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Title: **High rates of autism spectrum disorders (ASD) on the Avalon Peninsula, Newfoundland and Labrador, Canada**

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Abstract

INTRODUCTION: Recent studies report increases in the prevalence of Autism Spectrum Disorders (ASDs) in a number of geographical locations. Our aim was to determine the incidence and prevalence of children diagnosed with ASD, <15 years of age and living on the Avalon Peninsula at the time of diagnosis; and examine their demographic and care characteristics.

METHODS: Retrospective and prospective data was obtained from a patient database developed by the *Department of Child Development* in the Janeway Children's Hospital, which contains the identification and specific diagnosis of all children assessed for ASD from 2006 onwards. The cases of ASD were diagnosed by a multidisciplinary team using the Autism Diagnostic Observational Schedule (ADOS).

RESULTS: From 2006 to 2010, 290 children were diagnosis with ASD, averaging 58 new cases per year. The incidence of new cases increased from 10.6 to 17.2 cases per 10 000 from 2006 to 2010. The prevalence in 2010 was 1 in 136 or 73.4 cases/ 10 000. The prevalence among the children aged 4 in 2010 was 1 case of ASD per 78 individuals or 127.4 cases/ 10 000. The median age of diagnosis was 3.84 years (IQR: 2.76 to 6.17).

CONCLUSION: We found higher rates of ASD than had previously been reported for this population. The prevalence of this region is also high when compared to other populations. The high rate of diagnosis supports the need for a provincial ASD registry and comprehensive services for this patient population.

Introduction:

Autism spectrum disorders (ASDs) are a set of neurodevelopmental disorders associated with restrictive / repetitive behaviours and difficulties with verbal and interpersonal communication.[1-2] There is a good deal of variation in the specific symptoms and the severity of symptoms. ASDs are therefore often sub-categorized, including autism disorder, Asperger's syndrome and pervasive developmental disorder - not otherwise specified (PDD-NOS). Fombonne has reviewed 43 prevalence studies of ASD published since 1966 and found the average prevalence of autism was estimated at 20/10,000; for PDD-NOS at 30/10,000; and for all ASD at 60-70/10,000.[3] Other studies have found that boys are more likely than girls to have an ASD, with male-to-female ratios ranging from 2:1 to 6.5:1.[4] A number of studies report the prevalence of ASD is increasing in a number of geographical locations.[5-6] There is much debate, however, about the extent to which these increases are related to actual increased prevalence of the disease or other factors, such as increased awareness of the condition and changes in diagnostic criteria.[7]

While the cause of ASDs are unknown, the etiology appears to be multifactorial,[4] with both environmental factors and a significant genetic component.[8] For example, there is approximately a 5% increased risk of a child having ASD, when there is an older sibling with ASD and even higher when there are already 2 children with ASDs in the family.[9] There have also been a numerous gene defects associated with the condition.[10] The population of Newfoundland's Avalon Peninsula (Canada) has been shown to have a unique genetic make-up related to its founder population, with higher rates of certain conditions with a genetic etiology.[11,12,13] Previous studies looking at this pediatric

population have also found some of the highest global rates of type 1 diabetes mellitus,[14,15] which has been hypothesized to have a possible association to autism.[16] It is useful then to determine the prevalence for ASD in this part of the world. In fact, our study is one of only a few to present ASD prevalence data for any part of the Canadian population,[17,18,19,20,21,22] although work is underway to create a national autism database.[23]

Specifically, our aim was to determine the incidence and prevalence of children diagnosed with ASD living on NL' Avalon Peninsula at the time of diagnosis; and examine characteristics of the children who have been diagnosed. We also examine some of the diagnostic tests and referral pattern of these patients. Next to the unique genetic make-up of this population, the Avalon Peninsula was focused on because it is a well-defined geographic area, which encompasses over 50% of the population of Newfoundland.[24] There is only one pediatric development clinic for the area, to which most children suspected of having an ASD are referred, which assists in the ascertainment of cases. Previous studies examining the prevalence of autism have used various methods of case definition.[25] We ascertained cases of ASD based on a clinical assessment of a multidisciplinary team, in all cases including a developmental pediatrician. Almost all of the cases (98.6%) were confirmed using at least one module of the Autism Diagnostic Observational Schedule (ADOS).[26] In their review of ASD prevalence studies, Elsabbagh et al. found only one other prevalence study that used the ADOS as the primary method of cases ascertainment,[27] which is considered the clinical gold standard for diagnosing ASD.[28] Relying on clinical diagnosis with an ADOS is likely a conservative estimate of prevalence rates, given that many people in the

community with mild forms of ASD or others who do not seek care will not be included. Yet concerns about missed cases are partially mitigated for our population by the fact that all children with suspected ASD who live on the Avalon Peninsula either identified within the education system or by a primary care physician are referred to the Janeway Child Development Clinic for comprehensive assessment and diagnosis. In this way, our study allows for the possibility of capturing a large proportion of children with ASDs requiring clinical supervision for a defined population.

Methods:

This study used data from the Department of Child Development at the Janeway Children's Hospital and Rehabilitation Centre (St. John's, Newfoundland). Cases included were those with a diagnosis of non-syndromic ASD confirmed by a multidisciplinary team and who fit the DSM-IV-TR definition of ASD, age <15 years and living on the Avalon Peninsula, NL at the time of diagnosis. Cases that did not fit the diagnostic criteria as well as those who had been diagnosed with another genetic syndrome that may also have symptoms of ASD were excluded. Patients were all followed for a period within the Department of Child Development, which further alleviated concerns about misdiagnosis, including those related concerns with inaccurate ADOS due to the child having insufficient sleep, suffering another concurrent illness, or because of an apprehensive testing environment.

Cases were identified from two sources. Cases were first identified from an ASD register which was maintained by the Department of Child Development from 2005 onward. We

included all new cases identified from January 1, 2006 to December 31, 2010 to allow for the collection of data for complete years. This list of patients was then compared with the office records of ASD patients maintained by each developmental pediatrician in the Department to identify any discrepancies in order to help ensure that no new cases were missed. A standardized data abstraction form was developed and was piloted on 10 charts. The form was then revised and data was abstracted from the remaining charts. Charts were available for all identified cases.

We first examined the characteristics of new cases, including basic demographic information, categorization of the type of ASD, co-morbidities, what testing was employed to diagnose the condition, and some of the referral patterns of cases. We then calculated incidence by taking the number of new cases diagnosed for each year and dividing them by the population for the region <15 years of age as the population at risk. A mid-point estimate for the population at risk was calculated by averaging the population age 0-14 in 2006 with that population in 2011 based on Canada census data. Finally, we examined the cohort prevalence for all children born in 2006 (age 4 years in 2010). The numerator is all children in this cohort diagnosed with ASD by December 31, 2010, and the denominator is the average of children age 4 and 5 when the 2011 Canada Census was completed during the summer of 2011. The denominator was calculated in this manner as children born in 2006 would have either been 4 or 5 during data collection for the 2011 Canada Census. There were no population estimates available that included information on age and sex at the level of census divisions. Confidence intervals (95%) were generated for prevalence and incidence based on the Poisson error structure.

Descriptive analysis and chi square analysis were performed on other demographic data, using Stata 9 Software [29]. This study was approved by Newfoundland and Labrador's *Health Research Ethics Authority*.

Results:

Between 2006 and 2010, 290 new cases of autism spectrum disorder (ASD) were diagnosed within the study population (*Table 1*). For the new cases, the median age of diagnosis was 3.84 years (IQR: 2.76 to 6.17). Males accounted for 248 out of the 290 cases of ASD, making for a male to female ratio within our study population of 5.9:1. When specific diagnoses were examined, 80 (27.6%) were diagnosed as ASD, 140 (48.3%) as Autistic Disorder, 58 (20%) as Asperger's Disorder, and 12 (4.1%) with Pervasive Developmental Disorder-not otherwise specified. There was no significant variation in specific diagnosis based on year of diagnosis (Chi-squared test; p=0.784). At least one module of the ADOS was completed for 286 of the 290 cases (98.6%). The largest proportion was diagnosed using Module I (121/286; 42.3%). Of those diagnosed, 209 (72.1%) were referred to the Provincial Intensive Applied Behavioural Analysis Program, and 208 (71.7%) were referred for genetics follow-up. Data was collected on possible co-morbidities, however, data was missing on 167 (58%) to 290 (100%) of the cases depending on co-morbidity examined, which precluded meaningful analysis.

The yearly incidence in 2006 was 10.6/10,000 (95% CI: 7.7 to 14.4), increasing to 17.2/10,000 by 2010 (95% CI: 13.3 to 21.8) (*Table 2*). There was a statistically significant difference between the yearly incidence in 2006 compared to 2010 (p=0.01).

Cohort prevalence for children born in 2006 was calculated at the end of 2010, including children between 4 years and less than 5 years old. Out of an estimated cohort of 2668 children based on 2011 Canada census data, 34 of these children were diagnosed with ASD, giving an overall prevalence of 127.4 cases/10 000 or 1 in 78 (95% CI: 1 in 56 to 1 in 113). The cohort prevalence for children aged 4 at the end of 2010 was also calculated based on sex. The cohort prevalence for males was 1 in 44 (95% CI: 1 in 31 to 1 in 65). The cohort prevalence for females was 1 in 431 (95% CI: 1 in 147 to 1 in 2091).

Discussion:

Our study found that there is a high rate of children being diagnosed with autism spectrum disorders within the Avalon Peninsula, NL. The incidence of new cases of ASD identified also increased significantly between 2006 and 2010. Similar to the Autism and Developmental Disabilities Monitoring Network (ADDM) in the United States,[30] we estimate the point prevalence of a particular age cohort. The ADDM uses a survey of a cohort of children age 8 and reported a cohort prevalence of 113/10000 in 2008. Due to the timeline of our study and available data, we used a cohort of children age 4 at the end of 2010. Our cohort prevalence was 127.4/10 000. While both cohorts likely underreport the prevalence of autism, due to the fact that they do not include cases that have not been diagnosed by the age of data capture, by using a younger age cut-off, our study most likely underreports the prevalence to a greater extent. Dodds et al. reported that 58% of ASD diagnosis at a similar pediatric hospital in Halifax, Nova Scotia were at 4 years or younger and that only 12% of children were diagnosed beyond

10 years of age.[28] Our own data also shows that 64.8% of new cases were diagnosed by age 5. It is perhaps reasonable to estimate that the cohort estimate for the population of children born in 2006 in the Avalon Peninsula, NL would be as great as 33% higher than we report as subsequent cases are diagnosed.

Comparing the prevalence rates of our population to prevalence work, the findings for our 4 year cohort (127.4/10 000) were twice as high as the average prevalence reported in a systematic review by Elsabbagh et al. (62/10 000).[25] Of particular interest is work presented by the Ouellette- Kunzt et al., which calculates prevalence rates for the entire province of Newfoundland for some of the same period covered by our study.[22] They follow a 2-year birth cohort, born in 2000-2001, up to 2007. They report prevalence rates for this cohort at 4-5 years of age as 61.8/10,000 and 94.2/10,000 at 6-7 years.
Part of the disconnect could be that the Ouellette- Kunzt et al. use cases ascertained by "agencies that provide services to children with autism," where our study found that only 72.4% of diagnosed cases are reference to the provincial program for services. The extent to which this is the case would have to be determined by comparison of the two data sets. But Dodds et al. reported approximately the same level of correspondence (69.1%) between administrative data capture and clinically diagnosed cases in Nova Scotia. It also points to the difficulty in getting accurate prevalence data and may support the need to recreate a registry from multiple sources in order to ensure that all cases of autism in the region are being captured. Given the genetic make-up of the condition and the fact that only 71.1% of cases were referred to genetics, any attempt to establish a

registry in this region could try to incorporate the capture of genetic information, creating a powerful resource for conducting research in the region.

Study Limitations

While the study does make a contribution to better understanding the prevalence of autism, there are some limitations. Because of the small population studied, changing in the number of new cases identified will have a significant impact on the prevalence rates per 10,000. For both our cohort prevalence and incident rates, we could not ascertain for certain whether we captured all of the cases in the region. Rather we identified only the number of cases that were clinical assessed, so that our numbers are likely serve as a low estimate of the true number of cases in the region. Similarly, as discussed above, the cohort likely significantly underreports the number of cases in the cohort due to the early age of its cut-off. The impact of cases that may be on wait lists for initial clinical assessment also could not be ascertained. Finally, we were not able to capture changes in the underlying population, in terms of emigration and immigrations to the region, which may also impact the calculation of prevalence and incidence.

Conclusion:

ASDs pervades discussion in both the medical literature and public media due to its perceived rising incidence and prevalence, effects it has on the individual and their family, the elusive causes of the disease, as well as the need for proper assessments, diagnosis and supports. These results have significant implications for resource allocation within Newfoundland and Labrador. Resources required for enhance

opportunities for children with ASD extend into both health and education, which are both provincial responsibilities. This study highlights that need to establish an ASD registry for the province as well as the value of a standardized first assessment form for the evaluation of suspected cases of ASD, so that the accurate program planning can be put in place for these patients.

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Tables:

Table 1. Characteristics of cases of ASD diagnosed, ages 0-14 years, living in Avalon Peninsula

Characteristic	Absolute Number (n=290)	Frequency (%)
Sex		
Male	248	85.5
Female	42	14.5
Age at Diagnosis		
0 – <1	0	0
1 - <2	11	3.8
2 - <3	81	27.9
3 - <4	61	21.0
4 – <5	35	12.1
5 - <7	46	15.9
7 - <11	47	16.2
11 - <15	9	3.1
Specific Diagnosis		
ASD	80	27.6
AD	140	48.3
Asperger	58	20
CDD	0	0
PDD-NOS	12	4.1
ADOS		
Yes	286	98.6
No	4	1.4
ADOS Module		
I	121/286	42.3
II	80/286	28
III	85/286	29.7
IV	0	0
Genetics Referral		
Yes	208	71.7
No	1	0.3
Unknown	81	27.9
Neuroimaging		
Yes	94	32.4
No	187	64.5
Unknown	9	3.1
Provinical Autism Program Referral	209	72.4
Yes	77	26.9
No	2	0.7
Unknown		

Table 2: Number of new cases of ASD diagnosed, ages 0-14 years, living in Avalon Peninsula

Year	Number of Cases	Incidence per 10,000 population (95% CI)
2006	42	10.6 (7.7 to 14.4)
2007	56	14.2 (10.7 to 18.4)
2008	57	14.4 (10.9 to 18.7)
2009	67	17.0 (13.1 to 21.5)
2010	68	17.2 (13.3 to 21.8)
Total	**290**	

References:

[1] American Psychiatric Association: "Pervasive developmental disorders" in Diagnostic and statistical manual of mental disorders, Fifth edition. (Washington, DC: American Psychiatric Association, 2014).

[2] Rapin I and Tuchman RF. Autism: Definition, neurobiology, screening, diagnosis. Pediatr Clin N Am. 2008; 55 (5):1129-46.

[3] Fombonne E. Epidemiology of pervasive developmental disorders. Pediatr Res. 2009; 65 (5): 591-8.

[4] Johnson CP, Myers SM, Council on Children with Disabilities. Identification and Evaluation of Children With Autism Spectrum Disorders. Pediatrics. 2007; 120(502):1183-1215.

[5] Coo H, Ouellette-Kuntz H, Lloyd JE, Kasmara L, Holden J, Lewis S. Trends in Autism Prevalence: Diagnostic Substitution Revisited. J Autism Dev Disorder; 2008: 38:1036-1046.

[6] Matson JL, Kozlowski AM. The increasing prevalence of autism spectrum disorder. Research in Autism Spectrum Disorders; 2011 (5): 418-425.

[7] Bryson S. Brief Report: Epidemiology of Autism. J of Autism and Developmental Disorders. 1996; 26 (2): 165 – 168.

[8] Heil K, Schaaf CP. The genetics of autism spectrum disorder – A guide for clinicians. Curr Psychiatry Rep ; 15: 334.

[9] Muhle R, Trentcoste SV, Rapin I. The genetics of autism. Pediatrics. 2004;113(5):e472.

[10] Handrigan GR, Chitayat D, Lionel AC, Pinsk M, Vaags AK, Marshall CR, Dyack S, Escobar LF, Fernandez BA, Stegman JC, Rosenfeld JA, Shaffer LG, Goodenberger M, Hodge JC, Cain JE, Babul-Hirji R, Stavropoulos DJ, Yiu V, Scherer SW, Rosenblum ND. Deletions in 16q24.2 are associated with autism spectrum disorder, intellectual disability and congenital renal malformation. Journal of medical genetics 2013; 50 (3): 163-73.

[11] Sun G, Cahill F, Gulliver W, Yi Y, Xie Y, Bridger T, Pace D, Zhang H: Concordance of BAI and BMI with DXA in the Newfoundland Population. Obesity (Silver Spring). 2013; 21 (3): 499-503. doi: 10.1002/oby.20009.

[12] Mahoney K, Buckley D, Alam M, Penney S, Young TL, Parfrey P, Moore SJ: High incidence of pediatric idiopathic epilepsy is associated with familial and autosomal dominant disease in Eastern Newfoundland. Epilepsy Res. 2012; 98 (2-3): 140-7. doi: 10.1016/j.eplepsyres.2011.09.003.

[13] Eng B, Greenlay B, Waye JS: Characterisation of the British alpha 0-thalassaemia deletion: evidence of a founder effect in Newfoundland, Canada. Br J Haematol. 2009; 147 (1): 150-2. doi: 10.1111/j.1365-2141.2009.07825.x.

[14] Newhook LA, Curtis J, Hagerty D, Grant M, Paterson AD, Crummel C, Bridger T, Parfrey P. High incidence of childhood type 1 diabetes in the Avalon Peninsula, Newfoundland, Canada. Diabetes Care 2004 Apr; 27(4):885-888.

[15] Newhook LA, Penney S, Fiander J, Dowden J. Recent incidence of type 1 diabetes mellitus in children 0--14 years in Newfoundland and Labrador, Canada climbs to over 45/100,000: a retrospective time trend study. BMC Research Notes 2012; 5 (1):628.

[16] Freeman SJ, Roberts W, Daneman D. Type 1 diabetes and autism: is there a link? Diabetes Care. 2005; (4): 925-6.

[17] Bryson SE, Clark BS, Smith IM. First Report of a Canadian Epidemiological Study of Autistic Syndromes. J. Child. Psychol. Psychiatr 1998; 29 (4): 433-445.

[18] Ouellette-Kuntz H, Coo H, Yu CT, Chudley AE, Noonan A, Breitenbach M, et al. Prevalence of pervasive developmental disorders in two Canadian provinces. JPPID 2006; 3 (3):164-72.

[19] Fombonne E., Zakarian R, Bennett A, Meng L, McLean-Heywood D. Pervasive Development Disorders in Montreal, Quebec, Canada: Prevalence and Links with Immunizations. Pediatrics 2006; 118: e139-e151.

[20] Lazoff T, Zhong L, Piperni T, Fombonne E. Prevalence of Pervasive Development Disorders Among Children at the English Montreal School Board. Can J of Psychiatry 2010; 55 (11): 715 – 720.

[21] Ouellette-Kuntz H, Coo H, Lam M, Breitenbach, Hennessey PE, Jackman PD, Lewis S, Dewey D, Bernier FP, Chung AM. The changing prevalence of autism in three regions of Canada. J Autism Dev Disord 2013.

[22] Ouellette-Kuntz H, Coo H, Yu CT, Lewis ME, Dewey D, Hennessey PE, Jackman PD, Breitenbach MM, Holden JJ. Status Report – National Epidemiologic Database for the Study of Autism in Canada (NEDSAC). Chronic Diseases and Injuries in Canada 2012; 32 (2).

[23] Ouellette-Kuntz H, Coo H, Lam M, Breitenbach, Hennessey PE, Jackman PD, Lewis S, Dewey D, Bernier FP, Chung AM. The changing prevalence of autism in three regions of Canada. J Autism Dev Disord 2013.

[24] Newfoundland and Labrador Statistics Agency. Provincial Government of NL. 2006. http://www.stats.gov.nl.ca/Statistics/Census2006.

[25] Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcin C, Montiel-Nava C, Patel V, Paual CS, Wang C, Yasamy MT, Fombonne E. Global Prevalence of Autism and Other Pervasive Development Disorders. Autism Research; 2012; 5:160-179.

[26] Lord C, Rutter M, Goode S, Heemsbergen J, Jorda H, Mawhood L, and Schopler E: Autism Diagnostic Observation Schedule: A Standardized Observation of Communicative and Social Behavior. J of Autism and Dev Dis. 1989; 19 (2): 185 – 212.

[27] Brugha TS, McManus S, Bankart J, Scott F, Purdon S, Smith J, Bebbington P, Jenkins R, Meltzer H. Epidemiology of autism spectrum disorders in adults in the community in England. Arch Gen Psychiatry. 2011 May;68(5):459-65. doi: 10.1001/archgenpsychiatry.2011.38.

[28] Dodds L, Spencer A, Shea S, Fell D, Armson BA, Allen AC and Bryson S. Validity of autism diagnoses using administrative health data. Chronic Dis Can. 2009, 29 (3): 102-107.

[29] StataCorp LP, Texas, USA

[30] CDC. Prevalence of autism spectrum disorders---Autism and Developmental Disabilities Monitoring Network, United States, 2008. In: Surveillance Summaries, March 30, 2012. MMWR;61(No. SS-03):1-19.