Editor's Choice

Prevalence and characteristics of autism spectrum disorders in children with cerebral palsy

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ABBREVIATION
ASD Autism spectrum disorder

AIM To evaluate the prevalence of co-occurring autism spectrum disorders (ASDs) among children with cerebral palsy (CP), and to describe their characteristics.
METHOD The data of 1225 CP cases from four population-based registers (Iceland, Sweden, and two in France) and one population-based surveillance programme (North East England, UK) participating in the Surveillance of Cerebral Palsy in Europe Network (SCPE) were analysed. The ASD diagnoses were systematically recorded using category F84 of the International Classification of Diseases, 10th Revision. The registers provided data on children born between 1995 and 2006, while the cross-sectional survey in the UK concerned children aged 0 to 19 years, registered in 2010.
RESULTS Among the children with CP, 107 had an associated diagnosis of ASD – i.e., 8.7% of the study population (95% confidence interval 7.2–10.5). This proportion varied across centres from 4.0% to 16.7% but was independent of CP prevalence. Male sex, co-occurring epilepsy, intellectual disability, and better walking ability were associated with the coexistence of ASD.
INTERPRETATION Our findings support the need for a multidisciplinary approach to management of children with CP to adequately identify and address all facets of presentation, including ASD.

Perceiving the cerebral palsies as fully belonging to the vast field of developmental disabilities promotes a broader approach to their study, arguing for the need to evaluate other developmental disorders that may co-occur. The term cerebral palsy (CP) covers a group of permanent disorders of movement and posture, and various behavioural, emotional,[1–3] or psychiatric disorders[4–7] have been described among children with CP. Some studies have specifically evaluated the co-occurrence of autism spectrum disorders (ASDs) in these children, showing a higher prevalence than in the general population.[5,8–12] It has been suggested that several developmental disorders including CP, ASD, and also attention-deficit–hyperactivity disorder (ADHD) may share common underlying causes such as perinatal risk factors.[13] Other hypotheses, including recent extensive progress in genomic sequencing, raise the hope of major advances in knowledge of these disorders.[14–16] However, studies on co-occurring conditions are still needed to increase the understanding of the complexity of CP.[17]

Diagnostic practices for ASD have improved in recent decades. Greater attention is given to early signs and practitioners have increased awareness of these disorders. These advances give particular interest to the study of the diagnoses of these disorders in children with CP. A few studies have reported that ASD appeared to be more frequent in children with CP than in the general population, but the proportions varied according to the populations studied (general population of children with CP or not) and according to ASD screening methods (systematic screening or not). Also, very few studies have specifically addressed factors associated with ASD diagnosis in children with CP. One question of interest is whether known risk factors for ASD (perinatal factors, associated syndromes, epilepsy, male sex, or high maternal age) are also relevant for children with CP. Another point concerns intellectual disability that might be particularly associated with ASD in children with CP. For Zwaigenbaum,[18] this strong association raises the question of whether 'ASD and CP co-occur across the clinical continuum of each disorder, or mainly in association with intellectual disability?' Finally, the clinical characteristics of CP (particularly type of CP or severity of motor impairment), which may be

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more frequently associated with an increased risk of ASD, have rarely been studied, and with inconclusive results.

Our first objective was to evaluate the frequency of co-occurring ASD among children and young people with CP using population-based developmental disabilities registers and surveillance programmes in five areas of Europe. We then aimed to determine the effect of known risk factors for ASD in children with CP, whether increased risk of ASD is limited or not to children with intellectual disability, and whether some clinical characteristics of CP are particularly associated with ASD.

METHOD

Four registers (two in France, one in Iceland, and one in Western Sweden) and one population-based surveillance program (in North East England, UK) participating in the Surveillance of Cerebral Palsy in Europe Network (SCPE) took part in the study. Children were included if they fulfilled the definition of CP developed by the SCPE network.[19,20] This definition excludes progressive disorders and isolated hypotonia. We also excluded cases with a postneonatal cause of CP. Children were considered to have ASD if one of the diagnoses of category F84 of the International Classification of Diseases, 10th Revision (ICD-10) was reported in medical records. Table SI (online supporting information) presents the registers or surveillance programs involved, the generations studied, and the methodologies used in each area for case diagnosis and registration. CP prevalence is indicated in each centre, calculated according to the specific modalities of each centre. Each register obtained ethical approval according to current legislation in their country.

The following CP characteristics were considered. CP type was defined according to the SCPE classification.[20] The 'mixed/other' subtype includes cases where no form was predominant, mainly mixed forms with a spastic but non-predominant component. Subtypes were grouped for analysis in two categories: (1) spastic or mixed/other/unknown; (2) non-spastic (dyskinetic or ataxic). Walking ability was measured using a combination of two variables, the Gross Motor Function Classification System[21] (GMFCS) and a walking ability description (when GMFCS was unavailable). Walking ability was grouped in two categories: (1) 'walks independently'; or (2) 'aided, limited, or no walking', including those using hand-held mobility devices. A history of epilepsy was recorded but seizure type was not available. Intellectual disability was defined as IQ lower than 70.

Statistical analysis

To describe the population of each centre, the clinical characteristics corresponding to the variables of interest were presented for each of the centres and compared between them using χ^2 tests. To evaluate the co-occurrence of ASD and CP, the proportions of children with an ASD diagnosis (and 95% confidence intervals [CI] for these proportions) were presented in the same way. The characteristics studied addressed the aims of the study: (1) known ASD risk factors: sex, maternal age, preterm birth, low birthweight, admission to neonatal care unit, epilepsy, congenital malformations, or associated syndromes; (2) impact of concomitant intellectual disability; (3) clinical characteristics of CP which may be more frequently associated with increased risk of ASD: type of CP and severity of motor impairment.

These children's characteristics were compared according to whether they had associated ASD or not using χ^2 or Fisher exact tests, firstly in each centre and then for all the areas together. The effect of the association of each variable with a diagnosis of ASD was quantified by odds ratio (OR) using logistic regressions in each centre and in the pooled data. To determine whether the effect of the association of the different variables with an ASD diagnosis differed according to the centre, we tested for each variable an interaction with the centre in the model including the pooled data. When an interaction was significant, the effect of this variable on ASD diagnosis varied with the centre and the overall effect could not be calculated. When there was no interaction, the result of the pooled data was presented with a global OR (and exact 95% CI). To take into account differences in the distribution of the different variables according to centre, the overall effect was adjusted on the centre (adjusted OR). To examine whether the increased risk of ASD was limited or not to children with intellectual disability, the proportions of children with an ASD diagnosis was also presented according to the presence or not of intellectual disability.

All analyses were performed using STATA/IC statistical software (version 11.1; Stata Corp., College Station, TX, USA).

What this paper adds

- Among the children with cerebral palsy, 8.7% had a co-occurring autism spectrum disorder (ASD) diagnosis.
- Variations between geographical areas: 4.0% to 16.7%.
- Factors associated with ASD were male sex, epilepsy, intellectual disability, and less severe motor impairment.

RESULTS

In total, 1225 children with CP were included in this study (Table SII, online supporting information), of whom 107 (8.7%) had an associated diagnosis of ASD (95% CI 7.2–10.5). The proportion of children with ASD differed significantly across areas ($p<0.001$) from 4.0% for South East France to 16.7% in Iceland.

The characteristics of children with CP included in each area are presented in Table SII. There were significant differences between areas for almost all characteristics. Overall, 14.5% of children had a non-spastic form of CP. Epilepsy was present in 30.5% of children, ranging from 19.5% in the UK to 44.1% in Sweden. On average, 59.7% of children could walk independently and 46.9% had intellectual disability. Perinatal characteristics differed considerably between areas. The proportion of children born preterm (gestational age <37wks) ranged from 28.2% in

North East England to 52.1% in Iceland, and the proportion of children with low birthweight (<2500g) ranged from 36% in Sweden to 55.3% in Iceland. Birthweight was unavailable for North East England.

The characteristics of children with CP with and without associated ASD are described and compared in Table SIII (online supporting information). Results for each variable are presented separately for each area and pooled when there was no significant interaction between variable and area. Interaction with area was significant only for gestational age and birthweight.

Significantly more children diagnosed with ASD were males, with an adjusted OR of 1.8 (95% CI 1.2–2.8). The overall sex ratio was 2.1 for children with ASD, 1.6 among those with associated intellectual disability, and 2.4 among those without associated intellectual disability. No association was observed with maternal age at birth. Regarding perinatal data, the associations with term and birthweight were inconclusive because of a significant interaction (p=0.032 and p=0.006 respectively) of these effects with the areas studied. In Sweden, ASD was significantly associated with preterm birth (OR 2.0, 95% CI 1.0–4.0) and low birthweight (OR 2.3, 95% CI 1.2–4.7), while opposite and also significant results were observed in South West France (preterm birth OR 0.3, 95% CI 0.1–1.0; low birthweight OR 0.3, 95% CI 0.1–0.9). Similar to South West France, non-significant trends were observed in South East France (preterm birth OR 0.5, 95% CI 0.2–1.8; low birthweight OR 0.6, 95% CI 0.2–2.0), North East England (preterm birth OR 0.3, 95% CI 0.1–1.6), and Iceland (low birthweight OR 0.6, 95% CI 0.2–1.6). Malformations or associated syndromes showed no significant interactions with area and no significant associations with ASD.

Epilepsy was significantly associated with ASD (adjusted OR 1.7, 95% CI 1.1–2.5). Intellectual disability was more frequent in children with ASD (63%) than in those without ASD (45.3%; p=0.001). In other words, 6.4% of children with CP and no intellectual disability had co-occurring ASD, while 12.3% of children with intellectual disability had co-occurring ASD. The association with type of CP was not significant overall and no statistically significant interaction with area was found. However, in Sweden, the spastic type of CP was significantly associated with ASD (p=0.023), whereas a reverse but non-significant trend was observed for South East France and Iceland. Walking ability and intellectual disability findings were consistent between areas. Overall, children with CP and ASD showed better walking ability than those without ASD: 69.2% of children with ASD walked independently, compared with 58.8% of children without ASD (p=0.037).

DISCUSSION

In this population-based study, 8.7% of children with CP had an ASD diagnosis with large variations between areas. Male sex, epilepsy, intellectual disability, and better walking ability were associated with ASD. Associations with gestational age and birthweight were inconclusive, with opposite trends depending on area.

The difference in proportion of ASD between areas was marked. This probably reflects differences in the methodologies of the systematic assessment for all children with CP: for some this included systematic and specific screening for ASD; for others, not. It is not surprising that studies using systematic screening for ASD found the highest prevalence, as in Sweden and Iceland. In France, no systematic screening of ASD was done for the generations concerned here but it has been set up for more recent generations of children. Moreover, in France the increased prevalence of ASD in the general population in recent years seems to have been delayed compared with other countries.[22] The impact of this increase among children with CP is not known and we cannot rule out the possibility that the proportion of children with CP and co-occurring ASD may significantly increase among future generations. In North East England the large age range in this cohort may possibly have led to underestimation of ASD diagnosis in very young children, compared with ASD screening which may be done much later in other areas.

Despite these discrepancies, the total proportion of ASD was very similar to published results. In the USA, similar results from the Autism Developmental Disabilities Monitoring (ADDM) network of around 7% to 8% were reported[8,10,12] and were stable over time, while ASD prevalence in the general population increased significantly over the same period. In an Australian cohort of 183 children with CP, 7% had ASD.[16] A previous Swedish study of 186 children with CP found that 6.5% had a neuropsychiatric diagnosis, of which 4.8% had ASD and 1.6% had ADHD,[23] but the ASD diagnoses were not the result of systematic screening. Another Swedish study which systematically screened children with physical disabilities for ASD found a higher proportion of ASD (4/38 children).[11] A Turkish study found 15% of ASD among CP cases.[9] In this study, children were recruited from a clinical sample and had poorer walking ability than our population, although the proportions of children with intellectual disability or epilepsy were similar. The difference in ASD frequency observed between studies would seem to be because of the methodology used to assess ASD, with systematic clinical screening resulting in higher frequencies.

Other studies have analysed mental health and/or psychological problems more generally among children with CP. Some found an increased risk of behavioural problems, particularly ADHD,[4,6] while others described an increased risk of both emotional and behavioural disorders.[1,2,5] An overlap between ASD and ADHD diagnoses has been described,[3,7] as well as with other psychiatric disorders (anxiety disorders, mood disorders).[7] Children with CP seem at increased risk not only of ASD but also of other psychiatric problems, and more generally of emotional and behavioural disorders. We could not evaluate the presence of ADHD or other behavioural and emotional problems in our population. We cannot conclude that the diagnosis of

ASD is more specific and more frequent than other psychiatric disorders among children with CP.

In spite of discrepancies in the proportion of children with ASD, the associated factors were comparable between areas, except for perinatal data. However, we cannot rule out the possible lack of power of interaction tests, as for some variable categories the number of children was relatively small. Factors associated with ASD have rarely been studied among children with CP.

In our sample, male sex was associated with ASD. This trend was observed in three of the areas and reached significance in the pooled analyses. Given the strong association between ASD and male sex among the general population, it may seem surprising that this finding was not reported in other studies of children with CP.[8,9] However, in the latter two studies, ASD also occurred more often among males (Kilincaslan and Mukaddes[9] found that 68% of children with ASD and 58% of children without ASD were males), although this result was not statistically significant. In our study, as observed in the general population, the sex ratio among children with CP and ASD is lower when intellectual disability is associated. Yet, the sex ratio among children without intellectual disability remains much lower than that observed in the general population and the risk of ASD associated with male sex appears to be moderated by the presence of CP, independently of intellectual disability. Concerning epilepsy, the results seem unclear. Some studies have reported that epilepsy was associated with ASD[9] or with behavioural problems[6] among children with CP, but others failed to find such results.[4,8] Discrepancies between results do not seem easily explained by differences in the proportion with epilepsy in the samples studied. To our knowledge, the relationships between ASD and preterm birth or low birthweight among children with CP have never previously been investigated. Unfortunately, our results are inconclusive because of conflicting results observed in different areas. This may be partly due to differences in the proportion of preterm birth or low birthweight in each sample of children with CP. The proportion of preterm or low birthweight children was much lower in Sweden than in South West France, the two areas with clearly opposite trends. On the other hand, the proportion of preterm birth in the North East England sample was even lower than in the Swedish sample, and yet the trend in North East England was the same as in both the French registers. Further analysis, stratified for gestational age and maybe taking into account discrepancies between centres in the follow-up of infants born very preterm, is needed to better understand these associations.

Finally, known risk factors for ASD in the general population such as male sex, high maternal age, perinatal factors, or associated syndromes were not clearly found among our children with CP and, in some centres, preterm birth or birthweight results were the reverse of those expected. The population of children with CP and co-occurring ASD may be different than that of children with ASD only, and deserves to be better assessed.

Few studies have specifically focused on the clinical characteristics associated with ASD among children with CP. It is difficult to determine whether ASD is more common among certain clinical CP categories because symptoms are better identified in these categories, or because of a true association of clinical features. Our findings on walking ability raise the question of whether the risk of ASD is truly increased among children with less severe motor forms of CP because of different causative patterns or whether, more likely, ASD was harder to assess in the group with poorest mobility. Our results regarding type of CP were inconclusive, an association with the spastic form being observed in Sweden only. Results in the literature regarding walking ability are discordant. In line with our results, Kirby et al. clearly found that the proportion of children with co-occurring ASD was greater among those who walked independently[10] and similar results have also been found with behavioural or psychological problems.[1,2] In the study of Christensen et al.,[8] the proportion of children who walked independently was higher among children with ASD (73.9% compared with 57% among children without ASD), but this difference was not significant. However, no relationship with motility impairment was shown by Kilincaslan et al.[9] Children with severe motor impairment more often have impaired communication, which may hamper screening and investigation.

Lastly, intellectual disability is an important factor associated with a higher proportion of ASD in children with CP, as expected. This result has already been described in another study[9] specifically on co-occurring ASD and in several studies on more general psychiatric, behavioural, or psychological problems.[1,2,4,5] In our sample, 6.4% of children with CP without intellectual disability had co-occurring ASD, a proportion obviously higher than in the general population. Thus, one of the implications of our results is that children with CP appear to be at greater risk of ASD than the general population, independently of their level of intellectual functioning.

In conclusion, children with CP are clearly at increased risk of ASD including, to a lesser extent, those without intellectual disability. Practitioners should be aware that all children with CP should specifically be screened for ASD even if those with intellectual impairment seem particularly at risk. Greater attention should also be paid to children with poorest mobility to better ascertain the quality of ASD assessment among this group.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table SI: Descriptive characteristics of the studies involved

Table SII: Descriptive characteristics of the CP cases included

Table SIII: Characteristics of children with CP with (CP+ASD) or without (CP−ASD) associated ASD

REFERENCES

1. Parkes J, White-Koning M, Dickinson HO, et al. Psychological problems in children with cerebral palsy: a cross-sectional European study. *J Child Psychol Psychiatry* 2008; **49**: 405–13.
2. Sigurdardottir S, Indredavik MS, Eiriksdottir A, et al. Behavioural and emotional symptoms of preschool children with cerebral palsy: a population-based study. *Dev Med Child Neurol* 2010; **52**: 1056–61.
3. Suren P, Bakken IJ, Aase H, et al. Autism spectrum disorder, ADHD, epilepsy, and cerebral palsy in Norwegian children. *Pediatrics* 2012; **130**: e152–8.
4. Bjorgaas HM, Hysing M, Elgen I. Psychiatric disorders among children with cerebral palsy at school starting age. *Res Dev Disabil* 2012; **33**: 1287–93.
5. Goodman R, Graham P. Psychiatric problems in children with hemiplegia: cross sectional epidemiological survey. *BMJ* 1996; **312**: 1065–9.
6. Carlsson M, Olsson I, Hagberg G, Beckung E. Behaviour in children with cerebral palsy with and without epilepsy. *Dev Med Child Neurol* 2008; **50**: 784–9.
7. Leyfer OT, Folstein SE, Bacalman S, et al. Comorbid psychiatric disorders in children with autism: interview development and rates of disorders. *J Autism Dev Disord* 2006; **36**: 849–61.
8. Christensen D, Van Naarden Braun K, Doernberg NS, et al. Prevalence of cerebral palsy, co-occurring autism spectrum disorders, and motor functioning – Autism and Developmental Disabilities Monitoring Network, USA, 2008. *Dev Med Child Neurol* 2014; **56**: 59–65.
9. Kilincaslan A, Mukaddes NM. Pervasive developmental disorders in individuals with cerebral palsy. *Dev Med Child Neurol* 2009; **51**: 289–94.
10. Kirby RS, Wingate MS, Van Naarden Braun K, et al. Prevalence and functioning of children with cerebral palsy in four areas of the United States in 2006: a report from the Autism and Developmental Disabilities Monitoring Network. *Res Dev Disabil* 2011; **32**: 462–9.
11. Nordin V, Gillberg C. Autism spectrum disorders in children with physical or mental disability or both. I: clinical and epidemiological aspects. *Dev Med Child Neurol* 1996; **38**: 297–313.
12. Van Naarden Braun K, Christensen D, Doernberg N, et al. Trends in the prevalence of autism spectrum disorder, cerebral palsy, hearing loss, intellectual disability, and vision impairment, metropolitan Atlanta, 1991–2010. *PLoS ONE* 2015; **10**: e0124120.
13. Schieve LA, Tian LH, Rankin K, et al. Population impact of preterm birth and low birth weight on developmental disabilities in US children. *Ann Epidemiol* 2016; **26**: 267–74.
14. Erickson RP. The importance of de novo mutations for pediatric neurological disease – it is not all in utero or birth trauma. *Mutat Res, Rev Mutat Res* 2016; **767**: 42–58.
15. MacLennan AH, Thompson SC, Gecz J. Cerebral palsy: causes, pathways, and the role of genetic variants. *Am J Obstet Gynecol* 2015; **213**: 779–88.
16. McMichael G, Bainbridge MN, Haan E, et al. Whole-exome sequencing points to considerable genetic heterogeneity of cerebral palsy. *Mol Psychiatry* 2015; **20**: 176–82.
17. Gillberg C. The ESSENCE in child psychiatry: early symptomatic syndromes eliciting neurodevelopmental clinical examinations. *Res Dev Disabil* 2010; **31**: 1543–51.
18. Zwaigenbaum L. The intriguing relationship between cerebral palsy and autism. *Dev Med Child Neurol* 2014; **56**: 7–8.
19. Cans C. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). *Dev Med Child Neurol* 2000; **42**: 816–24.
20. Christine C, Dolk H, Platt MJ, et al. Recommendations from the SCPE collaborative group for defining and classifying cerebral palsy. *Dev Med Child Neurol Suppl* 2007; **109**: 35–8.
21. Palisano R, Rosenbaum P, Walter S, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997; **39**: 214–23.
22. van Bakel MM, Delobel-Ayoub M, Cans C, et al. Low but increasing prevalence of autism spectrum disorders in a French area from register-based data. *J Autism Dev Disord* 2015; **45**: 3255–61.
23. Himmelmann K, Uvebrant P. Function and neuroimaging in cerebral palsy: a population-based study. *Dev Med Child Neurol* 2011; **53**: 516–21.