# The prevalence of Autism Spectrum Disorder in Down Syndrome children attending the Child Development Centre in Universiti Kebangsaan Malaysia Medical Centre

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**ABSTRACT**

**Introduction: The main objective of this study was to determine the prevalence of Autism Spectrum Disorder (ASD) in Down Syndrome (DS) children attending the DS clinic at Child Development Centre Universiti Kebangsaan Malaysia Medical Centre (CDC-UKMMC) and to assess the appropriateness of using an M-CHAT as an ASD screener in this population. We traced the karyotype results of our study population from their medical record and compared this to study participant with a dual diagnosis of Down Syndrome-Autism Spectrum Disorder (DS-ASD). Lastly, we assessed the awareness among parents attending our DS follow up clinic regarding the possibility of an ASD diagnosis in DS children.**

**Materials and Methods: This a single-centre cross-sectional study among DS children aged 18-60 months who attend the DS follow up clinic in UKMMC. Overall, 24 children were recruited to our study. The accompanying parent was given the Modified Checklist for Autism in Toddlers (M-CHAT) questionnaire and a data collection sheet prior to their consultation. The chromosomal study was traced from their medical case notes. Children that were eligible for the study had their development assessed using the tool Schedule of Growing Skills II. The diagnosis of ASD was determined by the attending paediatrician using The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) criteria.**

**Results: The prevalence of dual diagnoses DS-ASD in our study population was 4.2%. Using M-CHAT as a screener, 8 children failed the M-CHAT, of whom only one was diagnosed with ASD. None of the children that passed the M-CHAT was diagnosed with ASD. Only 17 chromosomal study results were available for analysis, 2 children had mosaic DS whereas the remaining was caused by non-disjunction; the only DS-ASD patient had non-disjunction. Regarding parental awareness of dual diagnoses of ASD and DS, about 60% of the parents attending UKMMC clinic were aware of the possibility of ASD-DS diagnosis.**

**Conclusions: Our results suggest that ASD prevalence in our DS study population is consistent with those previously reported, and that paediatricians managing DS children should be aware of the dual diagnoses of ASD and DS when managing these patients. Even though, we are unable to make a definitive conclusion regarding the use of M-CHAT in this population of children due to the very small sample size, possibly a multi-centre research in the future may help elucidate this issue.**

**KEYWORDS:**
*Autism spectrum Autism spectrum disorder, Down syndrome, M-CHAT*

## INTRODUCTION

Down Syndrome (DS) is the most common recognized chromosomal abnormality and is caused by an extra chromosome 21. DS children have classical features and can be confirmed by karyotype studies. The most common karyotype in DS is non-disjunction and this accounts for about 90% of DS children; Robertsonian translocation and mosaic is less common and has been reported to be between 0.7-4% of cases.[1-3] The incidence of DS increases with increasing maternal age. It has a prevalence of 1:700 live birth worldwide.[4] In Malaysia it is reported that the incidence of Down syndrome is 1:860 to 1:981 live birth.[5]

The latest report by the Center of Disease Control and Prevention has reported that the prevalence of Autism Spectrum Disorder (ASD) in the general population surveyed may be as high as 1.8%.[6] It has also been reported that the diagnosis of ASD in children with concurrent chromosomal or genetic abnormality may also be higher.[7] Literature has reported an ASD prevalence in DS children to be between 2-20%.[8-10]

It is assumed that children with DS are generally affectionate and outgoing.[11] Nevertheless, more recent studies have shown that children with DS can have a dual diagnosis of Down Syndrome-Autism Spectrum Disorder (DS-ASD) which may present with behavioural challenges that are not typically associated with DS children. Children with a dual diagnosis tend to have a distinct behavioural symptomatology as compared to children with the diagnosis of ASD alone. Even though there have behavioural challenges, children with DS-ASD were found to have less severe social impairment as compared to children with the diagnosis of ASD in isolation.[12]

Thus, it is not uncommon for the recognition of dual DS-ASD diagnosis to be delayed as professionals may misinterpret their behaviour to be related to the cognitive and language

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delays.[10] Nevertheless, early diagnosis ASD in DS children could improve the developmental outcome and quality of life for families by the provision of appropriate early intervention.[13] Other than that, families have also reported frustrations and confusion when pervasive behaviours are not consistent with the expectation of a DS child.[13] Thus, timely diagnosis of ASD in these children would be beneficial not only to the child but also to their families and the community that supports them.

With these issues in mind, firstly we wanted to determine the prevalence of ASD in children with DS at the Child Development Centre, University Kebangsaan Malaysia Medical Centre (CDC-UKMMC) as well as the appropriateness of using The Modified Checklist for Autism in Toddlers (M-CHAT) in the DS population. M-CHAT is a recommended ASD screener for children 18-30 months which is available in English and its translation into Malay is publicly available.[14-15] We were also interested to determine if a difference exists between DS children with non-disjunction, Robertsonian translocation or mosaic DS and the diagnosis of ASD. Lastly, we wanted to assess the awareness of the parents attending our clinic regarding the possibility of ASD-DS dual diagnosis in their children, as we believe that a greater awareness would assist these children to obtain an earlier diagnosis and in turn access appropriate support and intervention.

## MATERIALS AND METHODS

This was a single-centre cross-sectional study of children with Down Syndrome between 18-60 months old. All children with Down syndrome who agreed to participate in this study seen in CDC-UKMMC from 1 January 2019 until 31 December 2019 were enrolled into the study. Down syndrome children who have moderate to severe hearing or visual impairment after correction with a hearing aid or glasses were excluded in our study. This study received approval from the ethics committee of UKMMC.

There were 68 DS children under follow-up at CDC-UKMMC DS clinic during the study period and 29 children were between 18-60 months old. However, only 24 children were recruited for the study after excluding those that did not agree to participate or did not fulfil the inclusion criteria.

All children and parents who were eligible for the study were given an explanation on their appointment day. One of the parents was requested to complete the M-CHAT form and data collection sheet including questions assessing parental awareness of dual DS-ASD diagnosis. This was followed by a Schedule of Growing Skills II (SGS II) assessment by a trained nurse and an assessment by the attending paediatrician experienced in the diagnosis of ASD. The attending paediatrician would address current medical concerns as well as assess the possibility of a concurrent ASD diagnosis based on the DSM-5 criteria. This includes a comprehensive history taking, physical examination and observation of behaviour during the consultation. Any children with an unclear diagnosis would be discussed and seen in our multidisciplinary clinic. This is a monthly clinic conducted at UKMMC to confirm the diagnosis of children with ambiguous clinical presentation. The professionals involved included a paediatrician, child psychiatrist, child psychologist, occupational therapist, and speech therapist. The karyotype results were traced from the medical records of the patients.

**Instruments**

a) Schedule of Growing Skills II (SGS II):

SGS II is a developmental screening tool that assesses 10 different domains for children below 60 months of age. It is a tool adapted from the United Kingdom (UK).[16] Its purpose is to provide an accurate and reliable method of developmental screening; it is easy to use and requires little training. It is not an in-depth diagnostic tool; however, it does provide pointers to the nature of the child's problem and assesses a child's development at a point of time. Although it is a British-based tool, SGS-II has been found to be a reliable and accurate tool for assessing development in disabled children in the local context based on a working paper by Haironi and Mariah from University Malaysia Sarawak in 2014.[17] In UKMMC, the SGS II assessments are performed by trained CDC clinic nurses prior to consultation with the paediatric medical team.

The SGS-II has 10 domains and is valid for use in children from birth to 60 months of age. The manual defines 'significant delay' as the developmental age being more than one age band below the chronological age.[16] This assessment uses a focused play based approach which includes clear instructions to guide the administration of the assessment activities as well as guide the gathering of specific information from the parent or caregiver.

For data analysis, we used the SGS-II definition of developmental delay.[16] Any children who were more than the one age band below their chronological age was considered to be delayed.

b) M-CHAT screening

M-CHAT is a screening tool for autism that has been translated to Malay and Chinese to be used in the local healthcare population and recommended for use in toddlers aged 18 months up to 30 months of age.[14] It is a 23-item yes/no parent report checklist that is simple and does require any parent training. It is necessary to train health care workers for accurate interpretation of the results.[14] In Malaysia, it is recommended that children are screened with M-CHAT at 18 and 30 months old.

M-CHAT is a screening tool for toddlers aged between 18-24 months. Early referral for possible diagnosis of ASD was initially recommended for any children who failed either 2 critical items or any 3 items in the M-CHAT questionnaire, based on an early study in 2001 which reported a sensitivity of 0.87 and a specificity of 0.95.[18] In current years, the scoring method has been updated and it is currently recommended that children with a total score of 3 – 6 should have a M-CHAT Follow-Up (M-CHAT/F) administered. A persistent score above the cut of point 3 is able to identify screen positive children, while those with a cut of point of 7 should be referred for evaluation without the need for further M-CHAT/F administration as an additional follow up with a M-CHAT/F will not alter the specificity or sensitivity of the screening test.[19] The positive predictive value in toddlers aged 16-30 months indicates that 54% of children who screen

**Table I: Demographic data**

| | Mean (SD) |
|---|---|
| Age at SGS II and MCHAT administration (months) | 46.2 (10.1) |
| Father's age (years) | 38 (5.5) |
| Mother's age (years) | 37.9 (5.5) |
| Mother's age at delivery (years) | 33.5 (5.1) |
| | **n (%)** |
| Gender | |
| Male | 16 (66.7%) |
| Female | 8 (33.3%) |
| Race | |
| Malay | 21 (87.5%) |
| Chinese | 3 (12.5%) |
| Indian / Others | 0 |
| **Parent's education level** | **n (%)** |
| Father | |
| Secondary education | 11 (45.8) |
| Post-secondary vocational certificate | 1 (4.2) |
| Tertiary education | 11 (45.8) |
| Not available | 1 (4.2) |
| Mother | |
| Secondary education | 8(33.3) |
| Post-secondary vocational certificate | 1 (4.2) |
| Tertiary education | 15 (62.5) |

**Table II: M-CHAT results vs. SGS II results**

| Developmental domain | M-CHAT score 0-2 n (%) | M-CHAT score>3 n (%) |
|---|---|---|
| Locomotor | | |
| Delay | 13 (54) | 7 (29) |
| No delay | 4 (17) | 0 (0) |
| Manipulative | | |
| Delay | 11 (46) | 6 (25) |
| No delay | 6 (25) | 1 (4) |
| Visual | | |
| Delay | 11 (46) | 6 (25) |
| No delay | 6 (25) | 1 (4) |
| Hearing & language | | |
| Delay | 15 (63) | 6 (25) |
| No delay | 2 (8) | 1 (4) |
| Speech & Language | | |
| Delay | 17 (71) | 7 (29) |
| No delay | 0 | 0 |
| Social interaction | | |
| Delay | 8 (33) | 5 (21) |
| No delay | 9 (38) | 2 (8) |
| Selfcare | | |
| Delay | 8 (33) | 5 (21) |
| No delay | 9 (38) | 2 (8) |
| Cognitive | | |
| Delay | 16 (67) | 7 (29) |
| No delay | 1 (4) | 0 (0) |

positive on a 2-staged M-CHAT (M-CHAT and M-CHAT/F) are likely to have ASD and 98% of these toddlers will have clinically significant developmental concern.[20]

M-CHAT has also been used among cognitively impaired pre-school children aged between 16-48 months and M-CHAT has positive predictive value of 60%-80% in this population.[21-22] The same tool has also been used specifically in children with DS, it was found to be a sensitive screening tool, however it's specificity is low for ASD.[9]

**ASD diagnosis**

The diagnosis of ASD was based on clinical judgement of the attending paediatrician based on The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria.[23] All children who came for follow up were seen by paediatricians experienced with the diagnosis of ASD. Any cases that had an unclear diagnosis were discussed with other members of the child development team.

Clinical diagnosis of ASD based on DSM-IV, DSM-5 and clinical judgment by an experienced clinician in children as young as 16 months is stable over time in 84% of cases. In

our study, all cases were diagnosed by experienced paediatricians and any unclear diagnosis discussed between the professionals and consensus reached. Diagnostic stability is highest when clinical judgment is combined with multidisciplinary team assessment.[24]

**Data analysis**

The results were analysed using the Statistical Package for Social Science (SPSS) version 20. Descriptive statistics was used. For continuous or linear data, we presented the results in mean and standard deviation, and for categorical data we presented the results in percentages.

## RESULTS

The demographic data is presented in table I. The participants in our study were between 18 to 60 months old and approximately two thirds were between 37 to 60 months old. The majority of our study population were boys (66.7%). Overall, 67% of mothers in our study had tertiary education, compared to 45.8% of fathers, and the mean parental age for both were similar.

Out of 24 subjects in our study, only one patient with DS was diagnosed with ASD using DSM-5 criteria.

In our sample, 15 of our children had karyotype study results consistent with non-disjunction DS, whereas 2 had mosaic DS. There were no study participants who had Robertsonian translocation. Results of 7 participants were unavailable.
We found that most children with DS have delay in their language and cognitive development which is not congruent with their social interactive developmental attainment. There was no difference in the developmental profile of DS children with non-disjunction as compared to those with the mosaic karyotype.

Using M-CHAT as a screening tool, 7 children failed the M-CHAT with a total score of 3 or more, and only one of them fulfilled the criteria for ASD diagnosis. None of the children who passed the M-CHAT were diagnosed with ASD, 5 of the children had an M-CHAT score of 0, while another 12 of them had a total score between 1-2.

When the M-CHAT scores were compared against the SGS II score, there was no statistical correlation between the two. However, it was noticed that approximately half of the children who were delayed passed the M-CHAT with a total score of 2 or less. This result is shown in table II.

In general, we found that the children who failed the M-CHAT had relatively lower cognitive scores compared to the other study subjects. Out of the 7 children who failed the M-CHAT, 6 had cognitive scores equivalent to a child younger than 18 months at the point of M-CHAT administration.

The one child with DS from our study who was diagnosed with ASD had severe developmental delay across all domains. He was 37 months; however, his cognitive age was equivalent to a child of 8 months old on the SGS II assessment.

15 out of 24 (62.5%) parents were aware of the presence of dual diagnosis in children. Seven of them received information from their local parent support group, 3 of them from their own reading either via the internet, books, or magazine and only 3 of them received information during follow up from their health care provider and 2 respondents did not answer the question regarding the source of information.

## DISCUSSION

In our sample of children only 1 out of 24 was confirmed to have ASD. This small sample size limited our ability to calculate the true prevalence of DS-ASD diagnosis in our study. Review of literature has reported a higher prevalence of ASD in the DS population. The prevalence of ASD in DS children are reported to be between 2-20%.[8-10] The variation in prevalence is partly attributed to use of different study populations, various methodologies and different diagnostic tools.

The developmental screening done in our sample showed that these children had comparatively better social and interactive skills as compared to their language and cognitive developmental domain. This is consistent with literature whereby DS children are generally known to be more sociable and tend to have joint attention that is comparative to typically developing children with the same developmental level, even though the majority of these children have severe delay in language development.[25-29] In addition to language delay, mild to moderate intellectual disability is also prevalent in DS children.[30] Most publications report that children with a dual DS-ASD diagnosis tend to have the lowest cognitive score.[25,31] However, children at all intellectual levels are also at risk of ASD.[32-33] The only child in our study who had a confirmatory diagnosis of ASD was the child with the lowest cognitive score.

M-CHAT has been used in both level 1 screening in a primary care setting as well as a level 2 screening for children with underlying developmental delay or other chromosomal abnormality.[9,34,35] It is a sensitive tool for detecting autism, but specificity is low in children with underlying developmental delay.[9,22] This seems consistent with our sample, whereby, approximately 70% of our children passed the M-CHAT screening despite their developmental delay and only 1 out of the 7 children who failed the M-CHAT screening was diagnosed with ASD. More recent publications have suggested the use of a follow-up telephone interview to reduce the false positive rate of M-CHAT.[18,20,34]

Two out of 17 (11%) children in our sample had mosaic DS. In a Malaysian study on karyotype characteristics of DS children, the percentage of mosaicism was reported as 4.7%.[2] Our findings were higher than expected, however, due to the small sample size, it may not reflect true population prevalence. It is believed that the higher number of abnormal cells will result in a greater manifestation of DS traits and a majority but not all of the studies report a higher IQ in children with mosaic DS as compared to their non-mosaic counterpart.[3,36] We postulated that children with mosaic DS may be less likely to have ASD symptoms and better

developmental outcomes. In our sample we did not find any difference in the cognitive and developmental profiles of children with mosaic DS as compared to their non-mosaic counterpart, and none of the mosaic DS children was diagnosed with ASD. This result is not surprising as ASD is a complex collection of symptoms with varying aetiology and the genetic abnormalities may not be able to be detected at a basic karyotype level.

When parental awareness of dual DS-ASD diagnosis was assessed, more than half of the parents in our study were aware of this possibility. Surprisingly only 3 parents in our sample reported receiving information from a health care professional, and instead most of them received information from their local support group. Even though the numbers were too small to be of statistical significance, this is an important reminder for health care professionals managing children with DS to be aware of the possibility of a dual diagnosis. The same message is also echoed in other previously published reports.[37-38] Previous studies have also supported the importance of parental support groups for the empowerment of parents and to promote better outcomes in children with DS.[39]

In our study, there are a few limitations. Our study was a single centre study, and the sample size was small thus this may not reflect the general population. The diagnosis of ASD was based on clinical judgement and DSM 5 criteria alone without the use of diagnostic tools due to resource and time limitations. Future studies should consider the use of standardized tools for diagnosis of ASD in the study design. In addition, we used SGS II, a developmental screener for assessment of our participant's developmental level. We recognize that a developmental screener can only give a brief snap-shot of child's developmental level and is not equivalent to other diagnostic developmental assessment tools, which can give a more thorough and in-depth assessment of a child. However, this tool was chosen in our study due to the resources available to us at that time. However, we found that using SGS II as a tool had benefits, including ease of administration, accessibility and convenience in our local setting as well as a simple result display that is beneficial to aid families to understand developmental concerns of their child and areas that require more attention. This may be a reasonable alternative in resource-limited settings. Despite these limitations, we believe this preliminary data could create greater awareness amongst clinicians managing DS children and encourage future studies to be done in collaboration with other institutions.

## CONCLUSIONS

We would like to highlight that ASD is not uncommon in the DS population and thus it is important to improve the awareness amongst clinicians and professionals who are serving them. Even though, we are unable to make a definitive conclusion regarding the use of M-CHAT in this population of children due to the very small sample size, possibly a multi-centre research in the future may help clarify this issue Lastly, professionals managing children with DS should routinely discuss possibilities of comorbidities and dual diagnosis such as ASD with parents and empower them to seek support from relevant health professionals as well as local parent support groups.

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