

https://dspace.org/

Autism Spectrum Disorder and Head Circumference in children under 5 years of age attending a public clinic in Johannesburg South Africa

BV van der Net; Renate Strehlau; Jacqueline Bezuidenhout

https://hdl.handle.net/10539/43493
DHET

Downloaded from a DSpace repository. https://dspace.org/

Research Article

Autism Spectrum Disorder and Head Circumference in children under 5 years of age attending a public clinic in Johannesburg, South Africa

Bianca Vieira van der Net*[1], Renate Strehlau[2], Jacqueline Kim Bezuidenhout[3]

[1]South Rand Hospital, Department of Speech Therapy and Audiology, School of Clinical Medicine: Child Health Neurodevelopment, Faculty of Health Sciences, University of Witwatersrand
[2]VIDA Nkanyezi Research Unit, Rahima Moosa Mother and Child Hospital, Department of Paediatrics and Child Health, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand
[3]Department of Paediatrics and Child health, School of Clinical Medicine, Faculty of Health Sciences, University of Witwatersrand

**Corresponding Author:* *biancavieiraslpa@gmail.com*

ABSTRACT

Introduction: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that is increasing in prevalence globally. There is an emerging field of research investigating the association between head circumference and ASD but there is a marked paucity of such data from Southern Africa.

Aim: To describe the head circumference (HC) measurement of children diagnosed with ASD and to investigate associations between HC, ASD severity levels and associated comorbidities.

Methods: A retrospective record review of children diagnosed with ASD attending a neurodevelopmental clinic at a large public hospital in South Africa was conducted. Demographic data and HC measurements from the first clinic visit were collected. The World Health Organization data set of head circumference norms were used as the comparator reference population. Statistical analysis was conducted using parametric, descriptive and inferential methods.

Results: Data from 135 children diagnosed with ASD were included. The sample population had a mean age of 43 months (range 13-61 months) and 107 (79%) were males. Thirty (22.2%) patients in the cohort had a HC which was classified as macrocephalic. Almost half (46.7%) had an ASD severity level of three and 94 (69.6%), had been diagnosed with a comorbidity. In this study no significant association was found between macrocephaly and ASD severity.

Conclusions: Measuring the HC during childhood is a cost-effective, simple and non-invasive procedure that may well assist professionals in raising suspicion of ASD at an early age. Early detection and intervention could optimise participation and integration for the individual living with this life-long neurodevelopmental disability.

Keywords: Autism phenotype, head circumference, macrocephaly, autism severity, early intervention.

INTRODUCTION

South Africa has prioritised coordinating and improving the management of individuals living with Autism Spectrum Disorder (ASD) as it is a complex, lifelong neurodevelopmental condition.(1) However, there is a paucity of data regarding ASD prevalence in the South African context. In 2013 it was estimated that there were 270 000 cases of ASD in South Africa with 5 000 new cases being diagnosed annually.(2) Van Biljon et al. (3) proposed that ASD prevalence in South Africa may be higher than that reported in developed countries because of higher rates of poverty, illiteracy and HIV/AIDS, which are factors postulated as contributing to the development of ASD. Defining the magnitude of the burden of ASD in South Africa would assist with the planning and provision of appropriate services.(4)

The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) (2013) defines ASD as a developmental disorder comprising impairments in social communication and interaction as well as demonstrating restrictive and repetitive behaviours. Autism Spectrum Disorder is diagnosed when the DSM-5 diagnostic criteria

are met and the behaviours significantly affect functioning and performance of daily activities.(5) Severity levels are classified according to the DSM-5 as those requiring support (level 1), those requiring substantial support (level 2) and level 3 would be those requiring very substantial support.(5) However, due to the diverse and spectral nature of ASD expression in each individual there is no conclusive behavioural or diagnostic indicator of ASD for a child less than 12 months of age.(6) Biological markers of ASD have been identified, one of them being the increase in brain size.(7) Structural neuroimaging research has made valuable contributions to our understanding of the neuro-anatomy of ASD. It has been demonstrated that brain growth in ASD is a dynamic process with an increase in total brain volume and early rapid brain overgrowth, as shown by increasing head circumference (HC) measurements, and is age related.(8) Head circumference measurement thus has a potential role as a proxy indicator for abnormal brain growth, thus assisting with the early identification of children with ASD.

The aim of this study was to describe the initial HC measurement of young children attending a neurodevelopmental clinic who had been diagnosed with ASD and to investigate association between HC, ASD severity level and associated comorbid conditions.

MATERIAL AND METHODS

Study Population

A retrospective, record review was conducted of children diagnosed with ASD who attended the neurodevelopmental clinic (NDC) at a large public hospital (Charlotte Maxeke Johannesburg Academic Hospital) in Johannesburg, SA. Data was collected from existing patient files over a 6 month period from 01 April 2019 through 30 September 2019. The NDC is run by two developmental Paediatricians who oversee the diagnosis and severity levels of each newly diagnosed child attending the clinic.

Paper records were included for review if the following inclusion criteria were met: confirmed ASD diagnosis as per the DSM-5 criteria and a documented HC measurement at the initial clinic visit when younger than five years of age. Records of children were excluded if the child had been diagnosed with a syndrome or condition associated with macrocephaly. Ethical approval for the study was obtained from the Human Research Ethics Committee (Medical) of the University of Witwatersrand.

Measurements

Interpretation of HC using the WHO growth charts necessitated chronological age in years and months as well as the HC measurement in centimetres (cm). The HC measurement recorded at the initial clinic visit was extracted from the child's NDC file. All HC measurements were obtained by the same group of nursing staff working in the NDC, all of whom had received appropriate training. A flexible, non-stretchable measuring tape was placed at the level of the supraorbital ridges, above the ears, and around the occiput so that the maximum HC was measured, as is standard practice.(9) HC measurements were recorded into the child's clinic file (in cm) by the nursing sister and plotted on the WHO HC chart (10) by the treating physician. Measurements for HC were categorised according to the WHO chart interpretation i.e. microcephaly as ≥2 standard deviations (SDs) below the mean for age and macrocephaly as ≥2 SD above the mean for age.

Demographic variables collected included: date of birth, sex, and ethnicity. The ASD severity level at first presentation, as assessed by the physician according to the DSM-5 criteria, as well as subsequently diagnosed comorbidities and special investigations listed in the patient file at the time of data collection. Special investigations included Magnetic Resonance Imaging (MRI), Electroencephalogram (EEG) and Computerised Tomography (CT) scan. Variables were directly entered into an electronic, password-protected database.

Statistical Analysis

Head circumference measurement data from the sample population were compared with the reference population HC values from the WHO data set. The sex differentiated WHO reference HC values are grouped according to SD above or below the mean HC for age.(10) A z-test was used to compare values from the study sample to the reference population. Critical values for normally distributed data were used and the null hypothesis rejected if the z-test statistic exceeded the critical value. An independent one-sample t-test was used in calculating the difference between sample and reference means.

When analysing the categorical data with regards to macrocephaly vs. no macrocephaly in specific age bands, the chi-squared test was used. The presence of macrocephaly vs. no macrocephaly was stratified according to age bands, per participant and the resultant proportion. Comparison of proportions expressed in percentages was calculated using the N-1 Chi-squared test and Fisher's exact test with sample size <5, with a 95% confidence interval. A p value <0.05 was considered statistically significant. Data analysis was performed using Microsoft Excel inbuilt statistical functions.

RESULTS

Demographics

Data from 135 patients met eligibility criteria and were included from the 378 clinic files reviewed. The mean age of the children at the initial NDC appointment was 43.04 months (3.6 years, range 13–61 months) and the majority of the children were male (107, 79.3%). Mean

age of the study sample at the time of data collection was 103.6 months (8.6 years). The distribution of race was Black (123, 91.1%); White (6, 4.4%); mixed race (4, 2.9%) and Indian (2, 1.4%). Data was sorted according to age categories spanning 12 months, the majority of males were in the ≥36–47 months age category and females in the younger ≥24–35-month age category (Figure 1). Although the number of children per category is small, a significantly higher proportion of females were in the younger, 24–35 months, age category (p = 0.0001) (Figure 1).

Head circumference measurements

HC measurements were categorised according to SD from the mean HC for age. Only 37.8% (n = 51) of the HC measurements fell within one SD above or below the mean for age. Just over half (51.85 %, 70/135) of the sample population's HC measurements were categorised as greater than 1 SD above the mean and of these 22.2% (30/135) met the criteria for macrocephaly (≥2 SD above the mean for age). No children aged 12-23 months had macrocephaly. Few children in the sample population, 14/135 (10.37%), had a HC more than 1 SD below the mean for age and only 4 (3.0%) children were categorised as having microcephaly (≤2 SD below the mean for age). More children were likely to have a HC greater than 1 SD above the mean for age (p = 0.055). Table 1 details HC measurement categories above and below the mean for males and females. Although groups are small, there was no significant sex distribution in children with macrocephaly.

The WHO reference population HC measurement norms allow for 3.13% of children aged 0-5 years without comorbidities to have macrocephaly. In our sample of children diagnosed with ASD, 22.2% (30/135) had a HC measurement which classified the child as macrocephalic for age. A greater proportion of the study sample had macrocephaly as compared with the WHO reference norms (z-test value 9.85) thus rejecting the null hypothesis. Similar results were found with the z-test for males and females – z-test value 7.95, critical value 1.65; and z-test value 6.10, critical value 1.65, respectively – therefore rejecting the null hypothesis and indicating a greater proportion of the sample patients to have macrocephaly compared with the WHO reference norms. Mean HC measurements of the sample population compared with the WHO reference norms, stratified by age group and sex are shown in Table 2. Male children in our sample between the ages of 36–59 months had significantly greater mean HC values than the expected norm. Similarly, mean HC values for females 24–35 months and 48–59 months of age significantly exceeded the reference norm.

ASD Severity

The majority of the sample population had an ASD severity level of 2 (45.19%) or 3 (46.67%) and only 11 children (8.15%) were classified with an ASD severity level of 1. Severity level did not differ significantly between male and female children. A macrocephalic HC measurement was most commonly recorded in children

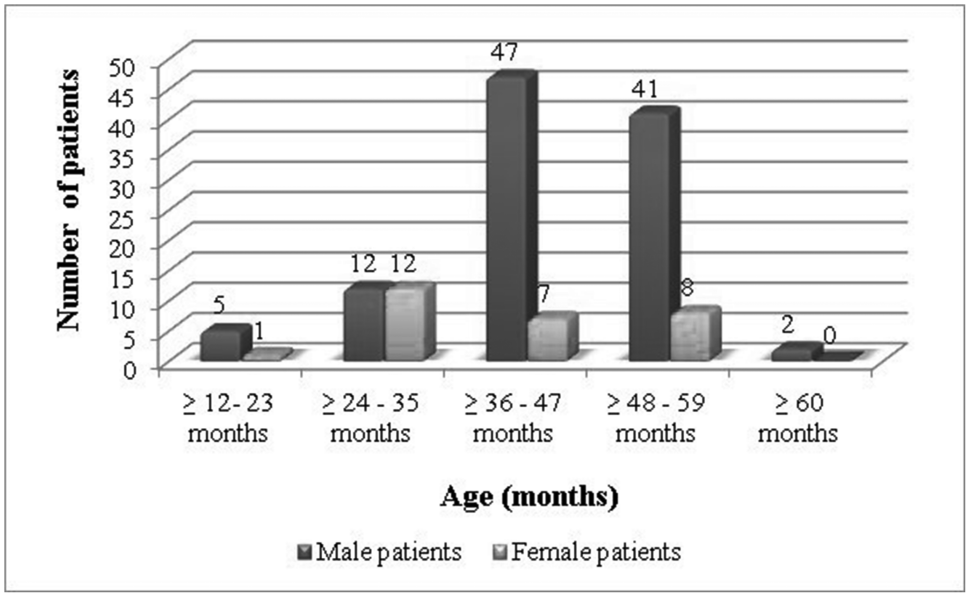

Figure 1: Age category distribution of male and female children attending the Neurodevelopmental Clinic diagnosed with Autism Spectrum Disorder

Table 1: Head circumference measurement distribution according to the standard deviation above and below the mean according to sex

	Total N = 135	Male N = 107	Female N = 28	P value
Age, mean (SD), months	43.04 (10.36)	43.89 (10.05)	39.79 (10.84)	0.0608
Age categories, N (%)				
12–23	6 (4.44)	5 (4.67)	1 (0.74)	0.3380
24–35	24 (17.78)	12 (11.21)	12 (42.86)	0.0001
36–47	54 (40)	47 (43.93)	7 (25)	0.0697
48–59	49 (36.30)	41 (38.32)	8 (28.57)	0.3413
>60	2 (1.48)	2 (1.87)	0	0.4676
HC within 1 SD of the mean, n (%)	51 (37.8)	37 (34.58)	14 (50.0)	0.1340
HC greater than the mean for age, n (%) <2 SD ≥2 to ≤3 SD ≥3 SD	40 (29.63) 15 (11.11) 15 (11.11)	35 (32.71) 13 (12.15) 9 (8.41)	5 (17.86) 2 (7.14) 6 (21.43)	0.055
HC less than the mean for age, n (%) 1- <2 SD 2- <3 SD	10 (7.41) 4 (2.96)	9 (8.41) 4 (3.74)	1 (3.57) 0	
Macrocephaly (≥2 SD above the mean for age, n (%)	30 (22.22)	22 (20.56)	8 (28.57)	0.3640
Microcephaly (≥2 SD below the mean for age), n (%)	4 (3.0)	4 (100)	0	

Table 2: Mean head circumference values of the sample population compared to the WHO reference population, stratified by age group and sex

Mean Head Circumference for Age								
	Male				Female			
Age category (months)	**N**	**Study population**	***Reference population**	**P value****	**N**	**Study population**	***Reference population**	**P value****
12–23	5	46.10	46.94	0.3148	1	48.20	45.80	#
24–35	12	50.21	49	0.2001	12	49.54	48	**0.0245**
36–47	47	51.28	49.77	**0.0001**	7	49.67	48.85	0.3636
48–59	41	51.99	50.41	**0.0001**	8	52	49.55	**0.0331**
≥60	2	53	50.74	#	0	No data	49.93	#

*Reference population taken from World Health Organization norms
**Single sample T-Test
unable to calculate due to small sample size

with ASD severity level 2 (31.2%), although there was no statistical significant difference between the three severity level groupings and the presence of macrocephaly (p = 0.068) (Table 3). In children presenting with a more severe level of impairment, ASD level 2 or 3, macrocephaly was more likely to be recorded in those diagnosed with a severity level of 2 (OR 2.4, 95%CI, p = 0.048). Significantly more comorbid conditions had been diagnosed in children with increasing ASD severity levels (p = 0.022).

Comorbidities

ASD was the primary diagnosis in all the patient records included in this analysis and a maximum of two comorbidities were recorded per patient. A total of 11 different comorbidities were identified among the 135 patients; including Attention Deficit Hyperactivity Disorder (ADHD), anxiety, asthma, chromosomal abnormalities, developmental delay, epilepsy, hyperactivity, intellectual disability (ID), language impairment and otitis media. Just less than one third of patients had no diagnosed comorbidity (30.4%).

Table 3: ASD severity level stratified by sex, age and the presence of macrocephaly

	ASD level 1 N = 11	ASD level 2 N = 61	ASD level 3 N = 63	P value
Sex, N (%)				
Male	10 (90.91)	49 (80.33)	48 (76.19)	0.5191
Female	1 (9.09)	12 (19.67)	15 (23.81)	
Age categories, N (%)				
12–23	1 (9.09)	5 (8.2)	0	
24–35	1 (9.09)	11 (18.03)	12 (19.05)	0.9438
36–47	5 (45.45)	22 (36.07)	27 (42.86)	
48–59	4 (36.36)	22 (36.07)	23 (36.51)	
>60	0	1 (1.64)	1 (1.59)	
Macrocephaly, N (%)	1 (9.09)	19 (31.15)	10 (15.87)	0.0679
Children diagnosed with comorbidities, N (%)	4 (36.37)	45 (73.77)	48 (76.19)	**0.0220**

The most commonly diagnosed comorbidity in the sample population was (ID) (42.9%) followed by ADHD (27.4%). The least commonly recorded comorbidities were language impairment (n = 1), anxiety (n = 1) and chromosomal abnormality (n = 1). Of the 30 macrocephalic patients, ID (13, 43.3%) and ADHD (9, 30%) were the comorbidities most commonly present.

Special investigations were recorded as having been conducted for 50 (37%) children. These included MRI scans (54%), CT scans (18%) and EEGs (28%). All EEG and CT scan results were within normal limits and only five MRI scans yielded abnormal results. The following abnormalities were identified on MRI: structural malformation of the temporal lobe; venous malformation of the temporal lobe; bilateral hyper-intensity in the posterior deep white matter; periventricular leukomalacia; and supratentorial ventriculomegaly with white matter volume loss and dilated perivascular spaces.

DISCUSSION

This descriptive, cross-sectional analysis of children less than five years of age in whom ASD had been diagnosed, showed 22% as having had a macrocephalic HC measurement at initial presentation to the NDC.

The wide age range of the sample population is ascribed to the variety of ages at which children are referred to the NDC and age at which the ASD diagnosis is made. The social, affective and behavioural nature of ASD makes identifying and diagnosing the condition intricate, multifaceted, resource-intense and time-consuming.(11,12) In a study conducted in a Western Cape Hospital in South Africa, the mean age of diagnosis of ASD was 3.5 years.(2) Similar to our findings, the mean age of ASD diagnosis of children attending a public South African ASD school was 3.9 years.(13) A study from the United Kingdom reported that the median age of diagnosis to be 4 years 7 months, with an interquartile range of 4 years.(14) Several epidemiological studies conducted across the United States of America reported a mean age of diagnosis of ASD between 4 and 5 years of age.(6) There is a dearth of research emanating from Africa surrounding ASD diagnosis, and Abubakar et al. noted in a systematic review that ASD research in Africa has predominantly been undertaken in SA and Nigeria.(15) This paucity of research may be related to the non-existence of ASD screening and diagnostic tools validated in the African context.(15) Contrary to a recent suggestion that ASD can potentially be diagnosed as early as 14 months,(16) in reality diagnosis of ASD this early is extremely difficult. Earlier diagnosis and intervention maximises the benefit of experience-dependent neuroplasticity, resulting in enhanced rates of learning for the child with ASD.(17)

The male predominance of our sample population is in keeping with multiple international findings.(18–21) Springer et al. reported a similar male-to-female ratio in a South African study of 58 children conducted in a NDC setting similar to the one in which our study was conducted.(2)Research exploring the demographics of an ASD population at public and private schools in the Gauteng Province of South Africa reported Black ethnicity as predominant (74.5%) with White (16.2%), mixed race (1.9%) and Indian (6.5%) constituting the remaining ethnicities.(13) Our study showed a similar demographic profile and closely represents the ethnicities present in South Africa.(22) There have been no racial or ethnic differences noted in other ASD prevalence studies.(19)

More than one fifth of our study population had a HC measurement classified as macrocephalic at initial presentation. This is slightly more than the percentage reported in a systematic review and meta-analysis of 27 studies, which reported that 15.7% of ASD individuals had macrocephaly and 9.1% with increased brain volume

on MRI.(23) However, this review included varying age ranges in their samples 2.9 to 33 years, which may have affected their findings as HC measurements in individuals with ASD are no longer different from typically developing peers after the fifth year of life.(24) A South African retrospective record review of 58 mainly pre-school children with ASD reported that 12.1% of the children had macrocephaly at presentation.(2) High prevalence of macrocephaly, up to 25%, have been reported in individuals with ASD.(19) Not only could age ranges affect the abovementioned findings, but small sample sizes too, as highlighted by Dinstein et al.(25) Structural MRI studies investigating total brain volume in children with ASD observed that by 4-5 years of age 15-20% had developed macrocephaly.(8)

Conditions co-existing with ASD have been increasingly recognised due to the DSM-5 now including further specifiers comorbid to ASD.(11) Comparable to findings in our sample population, approximately 45% of individuals with ASD have ID.(19) Data collected from patients with ASD across 11 North American states reported 31% to have concomitant ID varying by sex and ethnicity.(18) Common disorders that may overlap and hence complicate a primary ASD diagnosis are: language disorder, language-based learning disability, nonverbal learning disability, social communication disorder, ADHD and ID.(26) Identifying ADHD as a comorbid condition is crucial as it can feature prominently in ASD and a separate diagnosis assists in highlighting the individual's specific areas of difficulty.(11)

The majority of the special investigations conducted were MRI scans which were reported as showing a range of non-specific abnormalities in five cases. Clinical indication for conducting an MRI is based on signs or other symptomology evident upon neurological examination.(20) In the case of isolated macrocephaly in a child diagnosed with ASD, MRI is not immediately indicated due to the higher prevalence of macrocephaly in this population, whereas an MRI is indicated in microcephaly and developmental regression.(19,20). MRI has assisted greatly in investigating the neurobiology underpinning ASD,(8) however, imaging findings are highly heterogeneous.(20) MRI research in individuals with ASD has contributed to knowledge about the neurobiology, neurocircuitry and atypical cortical development.(8)

Children with moderately-severe and severe ASD are at an increased risk of poor cognitive performance, potentially due to their autistic features.(2) The severity of ASD in an individual should be defined as this can possibly contribute to an increased understanding of the phenotype of ASD.(27) Symptom severity can predict prognosis with less severely affected individuals having a more favourable prognosis.(19) Assessment of severity can also assist in appropriate school placement (13) and the anticipation and management of possible comorbid conditions.

LIMITATIONS

The WHO growth charts, although used throughout the public health sector in SA, are only available for ages 0-5 years old. This subsequently limited the number of patients meeting inclusion criteria for our study which limited the representation of older age groups. The inclusion of a control group and a more thorough data collection tool would allow further investigation into factors that may be specific to the South African population e.g. HIV exposure and infection. Furthermore, collecting additional anthropometric values for height and weight, as well as genetic investigations and findings, could have guided further exploration into HC findings.(28) The WHO reference HC values were obtained from children without obvious neuropsychiatric diagnoses. Thus differences were anticipated when used as comparison for HC measurements from children diagnosed with ASD. Ideally, diagnosis-specific reference norms should be used as comparison.

CONCLUSION

Health care workers, policy-makers, faith healers or traditional practitioners in sub-Saharan Africa have limited knowledge regarding ASD and this impacts negatively on the early identification and appropriate intervention for children presenting with symptoms of ASD. As the reported prevalence of ASD has increased significantly, simple screening tools with the inclusion of HC measurements could assist with early identification and referral. Our study found that routinely measuring and interpreting HC measurements, in individuals suspected of having ASD, can be used as a non-invasive, cost-effective and time-efficient assessment tool to possibly assist in earlier diagnosis and thus prompt early intervention services.

FUNDING ACKNOWLEDGMENT

This research received no grant from any funding agency.

DECLARATION OF CONFLICTING INTERESTS

The authors declares that there no potential, perceived, or real conflict of interest

REFERENCES

1. Franz L, Adewumi K, Chambers N, et al. Providing early detection and early intervention for autism spectrum disorder in South Africa: stakeholder perspectives from the Western Cape province. J Child Adolesc Ment Health. 2018; 30(3):149–165.
2. Springer PE, van Toorn R, Laughton B, Kidd M. Characteristics of children with pervasive developmental disorders attending a developmental clinic in the Western Cape Province, South Africa. S Afr J Child Health. 2013; 7(3):95–99.

3. van Biljon S, Kritzinger A, Geertsema S. A retrospective case report on demographic changes of learners at a school for children with Autism Spectrum Disorders in the Gauteng Province. S Afr J Childhood Educ. 2015; 5:1–26.
4. Bakare MO, Munir KM. Autism spectrum disorders (ASD) in Africa: a perspective. Afr J Psychiatry (Johannesbg). 2011; 14(3):208–210.
5. American Psychiatric Association. Diagnostic and statistical manual of mental sisorders, DSM-5. 5th ed. Washington, DC: Library of Congress Cataloging-in-Publication Data; 2013.
6. Zwaigenbaum L, Bauman ML, Stone WL, et al. Early identification of autism spectrum disorder: recommendations for practice and research. Pediatrics. 2015; 136(Supplement 1):S10–S40.
7. Parellada M, Penzol MJ, Pina L, et al. The neurobiology of autism spectrum disorders. Eur Psychiatry. 2014; 29(1):11–19.
8. Stigler KA, McDonald BC, Anand A, Saykin AJ, McDougle CJ. Structural and functional magnetic resonance imaging of autism spectrum disorders. Brain Res. 2011; 1380:146–161.
9. McKinney ES, James SR, Murray SS, Nelson K, Ashwill J. Maternal-child nursing. Missouri: Elsevier Health Sciences; 2018.
10. World Health Organization. WHO Child Growth Standards – Methods and Development China, Hong Kong: WHO Library Cataloguing-in-Publication Data; 2007 [1–237]. Available from: http://www.who.int/childgrowth/standards/second_set/technical_report_2.pdf?ua=1.
11. Shulman C, Rice CE, Morrier MJ, Esler A. The role of diagnostic instruments in dual and differential diagnosis in autism spectrum disorder across the lifespan. Child Adolesc Psychiatr Clin N Am. 2020; 29(2):275–299.
12. Lemay JF, Yohemas M, Langenberger S. Redesign of the autism spectrum screening and diagnostic process for children aged 12 to 36 months. Paediatr Child Health. 2018; 23(5):308–313.
13. Erasmus S, Kritzinger A, van der Linde J. Profiles of public and private autism-specific schools in Gauteng. S Afr J Child Educ. 2019; 9(1).
14. Brett D, Warnell F, McConachie H, Parr JR. Factors affecting age at ASD diagnosis in UK: no evidence that diagnosis age has decreased between 2004 and 2014. J Autism Dev Disord. 2016; 46(6):1974–1984.
15. Abubakar A, Ssewanyana D, Newton CR. A systematic review of research on autism spectrum disorders in Sub-Saharan Africa. Behav Neurol. 2016; 2016:3501910.
16. Goldson E, Angulo AS, Reynolds A, Raz DM. Child development & behavior. In: Hay Jr WW, Levin MJ, Abzug MJ, Bunik M, editors. Current diagnosis & treatment: pediatrics. 25th ed. New York, NY: McGraw-Hill Education; 2020.
17. Landa RJ. Efficacy of early interventions for infants and young children with, and at risk for, autism spectrum disorders. Int Rev Psychiatry. 2018; 30(1):25–39.
18. Baio J, Wiggins L, Christensen DL, et al. Prevalence of autism spectrum disorder among children aged 8 years – autism and developmental disabilities monitoring network, 11 sites, United States, 2014. MMWR Surveill Summ. 2018; 67(6):1–23.
19. Kliegman RM, Geme JW, Blum NJ et al. Autism spectrum disorder. In: Bridgemohan CF, editor. Nelson textbook of pediatrics. 21st ed. Canada: Elsevier; 2020. 294–302.
20. Hirtz DG, Wagner A, Filipek PA, Sherr EH. Autistic spectrum disorders. In: Swaiman KF, Ashwal S, Ferriero DM, et al., editors. Swaiman's pediatric neurology. 6th ed. Edinburgh: Elsevier; 2017. 1104–1136.
21. Kellerman RD, Rakel D. Autism. In: Brown R, editor. Conn's current therapy 2020. Philadelphia, PA: Elsevier; 2020. 767–770.
22. Lehohla P. Community survey 2016 in brief. In: Africa SS, editor. Pretoria: Stats SA Library Cataloguing-in-Publication (CIP) Data; 2016. 1–192.
23. Sacco R, Gabriele S, Persico AM. Head circumference and brain size in autism spectrum disorder: a systematic review and meta-analysis. Psychiatry Res. 2015; 234(2):239–251.
24. Voigt RG. Introduction to developmental-behavioral pediatrics: pediatric developmental assessment. In: Kline MW, editor. Rudolph's pediatrics. 23rd ed. New York, NY: McGraw-Hill Education; 2018.
25. Dinstein I, Haar S, Atsmon S, Schtaerman H. No evidence of early head circumference enlargements in children later diagnosed with autism in Israel. Mol Autism. 2017; 8(1):15.
26. Voigt RG. Autism spectrum disorder. In: Kline MW, editor. Rudolph's pediatrics. 23rd ed. New York, NY: McGraw-Hill Education; 2018.
27. Franz L, Chambers N, von Isenburg M, de Vries PJ. Autism spectrum disorder in Sub-Saharan Africa: a comprehensive scoping review. Autism Res Off J Int Soc Autism Res. 2017; 10(5):723–749.
28. Amaral DG, Li D, Libero L, et al. In pursuit of neurophenotypes: the consequences of having autism and a big brain. Autism Res. 2017; 10(5):711–722.

zydus
Dedicated To Life

Commercial Head Office
Southdowns Office Park, Building B, G/Floor,
22 Karee street, Centurion, 0157
Postal Address: Suite 100, Private Bag X 32
Highveld Park, 0169
Tel: +27 12 748 6400 Fax +27 12 748 6444
www.zydus.co.za

Dear Healthcare Professional

Zydus Healthcare SA (Pty) Ltd. is proud to announce the launch of **DAGLIF.**



DAGLIF is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

Monotherapy
As an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus.

Add-on combination therapy
In combination with glucose-lowering medicines, including metformin, a thiazolidinedione, a sulphonylurea, a dipeptidyl peptidase 4 (DPP4) inhibitor, or insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Zydus is an innovative global pharmaceutical company that develops, manufactures, and markets a broad range of healthcare products. The Zydus manufacturing facilities are approved by USFDA, MHRA UK, SAHPRA and other regulators. Zydus is dedicated to providing quality and affordable medicine to your patients.

Brand Name	Molecule	Strength	Pack Size	Product Schedule	Presentation	Nappi Codes	Bar Codes	SEP (excl-VAT)	SEP (incl-VAT)
DAGLIF 5	Dapagliflozin	5 mg	30	S4	Tablet	3006119001	6009697620021	R260.87	R300.00
DAGLIF 10	Dapagliflozin	10 mg	30	S4	Tablet	3006122001	6009697620038	R260.87	R300.00

DAGLIF will be available at UPD and your local wholesalers from 16 May 2023.
If further information is required, please refer to the Professional Information Leaflet approved by SAPRHA (3 August 2022).

Yours sincerely,

Rama Subramanian
Country Head

S4 Daglif 5MG 10MG
DAPAGLIFLOZIN



S4 **DAGLIF 5** film-coated tablets. Each film-coated tablet contains 5 mg dapagliflozin. Reg No. A55/21.2/0049
S4 **DAGLIF 10** film-coated tablets. Each film-coated tablet contains 10 mg dapagliflozin. Reg No. A55/21.2/0050

For full prescribing information refer to the approved package insert. Zydus Healthcare SA (Pty) Ltd. Block B, Southdowns Office Park, 22 Karee Street, Centurion, 0157. Tel: +27 (0)12 748 6400.
DAG/04/23.