age at assessment (months)	Median 64	Range 25 – 105
Age at diagnosis (months)	Median 43	Range 24 – 74
Age at symptom onset (months)	Median 24	Range 6 – 60
Delay to diagnosis (months)	Median 22	Range 0 – 46
Sex N (%)	Male 26 (81%)	Female 6 (19%)
Male/female ratio	4.3:1	
Nationality N (%)	South African 28 (88%) Other 4 (12%)	
Language N (%)	English 21 (66%) Xhosa 10 (31%) Afrikaans 1 (3%)	
Mother's age at birth (years)	Median 28.5	Range 15 – 43
Father's age at birth (years)	Median 29.5	Range 19 – 48
ASD diagnosis in a sibling	Yes 2 (6%)	No 30 (94%)
Family history of ASD in a relative	Yes 11 (34%)	No 21 (66%)

Based on clinical assessment, all children met the social communication criteria for the diagnosis of ASD. The frequency of restricted repetitive behaviour, interests and sensory sensitivity criteria is shown in Table 2. In terms of their symptom intensity characterisation using the Diagnostic Statistical Manual 5th edition (DSM-5) criteria, the majority of participants were either level 2 (requiring substantial support in all functional areas) 8 (25%) or level 3 (requiring very substantial support) 17 (53%). Table 3 has information on the developmental pattern and comorbid conditions. Participants were questioned about each of the developmental patterns typically observed in children with a diagnosis to determine their presence or absence and may have had more than one response.

Table 2: Diagnostic criteria,

Social communication criteria DSM-5 N (%)	
Social emotional reciprocity difficulty	32 (100)
Nonverbal communication difficulty	32 (100)
Establishing relationships difficulty	32 (100)
Restricted repetitive behaviours, interest and sensory problems (RRB) DSM-5 N (%)	
Stereotyped or repetitive behaviour	29 (91)
Insistence on sameness	28 (88)
Restricted fixated interests	30 (94)
Sensory hyper or hypo-reactivity	31 (97)
Number of DSM-5 RRB criteria out of four	N (%)

2 criteria	3 (9)
3 criteria	4 (13)
4 criteria	25 (78)
DSM-5 Severity levels	N (%)
Level 1 – requiring support	7 (22)
Level 2 – requiring substantial support	8 (25)
Level 3 – requiring very substantial support	17 (53)

Table 3: Developmental pattern and comorbidities

Developmental pattern		
Median age at first words in months (27 participants)	Median 14	Range 8 – 60
Language regression – N (%)	12 (38)	
Median age of language regression in months	Median 16.5	Range 11 – 19
Other developmental regression N (%)	2 (6) at ages 14 and 15 months	
Slow development since infancy N (%)	7 (22)	
Normal infant development then arrest N (%)	4 (13)	
Age of developmental regression in months	Median 25.5	Ages 14, 15, 36 and 60 months
Developmental quotient	Median 68.5	Range 7 – 90
Developmental level of function (28 participants)	N (%)	
Typical	5 (16)	
Mild	18 (56)	

Moderate	4 (13)
Severe	0
Profound	1 (3)
Behaviour issues N (%)	
Hyperactive behaviour	27 (84)
Sleep difficulty	16 (50)
Sleep initiation problems	15 (47)
Waking at night	7 (22)
Self-injury N (%)	14 (44)
Hand biting	4 (13)
Head banging	9 (28)
Scratching self	1 (3)
Banging chest	1 (3)
Hits self	1 (3)
Motor difficulty N (%)	8 (25)
Gross motor	5 (16)
Fine motor	6 (19)
Clumsiness	5 (16)
Seizure history	N (%)
History of seizures	6 (19)
Current seizures	2 (6)
Diagnosis of epilepsy	3 (9)
Current seizure medication	2 (6)
Seizure types	

Generalised tonic clonic	2 (6)
Infantile spasms	1 (3)
Febrile	2 (6)
Absence and focal seizures	0 (0)

All participants had an assessment using the Autism Diagnostic Observation Schedule second edition (ADOS-2). The majority 26 (81%) had module 1 administered while 6 (19%) had a module two administered. For module one users, only two (8%) had regular use of words and phrases, five (19%) had occasional phrases and mostly single words. The remainder had less than five words during the assessment in 3 (12%) or no words or word approximations in 16 (62%). In those participants assessed using a Module 1, the majority of vocalisations were not directed to any of the others in the room. Only two (8%) directed their vocalisation in a variety of contexts, nine (35%) only directed vocalisation in either an inconsistent or limited context. The remaining 15 children, (58%) were either nonverbal or did not direct vocalisation at all. While vocalising 22 (69%) participants had odd intonation with the remainder either having little variation in their tone (six children, 19%) or insufficient language to gauge in four (13%). Half of the module two participants used phrase speech with grammatical markings and the other half used phrase speech without grammatical markings. In 18 (56%) of participants, language was too limited to assess for echolalia or stereotypic use of language, only 2 (6%) did not demonstrate echolalia and 8 (25%) did not use stereotyped language despite using several words and or phrases in the assessment, while the remaining 12 (38%) had varying degrees of echolalia and 6 (19%) had some stereotypic or idiosyncratic language.

In the item: *use of another's hand like a tool*, 13 (41%) had some use of another's hand as a tool and seven (23%) had no spontaneous communication. Twelve (38%) participants did not demonstrate *use of another's hand like a tool* at all during the course of the assessment. Most

children did not demonstrate pointing (18 children, 56%), or use of other gestures (21 children, 66%).

There were 29 (91%) participants who demonstrated poorly modulated eye contact. Among module 1 participants, no participants (0%) demonstrated immediate appropriate social smile in response to one or two smiles given by the assessor and 19 (73%) did not show responsive smile, directed facial expression (17 children, 53%), or integrated gaze during overtures (14 children, 53%) at all during the assessment. A substantial number of participants (21 children, 60%) demonstrated some level of shared enjoyment during interaction, and response to name after presses by either the assessor or a caregiver (18 children,56%). In contrast, the majority of module one users (22 children, 80%) did not demonstrate direct requesting or giving (21 children,81%) during the session. Showing objects and initiation of joint attention was also reduced with only nine (28%) participants showing the assessor any items of interest and seven (22%) initiating joint attention. A slight preponderance of participants (18 children, 66%) did not show response to joint attention on pointing, in addition 15 participants (47%) did not demonstrate any social overtures. fifty percent of the module 1 users did not engage despite the efforts of the assessor.

There was a fairly even distribution of functional play ranging from spontaneous play in eight (26%) to no spontaneous play in six (20%) participants however participants were less likely to show imaginary play with half of participants not demonstrating pretend play at all during the session. There was also even distribution of unusual sensory behaviour with 25% not showing such behaviour and 29% having definite sensory behaviours. The remainder were equally divided in between. Only one (3%) participant did not demonstrate hand and finger mannerisms, however only four participants (12.5%) had them intensely enough to partly interfere with their assessment.

Most (30 children, 94%) did not have any self-injurious behaviour demonstrated during the ADOS-2 and the other two had possible self-injury demonstrated, however, there was report of previous self-injury in 14 (44%) participants with head banging and hand biting being the most common. All children had stereotyped or repetitive behaviour with 14 participants (44%) having more severe repetitive/stereotyped behaviour. Only three participants (10%) showed clear disruptive behaviour with the rest not showing signs of upset or regulating fairly well. No participants showed marked anxiety during the ADOS assessment and only seven (22%) had signs of mild anxiety. The rest had no sign of anxiety.

Six (19%) participants had a history of seizures and three (9%) had a diagnosis of epilepsy. However, the majority had hyperactivity which was reported in 27 (84%) participants. Sixteen (50%) participants also had sleep difficulties with sleep initiation being the most common.

Discussion

This is one of the first studies to describe detailed, prospectively collected phenotypic profile of children with ASD in the African context. In our cohort describing 32 children ranging from 2-9 years of age, results showed an expected preponderance of boy children with ASD. This is well described globally and is also similar to other local clinic cohorts(Springer et al., 2013), as well as descriptions in other African settings such as the Democratic Republic of the Congo (Mpaka et al., 2016) and other Low and middle income country (LMIC) settings such as India, Malaysia and Mexico (Kommu et al., 2017, González-Cortés et al., 2019, Sathyabama, 2019).

Reported developmental trajectories reported by caregivers included language regression in 38% at a median age of 16.5 months. In addition, 22% had slow development from infancy, 13% had typical initial development reported followed by general developmental plateauing and six percent had developmental regression in other developmental domains outside of language with a median age of onset of 25 months. Although the median age of use of first

words was 14 months, at the age of assessment the majority 81% of our participants had only single words or phrase speech which warranted the use of a module 1 ADOS-2 assessment with the expressive language limitations described above. The language in 56% of children in the cohort was too limited to assess the presence of echolalia or stereotyped language. In addition, there was limited use of pointing and gesture in our group. As early childhood language ability is a described predictor of later outcomes in children with ASD (Gillespie-Lynch et al., 2012), this high proportion of children with no meaningful expressive language is a concern for long term outcomes in children from our clinic. This is especially worth highlighting as the intervention services for children with ASD even in a specialised service in the public sector hospitals are limited in resource-poor environments such as South Africa and even less available in smaller urban centres and rural areas.

Our interest in the age of diagnosis is a reflection of the evidence that early and continuous intervention improves the outcome of children with developmental disability (Ramey and Ramey, 1998). There was a significant delay between parents noticing symptoms and the child receiving a diagnosis in our participants with the mean age that parents noticed symptoms being 24 months. However, the mean age of diagnosis of 43 months was similar to the 42 months reported by Springer et al (Springer et al., 2013). And compares favourably with the 5.52 years reported in a Mexican study (González-Cortés et al., 2019), the 6.3 years reported by Al-Salehi et al in Saudi Arabia (Al-Salehi et al., 2009), and the 8 years reported by Belhadj in Tunisia (Belhadj et al., 2006). This project did not explore the referral pathway utilised by families but this may have influenced time to diagnosis. The index of suspicion of practitioners seeing children for other reasons was also not explored but may also have influenced the time to diagnosis. Health services in the public sector in South Africa are not systems which facilitate continuity of relationships between families and children for well-child visits. The lack of provision in this system for well-child assessments outside of immunisation visits in infancy,

results in reliance on opportunistic surveillance by overburdened health care practitioners who are trained to focus on acute medical concerns such as infections or malnutrition which are highly prevalent in this environment. This may also be a factor in the skew towards severely affected children in our clinic cohorts across the continent, leaving mildly or moderately affected children with ASD undiagnosed and unsupported.

Behaviour problems were very common in the study population in this cohort. The most common behavioural problem noted in this group was hyperactive behaviour which was found in 87% of participants. This is significantly higher than findings in an Indian hospital cohort who described that out of a cohort of 201 children diagnosed with PDD using International Classification of Disease 10th edition (ICD10) criteria, 76% had a comorbid condition and 36.8% had a formal diagnosis of ADHD (Kommu et al., 2017). A significant 44% of our participants also had self-injurious behaviour reported but the majority did not demonstrate it during the course of the ADOS-2 with only two participants demonstrating this during the assessment. Sleep problems were common among participants and 50% of families reported challenges with sleep initiation for their children being most problematic. Sathyabama and colleagues (Sathyabama, 2019) reported that 30% of 331 children with ASD from a retrospective review of clinic participants had sleep problems, similar to findings by Springer and colleagues (Springer et al., 2013). Our higher proportion of children with ASD with reported sleep problems may be a result of direct probing in this prospective study when compared to the retrospective review design for the other studies.

Of our participants 19% had a previous history of seizures and 8% had a diagnosis of epilepsy. This is comparable with the findings by Springer and colleagues (Springer et al., 2013),

practicing in a similar context to that of this study, but higher than Gonzalez (González-Cortés et al., 2019) in Mexico who noted in their study that 3% of participants had a history of seizures.

With respect to categorisation of levels of support requirements, most of our participants i.e., 17 (53%) required very substantial support (Level 3) in their daily lives compared to 16% in a retrospective review from the Mexican retrospective review of hospital-based patients (González-Cortés et al., 2019). In this study they found that 48% of the participants required substantial support (level 2) compared to 25% in ours and 36% needing some support (level 1) compared to our 22%. This contrast in results may be because our setting was a quaternary referral level hospital which mays have the more complex cases referred.

The use of the ADOS-2 was a structured assessment of ASD in children and allowed us to not only describe phenotype in a standardise way in this group as well as allowing pulling out some of their behavioural and lifestyle nuances which may not otherwise have been identified. The use of the ADOS-2 also showed that the behaviours used to make a diagnosis of ASD in other contexts was common to the children in our clinic.

There were no participants with a diagnosed genetic condition in this cohort, this may partly be due to the limitations in genetic testing in this context (at that time only karyotyping and targeted testing for specific conditions). In addition, children with Tuberous Sclerosis and neurofibromatosis are seen in separate specialized clinics and are not part of the routine neurodevelopmental clinics. It should also be noted that consanguineous unions are less common in the cultural context compared to some others. However, other authors in this context have also noted low results from genetic and metabolic testing in the context of ASD. Further, expansion of genetic testing in the African context may reveal results which reflect

the wider variance in genomic variance in African populations and limitations of current reference panels largely informed by European ancestry populations (Springer et al., 2013).

Strengths and weaknesses

A strength of the study is that all study participants underwent an evaluation using a gold standard assessment tool that uses observation of the child and does not rely on parent report. All children were assessed by one assessor and data was collected prospectively allowing verification of information. However this may also potentially lead to selection bias. The study however had a limited number of participants with only 32 out of the calculated sample size of 54 participants enrolled due to a time limitation for data collection. This was possibly due to the limited recruitment time of the study. In addition, we had a low response rate from clinic patients who were called in to participate in the study when they did not have another appointment for assessment or therapy in the clinic. This may have been due to logistical challenges faced by caregivers during travel and transportation of patients who have behavioural difficulties however, caregiver fatigue or burnout may also have been a contributing factor particularly as it is more common in caregivers of children with ASD who have behavioural difficulties (Lecavalier et al., 2006).

The study was also conducted in a quaternary referral unit which is likely to have affected the severity of participants as often only the most severe cases are referred into the unit.

Recommendations

The delay in diagnosis following the recognition of symptoms could possibly be mitigated by use of basic screeners at well child visits at primary care level with appropriate referral. Kakooza et al (Kakooza-Mwesige et al., 2014) used a modified ten questions screening tool in Uganda which showed modest sensitivity but had the added benefit of detecting other causes of disability. Early detection would aid in allowing the child and family to get assistance at an

age when they are most likely to benefit from interventions. Sensitizing health workers to the early symptoms of ASD and clear referral pathways would also reduce time to diagnosis.

Conclusion:

The population in this study represented the more severe ASD phenotype despite comparable or lower age of diagnosis to other studies. Further research is needed to determine which clinical factors more accurately predict future outcomes in children with ASD in this resource-limited context.

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Statement of interest

The authors have no conflicts of interest to declare.

Authors Contributions

All of the authors were involved in the conceptualisation of the study design, data collection and entry, write up and revisions. All the authors have approved the final version of the paper.

References

Al-Salehi SM, Al-Hifthy EH and Ghaziuddin M (2009) Autism in Saudi Arabia: presentation, clinical correlates and comorbidity. *Transcult Psychiatry,* **46,** 340-7.

Anonymous. *2012.06_western_cape_overview1_0.pdf* [Online]. [Accessed 3 MARCH 2016 2016].

Association AP (2013) *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*, American Psychiatric Pub.

Bakare MO and Munir KM (2011a) Autism spectrum disorders (ASD) in Africa: a perspective. *African journal of psychiatry,* **14,** 208-210.

Bakare MO and Munir KM (2011b) Excess of non-verbal cases of autism spectrum disorders presenting to orthodox clinical practice in Africa - a trend possibly resulting from late diagnosis and intervention. *S Afr J Psychiatr,* **17,** 118-120.

Barnevik-Olsson M, Gillberg C and Fernell E (2010) Prevalence of autism in children of Somali origin living in Stockholm: brief report of an at-risk population. *Developmental Medicine & Child Neurology,* **52,** 1167-1168.

Barnevik–Olsson M, Gillberg C and Fernell E (2008) Prevalence of autism in children born to Somali parents living in Sweden: a brief report. *Developmental Medicine & Child Neurology,* **50,** 598-601.

Belhadj A, Mrad R and Halayem MB (2006) [A clinic and a paraclinic study of Tunisian population of children with autism. About 63 cases]. *Tunis Med,* **84,** 763-7.

Boat TF, Wu JT, On Children B, Of Medicine I, Of Behavioral D, Sciences S and Of Sciences TNA (2015) Prevalence of Autism Spectrum Disorder.

Gillespie-Lynch K, Sepeta L, Wang Y, Marshall S, Gomez L, Sigman M and Hutman T (2012) Early childhood predictors of the social competence of adults with autism. *Journal of autism and developmental disorders,* **42,** 161-174.

González-Cortés T, Gutiérrez-Contreras E, Espino-Silva PK, Haro-Santa Cruz J, Álvarez-Cruz D, Rosales-González CC, Sida-Godoy C, Nava-Hernández MP, López-Márquez FC and Ruiz-Flores P (2019) Clinical Profile of Autism Spectrum Disorder in a Pediatric Population from Northern Mexico. *Journal of autism and developmental disorders,* **49,** 4409-4420.

Honeth I, Laughton B, Springer PE, Cotton MF and Pretorius C (2019) Diagnostic accuracy of the Molteno Adapted Scale for developmental delay in South African toddlers. *Paediatr Int Child Health,* **39,** 132-138.

Kakooza-Mwesige A, Ssebyala K, Karamagi C, Kiguli S, Smith K, Anderson MC, Croen LA, Trevathan E, Hansen R and Smith D (2014) Adaptation of the "ten questions" to screen for autism and other neurodevelopmental disorders in Uganda. *Autism,* **18,** 447-457.

Kommu JVS, Gayathri K, Srinath S, Girimaji SC, Seshadri SP and Gopalakrishna G (2017) Profile of two hundred children with Autism Spectrum Disorder from a tertiary child and adolescent psychiatry centre. *Asian journal of psychiatry,* **28,** 51-56.

Laughton B. (2011) *The reliability of the Molteno Adapted Development Scale in predicting developmental outcomes at 2 years, in prematurely born very low birth weight infants.*

Lecavalier L, Leone S and Wiltz J (2006) The impact of behaviour problems on caregiver stress in young people with autism spectrum disorders. *Journal of Intellectual Disability Research,* **50,** 172-183.

Lord C, Rutter M, Dilavore PC, Risi S, Gotham K and Bishop SL (2008) *Autism diagnostic observation schedule (ADOS): Manual*, Western Psychological Services Los Angeles.

Mankoski RE, Collins M, Ndosi NK, Mgalla EH, Sarwatt VV and Folstein SE (2006) Etiologies of autism in a case-series from Tanzania. *Journal of autism and developmental disorders,* **36,** 1039-1051.

Mpaka DM, Okitundu DLEA, Ndjukendi AO, N'situ AM, Kinsala SY, Mukau JE, Ngoma VM, Kashala-Abotnes E, Ma-Miezi-Mampunza S, Vogels A and Steyaert J (2016) Prevalence and

comorbidities of autism among children referred to the outpatient clinics for neurodevelopmental disorders. *Pan Afr Med J,* **25,** 82.

Ramey CT and Ramey SL (1998) Early intervention and early experience. *American Psychologist,* **53,** 109-120.

Sathyabama R (2019) Clinical characteristics and demographic profile of children with Autism Spectrum Disorder (ASD) at child development clinic (CDC), Penang Hospital, Malaysia. *The Medical journal of Malaysia,* **74,** 372-376.

Springer PE, Van Toorn R, Laughton B and Kidd M (2013) Characteristics of children with pervasive developmental disorders attending a developmental clinic in the Western Cape Province, South Africa. *South African Journal of Child Health,* **7,** 95-99.

Thesis discussion and conclusion

Discussion.

We conducted a cross sectional study to map the clinical profile of children with ASD in our context with the aim of answering the question of describing the clinical phenotype of ASD in our context and testing the hypothesis that our clinical phenotype is comparable to that found in other settings. Our findings demonstrated that while the signs and symptoms used for diagnosis of ASD may be similar to those on other contexts, symptoms may be more severe in our clinical populations.

Uptake and Demographic characteristics

We had a lower uptake of children with ASD into the study than anticipated. This may be due to the fact that the population may be highly mobile with frequent changes in communication details. Transport and travel logistics with a child with behavioural difficulty may be difficult resulting in caregivers preferring to minimise travel in the context of a public transport system that is largely reliant on small crowed vans run by private operators with no fixed schedule or predictability. The timeframe for data collection was also limited resulting in lower numbers.

Most of our participants were South African citizens with the majority of those coming from English speaking households followed by IsiXhosa and Afrikaans. This may be more of a reflection of social preference than an indication of ancestry or first language distribution. The age at diagnosis was comparable to or lower than other contexts with different resource levels. However, there was a significant time-lag to diagnosis in our population similar to what has been found elsewhere (Kommu et al., 2017, González-Cortés et al., 2019). Further research is needed to define clinical referral pathways for ASD as well as implementation projects to sensitise communities as well as practitioners regarding developmental disabilities in general

and ASD in particular with focus on the use of simple screening tools such as the ten-questions screening tool that may be self-administered by parents or used by practitioners (Kakooza-Mwesige et al., 2014).

Clinical phenotype

Our study demonstrated that the phenotype of participants seen in our clinic may be more severe than in other studied populations in terms of the need for support despite the comparable age of diagnosis in our study. Our participants were more likely to be non-verbal or use only single words and this may have implications on longer term outcomes. Regression in spite of normal initial development was also common in our cohort. This study did not however explore the implications of this more severe phenotype on caregiver stress or fatigue levels.

Behaviours

Comorbid symptoms such as hyperactive behaviour, sleep difficulties and self-injury were very common in this group. Further exploration of the impact of behavioural problems on caregivers is therefore warranted.

Strengths and Limitations

This study collected data prospectively and used a gold standard diagnostic tool to delineate the symptoms and signs of ASD. However, the small patient number and the location of the project at a quaternary unit limit the generalisability of this project and may be the reason why the sample is on the more severe end of the clinical spectrum.

Implications for practice and research

In order to detect developmental delays and disabilities such as ASD early to optimise outcomes from early intervention, primary care screening of developmental problems and

implementation of practitioner education programs could reduce the time-gap to the diagnosis of ASD.

There is need to further explore the impact of the more severe clinical profile in young children with ASD on their caregiver wellbeing as well as their longer-term social outcomes. A population level exploration of the clinical profile in this context may reveal a similar profile in the broader population with ASD than a hospital-based study such as ours.

9 Appendices

9.1 Appendix 1: Data collection sheet

Data collection sheet

Date _____ Patient Number _____

9.2 Demographic information

- Name _____
- Number of participant_____
- Age_____
- Date of birth_____
- Sex: male ☐ female ☐
- Nationality: South African ☐ other ☐ (specify)_____
- Age at onset of symptoms/ Age at first parental concern in months: _____
- Age at diagnosis (months): _____
- Home language: English ☐ Xhosa ☐ Afrikaans ☐

  Other ☐ (specify): _____

9.3 DSM 5 Diagnostic criteria present

Which of the following diagnostic criteria does the participant meet? (Check all that apply)

9.3.1 Social communication

Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:

1. ☐ Deficits in social-emotional reciprocity, ranging, for example,
from abnormal social approach
and failure of normal back-and-forth conversation;
to reduced sharing of interests, emotions, or affect;
to failure to initiate or respond to social interactions.

_____

_____

2. ☐ Deficits in nonverbal communicative behaviours used for social interaction, ranging, for example, from
poorly integrated verbal and nonverbal communication;
to abnormalities in eye contact and body language
or deficits in understanding and use of gestures:
to a total lack of facial expressions and nonverbal communication.

_____

_____

3. ☐ Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behaviour to suit various social contexts;

to difficulties in sharing imaginative play or in making friends;
to absence of interest in peers.

_____

_____

Total number _____

9.3.2 Restricted repetitive behaviours

Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by at least two of the following, currently or by history:

1. ☐ Stereotyped or repetitive motor movements, use of objects, or speech

(e.g., simple motor stereotypies,
lining up toys or flipping objects,
echolalia,
idiosyncratic phrases).

_____

_____

2. ☐ Insistence on sameness,

inflexible adherence to routines,
or ritualized patterns of verbal or nonverbal behaviour
(e.g., extreme distress at small changes,
difficulties with transitions,
rigid thinking patterns,
greeting rituals,
need to take same route or eat same food every day).

_____

_____

3. ☐ Highly restricted, fixated interests that are abnormal in intensity or focus

(e.g., strong attachment to or preoccupation with unusual objects,
excessively circumscribed or perseverative interests).

_____

_____

4. ☐ Hyper- or hypo-reactivity to sensory input

or unusual interest in sensory aspects of the environment
(e.g., apparent indifference to pain/temperature,
adverse response to specific sounds or textures,
excessive smelling or touching of objects,
visual fascination with lights or movement).

_____

_____

Total number _____

9.3.3 Severity level

- Level 1: Requiring support ☐
- Level 2: Requiring substantial support ☐
- Level 3: Requiring very substantial support ☐

9.4 Developmental Pattern

- Age of first words (in months) _____
- Regression of language milestones yes ☐ no ☐
    - If yes at what age (months)_____
- Developmental Regression yes ☐ no ☐
    - If yes what age? (months)_____
- Slow development from infancy yes ☐ no ☐
- Normal infant development then arrest yes ☐ no ☐
    - If yes from what age? (months) _____

9.5 Comorbid Factors

- Self-injury yes ☐ no ☐
    - If yes
        - Hand biting ☐
        - Head banging ☐
        - Excessive self-scratching or rubbing ☐
        - Other ☐ Specify

          _____
- Motor difficulty yes ☐ no ☐
    - Gross Motor difficulty/delay yes ☐ no ☐
    - Fine Motor difficulty/delay yes ☐ no ☐
    - Increased clumsiness yes ☐ no ☐
- Any history of seizures yes ☐ no ☐
- Are there seizures currently yes ☐ no ☐
- Epilepsy yes ☐ no ☐
    - Seizure type (tick all that apply)
        - Generalised tonic clonic ☐
        - Absence seizures ☐

        - Other generalised seizures ☐. Specify _____
        - Focal seizures ☐
            - No loss of awareness ☐
            - Loss of awareness ☐
    - Anti-epilepsy medication yes ☐ no ☐
        - Valproate ☐
        - Carbamazepine ☐
        - Lamotrigine ☐
        - Phenobarbitone ☐
        - Other ☐ Specify type(s) _____
- Hyperactive behaviour yes ☐ no ☐
- Intellectual disability yes ☐ no ☐
- Sleep difficulty yes ☐ no ☐
    - Difficulty initiating sleep ☐
    - Waking up at night ☐

Other comorbid difficulties

_____

_____

9.6 Aetiologic Factors

- Mothers age at birth _____
- Fathers age at birth _____
- Family history of autism yes ☐ no ☐
- Autism diagnosis in a sibling yes ☐ no ☐
- Consanguinity of parents yes ☐ no ☐
- Diagnosed genetic condition yes ☐ no ☐
    - If yes specify
        - Fragile x syndrome ☐
        - Tuberous sclerosis ☐
        - Other ☐ Specify_____
- Gestational age in weeks_____

- Prematurity yes ☐ no ☐
- Birthweight (g) _____
- Birth asphyxia yes ☐ no ☐
- Apgar score 1 min _____ 5 min _____
- Antenatal infection yes ☐ no ☐
    - If yes specify _____
- Mode of delivery
    - Normal vertex ☐
    - Caesarean section ☐
    - Instrumental ☐
    - Breech ☐
    - Other ☐ Specify _____
- Other complications during pregnancy or delivery

_____
_____
_____
___

9.7 Developmental level of function (months)

- Gross motor_____
- Fine motor_____
- Personal social_____
- Language_____
- Overall level of function_____
- Developmental quotient_____
- Normal ☐ mild ☐ moderate ☐ severe ☐ profound ☐

9.8 ADOS Scores

Age at ADOS_____

Module used _____

SOCIAL COMMUNICATION AND INTERACTION tick

- Number of Language /communication symptoms _____
- Social interaction symptoms _____
- Total number of symptoms _____

- Verbal ☐ Non-verbal ☐
- SC Score_____

RESTRICTED REPETITIVE BEHAVIOURS tick

- Repetitive behaviours number_____
- Total number of symptoms_____
- RRB Score _____

ADOS SCORE

- TOTAL score _____
- Rating _____
- Level: autism ☐ autism spectrum ☐ not Autism ☐

9.9 Appendix 2: English consent form

English consent form

Consent form for "Clinical Profile of Children with Autism Spectrum Disorder in a Developmental Clinic in Western Cape" study.

Principal investigator: **Dr L Mudawarima**
Senior Registrar Neurodevelopmental Paediatrics
Red Cross Children's Hospital
Rondebosch, Cape Town
Contact number: 0794046173

Your child is being invited to take part in a research project and we would like to ask for your consent. Please take some time to read the information presented here which will explain the details of the project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you understand what the research entails and how you and your child may be involved. Your participation is entirely voluntary. If you or your child is at all uncomfortable with the process you may contact myself, Dr L Mudawarima, or Prof K Donald.

This study has been approved by the Committee for Human Research at the University of Cape Town and will be conducted according to the ethical guidelines and principles of the International Declaration of Helsinki, South African Guidelines for Good Clinical Practice and Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

This study wants to look at the characteristics of children with autism spectrum disorder in Cape Town.

What would participation in this study involve?

We would like to ask you as parent/care giver to participate in an interview about what your child's behaviour and history is like. This will take approximately fifteen to twenty minutes of your time. After finding out basic information such as name, age and sex, we would like to know when you first suspected there was something wrong with your child and what kind of things you noticed. We would also like to know what behaviour you are currently seeing in your child and about any other problems that your child experiences that is related to autism spectrum disorder. Then we would like your child to participate in an assessment that involves play structured in such a way as to demonstrate which autistic behaviours they have. This assessment is usually about 45 minutes to an hour.

Participation is entirely voluntary. If you decide that your child should not participate in this study, it will not affect the way we treat your child. He/she will continue to receive the same standard of care that he presently experiences.

Will you benefit from taking part in this research?

The information from this study can help us improve our knowledge of which problems children with Autism Spectrum Disorder in Cape Town have and motivate for better services for them. In addition, the assessment on your child may help to show what their strengths and weaknesses are and therefore help your doctor and therapists in the care of your child. A report of the findings of the assessment will be made available to your doctor. If a problem is detected during the assessment, the information will be passed on to the doctor who is managing your child to allow them to follow them up further.

Who will have access to your child's records?
All information collected will be treated as confidential and protected. If it is used in a publication or thesis, the identity of the participant will remain anonymous. The only people who will have access to the personal information collected will be Dr L Mudawarima. As part of the study the research records may need to be reviewed by auditors or the Research Ethics Committee.

Will you be paid to take part in the study and are there any costs involved?
There are no costs involved in participation in the study. The study participants will receive R100 stipend towards their transport.

Is there anything else you should know or do?
Please don't hesitate to contact Dr Louisa Mudawarima (0794046173) should you have any further queries or encounter any problems
You can contact the Committee for Human Research at 021-4066338 (Health sciences faculty, Research Ethics Committee, Room E52-24 Groote Schuur Hospital, Old Main Building, Observatory, 7925) if you have any concerns or complaints that have not been adequately addressed by your study doctor.

CONSENT
By signing below, I_____
Give consent for my child _____
to take part in the research study entitled:

Clinical Profile of Children with Autism Spectrum Disorder in a Developmental Clinic in Western Cape

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered
- I understand that taking part in this study is voluntary and I have not been pressurized to take part

I may choose to leave the study at any time and will not be penalized or prejudiced in any way.

Signed at (place) _____ on (date) _____

_____ _____

Signature of guardian/parent **Signature of witness**

Relationship to child: _____

9.10 Appendix 3: Child assent form

Child Assent Form

We are doing a study to learn about people who have Autism Spectrum Disorder (ASD). We are asking you to help because we don't know very much about how ASD affects children in the Western Cape.

If you agree to be in our study, we are going to ask you and your family some questions about the things you experience as a result of Autism Spectrum Disorder. For example, we would like to know when they first realised you may have ASD and what sort of things you experience now. After that, we will have an observation of you while we play different games to try and see which signs of autism you have.

You can ask questions about this study at any time. If you decide at any time not to finish, you can ask us to stop.

The questions we will ask are only about what you experience. There are no right or wrong answers and no right or wrong reactions because this is not a test.

If you sign this paper, it means that you have read this and that you want to be in the study. If you don't want to be in the study, don't sign this paper. Being in the study is up to you, and no one will be upset if you don't sign this paper or if you change your mind later.

Your signature: _____

Date _____

Your printed name: _____

Date _____

Signature of person obtaining consent: _____

Date _____

Printed name of person obtaining consent: _____

Date _____

9.11 Appendix 4: ethics approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

21 November 2016

HREC REF: 702/2016

A/Prof K Donald
Developmental Paediatrics
School of Child & Adolescent Health
Red Cross Children's Hospital

Dear A/Prof Donald

PROJECT TITLE: CLINICAL PROFILE OF CHILDREN WITH AUTISM SPECTRUM DISORDER IN A DEVELOPMENTAL CLINIC IN THE WESTERN CAPE (MPHIL CANDIDATE - DR L MUDAWARIMA)

Thank you for your response to the Faculty of Health Sciences Human Research Ethics Committee dated 12 November 2016.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th November 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period. (Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

The HREC acknowledge that the student Dr Louisa Mudawarima will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.

HREC 702/2016

Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 702/2016

9.12 Appendix 5: Ethics Extension

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS011: Study deviation

HREC office use only (FWA00001837; IRB00001938)			
This serves as acknowledgement of a protocol deviation as described below.			
Chairperson of the HREC signature		Date	7/5/20

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	29/04/2020
HREC REF Number	HREC702/2018
Project Title	Clinical Profile of Children with Autism Spectrum Disorder in a Developmental Clinic in Western Cape
Protocol number (if applicable)	
Principal Investigator	Associate Professor K. A. Donald
Department / Office Internal Mail Address	Paediatrics and Child Health Division of Developmental Paediatrics

2. Protocol deviation description

Please describe the deviation below, including the reason why the deviation occurred.
Delayed study write-up following student emigration and bereavement

3. Follow-up actions

3.1 Please describe any follow-up action(s) taken or planned as a result of this deviation e.g. DSMB reporting, report to sponsor, informing participants.
Planned writeup by end of year submission date
3.2 Please describe what action(s) have or will be taken to prevent similar deviations in future.
Coordination with Head of Division

4. Principal Investigator's acknowledgement of responsibility

This signature indicates the PI has reviewed the deviation, taken appropriate follow-up action and implemented or plans to implement preventative steps where possible.

HUMAN RESEARCH ETHICS COMMITTEE
27 MAY 2020
FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Signature of PI		Date	29/04/2020

9.13 APPENDIX 6: Permission to Conduct Research

Western Cape Government
Health

Dr AS Booysen
Manager: Medical Services
Email: Tony.Booysen@Westerncape.gov.za
Tel: +27 21 658 5788 fax: +27 21 658 5166
RXH: RCC54

Dr L Mudawarima
Red Cross War Memorial Children's Hospital

Dear Dr L Mudawarima

APPROVAL OF RESEARCH

PROJECT TITLE: CLINICAL PROFILE OF CHILDREN WITH AUTISM SPECTRUM DISORDER IN A DEVELOPMENTAL CLINIC IN THE WESTERN CAPE

It is a pleasure to inform you that approval is hereby granted to conduct the above-mentioned study at Red Cross War Memorial Children's Hospital.

Yours sincerely,

Dr AS Booysen
Manager: Medical Services
Date: 13.12.16

9.14 Appendix 7: Instructions to Authors

Accessed from Acta Neuropsychiatrica on 13March 2021
https://www.cambridge.org/core/journals/acta-neuropsychiatrica/information/instructions-contributors

"Instructions for authors

Acta Neuropsychiatrica, the official Journal of Scandinavian College of Neuropsychopharmacology, is an international journal focussing on translational neuropsychiatry. It publishes high-quality original research papers and reviews. The Journal's scope specifically highlights the pathway from discovery to clinical applications, healthcare and global health that can be viewed broadly as the spectrum of work that marks the pathway from discovery to global health.

The steps of translation that are within the scope include: 1) fundamental discovery, 2) bench to bedside, 3) clinical trials, 4) translation to clinical guidelines, 5) health policy and usage, and 6) global health.

Research covering molecular biology, genetics, pharmacology, imaging and epidemiology is welcome as it contributes to enhancing the field.

Acta Neuropsychiatrica welcomes full-length **Original Research Articles, Short Communications, Commentaries, Review Articles, Method/protocol Articles, Perspectives, and Research Letters.** Debate is encouraged in the form of **Letters to the Editor**.

All articles published in *Acta Neuropsychiatrica* undergo peer review.

In submitting a manuscript to *Acta Neuropsychiatrica*, all authors must agree to abide by all relevant COPE policies, including its Guidelines for Responsible Conduct Regarding Scientific Communication. Manuscripts with multiple authors are reviewed with the explicit understanding that all authors have seen and approve of the submitted version and agree to abide to the policies.

POLICY ON ETHICS

It is expected that authors submitting papers to *Acta Neuropsychiatrica* will have conducted their work in accordance with relevant ethical standards. Procedures involving experiments on human subjects should be in accordance with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accordance with the Helsinki Declaration of 1975. Procedures involving experimentation on animals should be done in accordance with the guidelines of the country/institution in which the experiments were done.

Acta Neuropsychiatrica recognizes its responsibility to ensure that questions of scientific misconduct or dishonesty in research are adequately pursued. Should scientific misconduct or dishonesty be suspected or alleged, *Acta Neuropsychiatrica* follows the recommended procedures outlined by the Committee on Publication Ethics (COPE).

POLICY ON PREPUBLICATION

Acta Neuropsychiatrica does not consider manuscripts that have been previously published.

Posting to a preprint server such as bioRxiv, Authorea, Open Science Framework, etc. is not considered prior publication. Posting a manuscript to a preprint server while under review is allowed up until the point of acceptance. Abstracts, theses, posters, or manuscripts that have been posted on the Internet for the purpose of receiving commentary from the community are not considered prior publication. Online posting is typically done at a prepublication repository that has been designed for that purpose but posting on an institutional website or other Internet location is acceptable.

It is essential that any material submitted to *Acta Neuropsychiatrica* be original to the authors and that any copyright, license, or permission is obtained prior to submission. See Policy on Copyright for more details.

POLICY ON MOLECULAR DATA

Protein and nucleic acid sequences: Newly determined nucleotide or protein sequences must be deposited in GenBank, EMBL-EBI, or the DDBJ Center. Accession numbers must be reported in the manuscript and data must be available upon acceptance and publication of the manuscript. No data are to be withdrawn following publication.

Genomic and proteomic data: Authors of papers that include functional genomics data such as microarray, ChIP-sequencing, RNA-Seq, or other high-throughput data are required to deposit the data in a MIAME-compliant database such as GEO, ArrayExpress, or CYBEX, and to provide accession numbers. Data must be publicly accessible upon acceptance and publication of the manuscript. No data are to be withdrawn following publication.

Authors of papers that include proteomics data should comply with the guidelines developed by Molecular and Cellular Proteomics (https://www.mcponline.org/page/content/mass-spec-guidelines).

POLICY ON COMPUTER CODE AND SOFTWARE

Computational models: We recommend that new computer code be deposited in a suitable repository such as GitHub, ModelDB, BioModels, CellML, or Visiome. Studies using custom code central to the conclusions should include a statement in the Materials and Methods section, under the heading “Code Accessibility”, indicating whether the code can be accessed and how, including any accession numbers or restrictions; code should also be cited in the references. Code should be available upon acceptance and publication of the manuscript.

Software: If new software or a new algorithm is used for data analysis, authors are encouraged to deposit it in an appropriate public repository. A statement should be included in the Materials and Methods section, under the heading “Software

Accessibility", indicating whether the software or algorithm can be accessed and how, including any accession numbers or restrictions.

POLICY ON IMAGE MANIPULATION

Original data: The editors reserve the right to request any original, unprocessed data from authors at any stage in the submission, review, or publication process, including after publication. Failure to provide requested information may result in publication delays, rejection, or revocation of acceptance.

Image manipulation: All images in manuscripts accepted for publication will be screened for any indication of manipulation that is inconsistent with the following guidelines. Manipulation that violates these guidelines may result in production delays or revocation of acceptance.

- No specific feature within an image may be enhanced, obscured, moved, removed, or introduced.
- Constructing figures using images taken from different parts of the same gel or from different gels is discouraged. When this is necessary, it must be made explicit by the arrangement of the figure (e.g., using dividing lines) and in the text of the figure legend.
- Recordings obtained at different time points or from different sites must not be spliced together to give the appearance of a continuous record. Authors must make it clear in the figure legend how many different recordings are illustrated.
- Adjustments to images or recordings are acceptable if they are applied uniformly to all portions of the image or recording, and if they do not obscure, eliminate, or misrepresent information present in the original, including the background. Adjustments involving filtering or scaling (e.g., brightness, contrast, or color balance) must be applied to every pixel in the image or applied uniformly to an entire recording. Nonlinear adjustments (e.g., changes to gamma settings) or deleting portions of a recording (e.g. leak subtraction or stimulus artifacts) must be disclosed in the figure legend.
- The minimum resolution for images is 300 dpi. Vector-format is preferred.
- At the time of acceptance, authors will be required to submit uncropped images of complete gels for comparison to the prepared figures. If original data cannot be produced, the acceptance of the manuscript may be revoked.

POLICY CONCERNING AVAILABILITY OF MATERIALS AND DATA

Authors must agree to make freely available to colleagues in academic research any clones of cells, nucleic acids, antibodies, etc. that were used in the research reported and that are not available from commercial suppliers.

Authors should, when possible, honor requests for access to any form of published data for appropriate scientific use. The editors reserve the right to request any original data from authors at any stage in the review or publication process, including after

publication. Failure to provide requested information may result in publication delays or revocation of acceptance

Submission

All manuscript submissions to Acta Neuropsychiatrica must be completed electronically through the Acta Neuropsychiatrica ScholarOne Manuscripts (formerly known as Manuscript Central) website: http://mc.manuscriptcentral.com/acn

Submissions will be considered provided that papers are previously unpublished, and are not offered simultaneously elsewhere; that all authors have read and approved the content and agree to the submission of the manuscript to the Journal.

Acta Neuropsychiatrica employs a plagiarism detection system for all submitted papers. By submitting your manuscript to this journal you accept that your manuscript will be screened for plagiarism against previously published works.

Review process

All manuscripts submitted to the journal will first be editorially reviewed by the Editor-in-Chief, who will then assign the papers to a subject-specific Associate Editor.

The authors should suggest three to five potential peer reviewers in their submission. The contact details of suggested reviewers should be institutional email addresses where possible, or contain information which will help the editor to verify the identity of the reviewer (for example ORCiD or a main reference stated in the cover letter). Should there be any non-preferred reviewers, a proper explanation must be given in the cover letter.

The Associate Editor will then assign at least two independent referees to review each paper. Based on the referee reports received along with input from the Associate Editor, the Editor-in-Chief will decide to either reject, request revisions or accept the manuscript.

Once a revised version is received, the Editors and referees will evaluate the revised manuscript. Authors will then be notified of whether their paper has been accepted or rejected for publication in the Journal.

All manuscripts accepted for publication are subject to editing by the publisher for presentation, style and grammar. The Editor-in-Chief's decision is final.

Categories of papers

Acta Neuropsychiatrica accepts the following contributions:

Original research articles

Original articles report the results of original research and are intended for full- scale basic or clinical studies including large controlled trials. Translational work is encouraged, but not required. Original articles should not exceed 6,500 words

(not including references, figures and tables) and should include an abstract of up to 250 words and 5 keywords in strict accordance with Medical Subject Headings (https://meshb.nlm.nih.gov/search). (Exceptions to the length limitation will be considered for unusually large or complex studies).

Short communications

This category is for 'fast-breaking' new work, which is of great potential interest and can be succinctly presented. Papers in this category may contain up to 2,500 words (not including references, figures and tables) and should include a maximum of 25 references, up to 2 illustrations (figures or tables), an abstract of up to 150 words and 5 keywords in strict accordance with Medical Subject Headings (https://meshb.nlm.nih.gov/search).

Commentaries

Commentaries focus attention on scientific issues in the field of the journal, and should highlight, discuss and amplify these issues. Commentaries may contain up to 5,000 words (not including references, figures and tables) and should include an abstract of up to 250 words and 5 keywords in strict accordance with Medical Subject Headings (https://meshb.nlm.nih.gov/search). Commentaries are invited by the Editor-in-Chief.

Method/Protocol articles

Acta Neuropsychiatrica will publish a limited number of Method/Protocol articles, which focus on protocols and on novel methods providing significant improvements and extensions to already established research areas. Method/Protocol articles may be invited by the Editors but can also be submitted. Method/Protocol articles may contain up to 6,000 words (not including refs, figs and tables) and should include an abstract of up to 250 words. and 5 keywords in strict accordance with Medical Subject Headings (https://meshb.nlm.nih.gov/search). (Exceptions to the length limitation will be considered if justified by the scope of the paper).

Review articles

Acta Neuropsychiatrica <="" i="" style="box-sizing: border-box;">will publish a limited number of scholarly, comprehensive reviews that summarize and critically evaluate research in the field addressed and identify future implications. Reviews may be invited by the Editors but can also be submitted. Reviews may contain up to 10,000 words (not including references, figures and tables) and should include an abstract of up to 250 words and 5 keywords in strict accordance with Medical Subject Headings (https://meshb.nlm.nih.gov/search). (Exceptions to the length limitation will be considered if justified by the scope of the Review).

Perspectives articles

<="" i="" style="box-sizing: border-box;">Acta Neuropsychiatrica will publish a limited number of Perspective articles that critically perspective research in the field addressed and describe future potentials. Perspectives may be invited by the Editors but can also be submitted. Perspectives may contain up to 10,000 words (not including references, figures

and tables) and should include an abstract of up to 250 words and 5 keywords in strict accordance with Medical Subject Headings (https://meshb.nlm.nih.gov/search). (Exceptions to the length limitation will be considered if justified by the scope of the Perspectives).

Protocol articles

Acta Neuropsychiatrica will publish a limited number of Method/Protocol articles, which focus on protocols and on novel methods providing significant improvements and extensions to already established research areas. Method/Protocol articles may be invited by the Editors but can also be submitted. Method/Protocol articles may contain up to 6,000 words (not including references, figures and tables) and should include an abstract of up to 250 words and 5 keywords in accordance with Medical Subject Headings (https://meshb.nlm.nih.gov/search).

Debate papers

Letters to the Editor are welcomed to the Acta Neuropsychiatrica debate section, especially if they relate to ongoing debates or comment on recent publications in the Journal. A maximum of 5 references can be included in papers published in the Debate Section.

Research letters

Acta Neuropsychiatrica welcomes submissions of Research Letters, which represent an opportunity to publish (preliminary) research findings that are of interest to the field. Research Letters are "unstructured", i.e. without the subheadings used in the full-length manuscripts. The length of the letters should be approximately 750-1000 words and a maximum of 5 references can be included. The authors may include a small table or figure in the submission. Abstracts are not used for Research Letters.

Papers in all categories, whether invited or submitted, will be peer reviewed.

Manuscript style

Consult a current issue of the Journal for style and format. The manuscript should be typed double-spaced throughout on 'Letter' or A4 paper. Pages should be numbered sequentially beginning with the Title Page. Margins should not be less than 2.5 cm on all sides, and the font should be clearly legible and uniform throughout.

Title page (Page 1)

All manuscripts should contain a concise, informative title (max 15 words; abbreviations, acronyms, colon, semicolon or the like are not allowed), the authors' names, the names in English of departments and institutions to be attributed, and their city and country of location. Please also include a running title with a maximum of 50 characters (letters and spaces). Name, telephone number, fax number, e-mail address and full postal address of the corresponding author should be stated.

Abstract and keywords (Page 2)

Abstract not exceeding 250 words (150 for short communications) with the following structure:

Objective: State the objective of the study and the main hypothesis tested in the second sentence.

Methods: Describe the basic design of the study as well as its setting, participants and key measurements or outcomes. Describe, if appropriate, the essential features of any interventions, including their method and duration of administration. For systematic reviews, list the data sources used, including time restrictions and search terms. Provide the number of studies reviewed and the selection criteria.

Results: Provide data for the key measurements in this section. Give confidence intervals for differences where appropriate or other measures of statistical significance. All data in the abstract must be reported in the text of the paper as well.

Conclusion: Briefly summarise the main findings and potential application. A consideration of the significance of the study and recommendations for further work should appear in the main text, not the abstract.

The main part of the Abstract should be devoted to Results.

5 keywords in strict accordance with Medical Subject Headings (https://meshb.nlm.nih.gov/search)

For Original Articles and Short Communications specifically

Significant Outcomes

Provide up to 3 Significant Outcomes encapsulating the 'take-home messages' of the article, and identify the main issues addressed with particular emphasis on the scientific significance. The Significant Outcomes are to be presented succinctly (1 max 2 sentences each), in tabulated form, and logically emerge from the conclusions of the paper (without repeating). However, they must not be dogmatic, raise new issues or pose further questions.

Limitations

In addition, each original article must cite up to 3 noteworthy Limitations. These should inform the reader about potential weaknesses, for instance in aspects of study design, methodology, analyses, the wider generalizability, or the wider application of findings.

The Significant Outcomes and the Limitations are placed immediately below the Abstract/Keywords.

For Review Articles specifically

Summations

Provide up to 3 significant Summations encapsulating the 'take-home messages' of the paper, and identify the main issues addressed with particular emphasis on their clinical and/or scientific significance. The Summations should be presented succinctly (1 max 2 sentences each), in tabulated form, and logically emerge from the conclusions of the paper (without repeating). However, they must not be dogmatic, raise new issues or pose further questions.

Considerations

In addition, each review article must cite up to 3 noteworthy Considerations in which authors essentially criticise the summations and include any caveats or limitations either of the review process or its conclusions.

The Summations and Considerations are placed immediately below the Abstract/Keywords.

For Perspectives/Method/Protocols articles specifically:

Summations

Provide up to 3 significant Summations encapsulating the 'take-home messages' of the paper, and identify the main issues addressed with particular emphasis on their clinical and/or scientific significance. The Summations should be presented succinctly (1 max 2 sentences each), in tabulated form, and logically emerge from the conclusions of the paper (without repeating). However, they must not be dogmatic, raise new issues or pose further questions.

Perspectives

In addition, each perspective article must cite up to 3 noteworthy perspectives in which authors essentially criticise the summations and include any caveats or limitations either of the perspective or its conclusions. The Summations and Perspectives are placed immediately below the Abstract/Keywords.

Manuscript body (from page 3) – Review articles

Authors are required to base the manuscript on the structure outlined in the PRISMA checklist:

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One to two pages, providing an appropriate background to the article, drawing on relevant literature and explaining the research question to be addressed. The introduction should be concluded by the subtitle Aims of the Study (3 to 5 lines without literature references and abbreviations).

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Acknowledgements

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For papers concerning neuropsychopharmacological treatments, Acta Neuropsychiatrica encourages authors to utilize the 'Neuroscience-based Nomenclature'

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9.15 appendix 8: Autism Diagnostic Observation Schedule.

This is commercial copyrighted material that cannot be shared openly. The information sheet for the product is shared below.

Autism Diagnostic Observation Schedule™, Second Edition (ADOS™-2)

MODULES 1 THROUGH 4 BY CATHERINE LORD, PHD, MICHAEL RUTTER, MD, FRS, PAMELA C. DILAVORE, PHD, SUSAN RISI, PHD, KATHERINE GOTHAM, PHD, AND SOMER L. BISHOP, PHD

TODDLER MODULE BY CATHERINE LORD, PH.D., RHIANNON J. LUYSTER, PH.D., KATHERINE GOTHAM, PH.D., AND WHITNEY GUTHRIE, M.S.

This revision improves an instrument already viewed as the "gold standard" for observational assessment of autism spectrum disorders (ASDs). With updated protocols, revised algorithms, a new Comparison Score, and a Toddler Module, the ADOS-2 provides a highly accurate picture of current symptoms, unaffected by language. It can be used to evaluate almost anyone suspected of having ASD—from 1-year-olds with no speech to adults who are verbally fluent.

Like its predecessor, the ADOS-2 is a semistructured, standardized assessment of communication, social interaction, play, and restricted and repetitive behaviors. By observing and coding these behaviors, you can obtain information that informs diagnosis, intervention, treatment planning, and educational placement.

Five Modules

The ADOS-2 includes five modules, each requiring just 40 to 60 minutes to administer. The individual being evaluated is given only one module, selected on the basis of his or her expressive language level and chronological age.

- Toddler Module—for children between 12 and 30 months of age who do not consistently use phrase speech
- Module 1—for children 31 months and older who do not consistently use phrase speech
- Module 2—for children of any age who use phrase speech but are not verbally fluent
- Module 3—for verbally fluent children and young adolescents
- Module 4—for verbally fluent older adolescents and adults

Each module engages the examinee in a series of activities involving interactive stimulus materials (all included in the ADOS-2 Kit). To illustrate, activities in Module 3 are listed below:

- Construction Task
- Make-Believe Play
- Joint Interactive Play
- Demonstration Task
- Description of a Picture
- Telling a Story From a Book
- Cartoons
- Conversation and Reporting
- Emotions
- Social Difficulties and Annoyance
- Break
- Friends, Relationships, and Marriage
- Loneliness
- Creating a Story

Standardized Administration, Coding, and Scoring

Each ADOS-2 module has its own Protocol Booklet, which structures the administration and guides you through coding and scoring. As you administer activities, you observe the examinee and take notes. Immediately afterward, you code the behaviors observed. Then you use the algorithm form for scoring.

In Modules 1 through 4, algorithm scores are compared with cutoff scores to yield one of three classifications: *autism*, *autism spectrum*, or *non-spectrum*. The difference between autism and autism spectrum classifications is one of severity, with the former indicating more pronounced symptoms. In the Toddler Module, algorithms yield "ranges of concern" rather than classification scores.

The Most Accurate Picture of Current ASD Symptoms

With improved algorithms, the ADOS-2 demonstrates strong predictive validity. It gives you a highly accurate picture of current ASD-related symptoms, based on real-time observations. Physicians, clinical psychologists, school psychologists, speech–language pathologists, and occupational therapists can use ADOS-2 results to inform diagnosis, intervention, educational placement, and treatment planning. Because it can be used with a wide range of children and adults, the ADOS-2 is an essential addition to any hospital, clinic, or school that serves individuals with developmental disorders.

10 Full reference List

Al-Salehi SM, Al-Hifthy EH and Ghaziuddin M (2009) Autism in Saudi Arabia: presentation, clinical correlates and comorbidity. *Transcult Psychiatry,* **46,** 340-7.

Anonymous. *2012.06_western_cape_overview1_0.pdf* [Online]. [Accessed 3 MARCH 2016 2016].

Association AP (2013) *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*, American Psychiatric Pub.

Bakare MO and Munir KM (2011a) Autism spectrum disorders (ASD) in Africa: a perspective. *African journal of psychiatry,* **14,** 208-210.

Bakare MO and Munir KM (2011b) Excess of non-verbal cases of autism spectrum disorders presenting to orthodox clinical practice in Africa - a trend possibly resulting from late diagnosis and intervention. *S Afr J Psychiatr,* **17,** 118-120.

Barnevik-Olsson M, Gillberg C and Fernell E (2010) Prevalence of autism in children of Somali origin living in Stockholm: brief report of an at-risk population. *Developmental Medicine & Child Neurology,* **52,** 1167-1168.

Barnevik–Olsson M, Gillberg C and Fernell E (2008) Prevalence of autism in children born to Somali parents living in Sweden: a brief report. *Developmental Medicine & Child Neurology,* **50,** 598-601.

Belhadj A, Mrad R and Halayem MB (2006) [A clinic and a paraclinic study of Tunisian population of children with autism. About 63 cases]. *Tunis Med,* **84,** 763-7.

Boat TF, Wu JT, On Children B, Of Medicine I, Of Behavioral D, Sciences S and Of Sciences TNA (2015) Prevalence of Autism Spectrum Disorder.

Bolton S, Mcdonald D, Curtis E, Kelly S and Gallagher L (2014) Autism in a recently arrived immigrant population. *European Journal of Pediatrics,* **173,** 337-343.

Cdc. *CDC | Data and Statistics | Autism Spectrum Disorder (ASD) | NCBDDD* [Online]. Available: http://www.cdc.gov/ncbddd/autism/data.html [Accessed 16 February 2016].

Dhadphale M, Lukwago M and Gajjar M (1982) Infantile autism in Kenya. *The Indian Journal of Pediatrics,* **49,** 145-148.

Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcín C, Montiel-Nava C, Patel V, Paula CS and Wang C (2012) Global prevalence of autism and other pervasive developmental disorders. *Autism Research,* **5,** 160-179.

Fombonne E, Heavey L, Smeeth L, Rodrigues LC, Cook C, Smith PG, Meng L and Hall AJ (2004) Validation of the diagnosis of autism in general practitioner records. *BMC Public Health,* **4,** 5.

Gillespie-Lynch K, Sepeta L, Wang Y, Marshall S, Gomez L, Sigman M and Hutman T (2012) Early childhood predictors of the social competence of adults with autism. *Journal of autism and developmental disorders,* **42,** 161-174.

González-Cortés T, Gutiérrez-Contreras E, Espino-Silva PK, Haro-Santa Cruz J, Álvarez-Cruz D, Rosales-González CC, Sida-Godoy C, Nava-Hernández MP, López-Márquez FC and Ruiz-Flores P (2019) Clinical Profile of Autism Spectrum Disorder in a Pediatric Population from Northern Mexico. *Journal of autism and developmental disorders,* **49,** 4409-4420.

Honeth I, Laughton B, Springer PE, Cotton MF and Pretorius C (2019) Diagnostic accuracy of the Molteno Adapted Scale for developmental delay in South African toddlers. *Paediatr Int Child Health,* **39,** 132-138.

Jones LA and Campbell JM (2010) Clinical characteristics associated with language regression for children with autism spectrum disorders. *J Autism Dev Disord,* **40,** 54-62.

Juneja M, Mukherjee SB and Sharma S (2005) A descriptive hospital based study of children with autism. *Indian Pediatrics,* **42,** 453-458.

Kakooza-Mwesige A, Ssebyala K, Karamagi C, Kiguli S, Smith K, Anderson MC, Croen LA, Trevathan E, Hansen R and Smith D (2014) Adaptation of the “ten questions” to screen for autism and other neurodevelopmental disorders in Uganda. *Autism,* **18,** 447-457.

Kanner L (1943) *Autistic disturbances of affective contact*, publisher not identified.

Kommu JVS, Gayathri K, Srinath S, Girimaji SC, Seshadri SP and Gopalakrishna G (2017) Profile of two hundred children with Autism Spectrum Disorder from a tertiary child and adolescent psychiatry centre. *Asian journal of psychiatry,* **28,** 51-56.

Laughton B. (2011) *The reliability of the Molteno Adapted Development Scale in predicting developmental outcomes at 2 years, in prematurely born very low birth weight infants.*

Lecavalier L, Leone S and Wiltz J (2006) The impact of behaviour problems on caregiver stress in young people with autism spectrum disorders. *Journal of Intellectual Disability Research,* **50,** 172-183.

Lord C, Rutter M, Dilavore PC, Risi S, Gotham K and Bishop SL (2008) *Autism diagnostic observation schedule (ADOS): Manual*, Western Psychological Services Los Angeles.

Lotter V (1966) Epidemiology of autistic conditions in young children. *Social psychiatry,* **1,** 124-135.

Mahajnah M, Sharkia R, Shalabe H, Terkel-Dawer R, Akawi A and Zelnik N (2015) Clinical characteristics of autism spectrum disorder in Israel: impact of ethnic and social diversities. *Biomed Res Int,* **2015,** 962093.

Malhi P and Singhi P (2012) Regression in children with autism spectrum disorders. *Indian Journal Of Pediatrics,* **79,** 1333-1337.

Mankoski RE, Collins M, Ndosi NK, Mgalla EH, Sarwatt VV and Folstein SE (2006) Etiologies of autism in a case-series from Tanzania. *Journal of autism and developmental disorders,* **36,** 1039-1051.

Mpaka DM, Okitundu DLEA, Ndjukendi AO, N'situ AM, Kinsala SY, Mukau JE, Ngoma VM, Kashala-Abotnes E, Ma-Miezi-Mampunza S, Vogels A and Steyaert J (2016) Prevalence and comorbidities of autism among children referred to the outpatient clinics for neurodevelopmental disorders. *Pan Afr Med J,* **25,** 82.

Neuropsychopharmacology SCO. *Acta Neuropsychiatrica Instructions for authors* [Online]. Cambridge core: Cambridge core. Available: https://www.cambridge.org/core/journals/acta-neuropsychiatrica/information/instructions-contributors# [Accessed 13 March 2021].

Philofsky A, Fidler DJ and Hepburn S (2007) Pragmatic language profiles of school-age children with autism spectrum disorders and Williams syndrome. *Am J Speech Lang Pathol,* **16,** 368-80.

Ramey CT and Ramey SL (1998) Early intervention and early experience. *American Psychologist,* **53,** 109-120.

Ritvo ER, Ritvo R, Freeman BJ and Mason-Brothers A (1994) Clinical characteristics of mild autism in adults. *Compr Psychiatry,* **35,** 149-56.

Sathyabama R (2019) Clinical characteristics and demographic profile of children with Autism Spectrum Disorder (ASD) at child development clinic (CDC), Penang Hospital, Malaysia. *The Medical journal of Malaysia,* **74,** 372-376.

Seif Eldin A, Habib D, Noufal A, Farrag S, Bazaid K, Al-Sharbati M, Badr H, Moussa S, Essali A and Gaddour N (2008) Use of M-CHAT for a multinational screening of young children with autism in the Arab countries. *International Review of Psychiatry,* **20,** 281-289.

Springer PE, Van Toorn R, Laughton B and Kidd M (2013) Characteristics of children with pervasive developmental disorders attending a developmental clinic in the Western Cape Province, South Africa. *South African Journal of Child Health,* **7,** 95-99.