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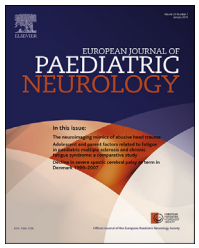

Review article

A systematic review of comorbidity between cerebral palsy, autism spectrum disorders and Attention Deficit Hyperactivity Disorder

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ABSTRACT

Objectives: The aim of this systematic review was to examine the incidence and prevalence of comorbidity between Cerebral Palsy (CP), Autism spectrum disorders (ASDs) and Attention-Deficit/Hyperactivity Disorder (ADHD).

Methods: We searched for articles indexed in PubMed, EBSCOhost, Scopus, Web of Science and other potentially relevant internet sources using a combination of expressions including "cerebral palsy" AND "autism" OR "ASD" OR "pervasive development disorder" AND "Attention Deficit Hyperactivity Disorder" OR "ADHD".

Results: We identified 2542 studies on CP and ASD and 998 studies on CP and ADHD. After screening titles and abstracts and removing duplicated studies, 47 full papers (CP and ASD n = 28; CP and ADHD n = 19) were downloaded and screened for eligibility. Twenty-eight (CP and ASD n = 16; CP and ADHD n = 12) studies were identified in the peer-review literature. Based on this systematic review, ASD and ADHD seem to be more common in people with CP than in the general population, yet the gold standard methods for diagnosing ASD or ADHD are not suitable for children with motor problems.

Conclusions: Assessing the occurrence of ASD and ADHD would improve the significant cost of healthcare, therapies, and overall daily living for families with children affected by CP. However, psychometric studies are needed in the future to promote development of measures suitable for individuals with CP. In addition, this review highlights the paucity of peer-reviewed studies investigating the occurrence of ASD and ADHD in children with different CP subtypes or functional abilities, and there are still some open questions about pathogenic mechanisms common to CP, ASD and ADHD.

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1. Introduction

Cerebral Palsy (CP) is a group of lifelong neurological disorders and a major cause of childhood disability. According to previous population-based studies from countries around the world, prevalence estimates for CP range from 1.5 to more than 4 per 1000 live births or children of a defined age range.[1–3]

The Executive Committee on the Definition and Classification of Cerebral Palsy delineated the definition of this disorder with the intent of providing a common conceptualization of this clinical entity for use by a broad international audience.[4] CP was defined as a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.[4] The prevailing trend in clinical practice is to classify CP by functional independence in terms of gross motor function, fine motor function, and communication abilities through the Gross Motor Function Classification System (GMFCS),[5] the Manual Abilities Classification System (MACS),[6] and the Communication Function Classification System (CFCS).[7] These measures were designed to better delineate the functional profile of children with CP by focusing on activity and participation levels.[8]

Motor disorders in CP are often associated with disturbances of sensation, perception, cognition, communication, behavior, and epilepsy.[1,9] In addition, a recent systematic review and meta-analysis showed increased risk rates for emotional lability, irritability, impulsiveness and behavioral problems in people with CP.[10] All these conditions are a wide range of common disorders that may be associated with other Neurodevelopmental Disorders (NDDs) such as Attention Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum disorder (ASD), Learning Disabilities (LD), Intellectual Disability (ID), Speech and Language Delay, Developmental Delay (DD), and Developmental Coordination Disorder (DCD).[11,12] Indeed, comorbidity with other NDDs could directly or indirectly influence habilitation and rehabilitation of children or adults with CP. For this reason, it is very important to establish the impact of comorbidities in CP patients in order to promote their adjustment and participation as well as subjective and relational well-being. Currently, there is an unambiguous link between CP and other NDDs.[13] Based on previous studies, the same genetic risk factors could underlie different pathological phenotypes.[13,14] Yet, similar phenotypes could have different genetic risk factors.[13,15] Therefore, many NDDs – rather than being distinct conditions – may be part of a continuum of clinical expression. As suggested by Zwaigenbaum, injury-related processes versus genetically influenced developmental processes in the comorbidity between CP and other NDDs remain an interesting and challenging question.[16] Further studies on comorbid conditions are needed to increase our understanding of the complexity of CP.

Recently, the National Institute for Health and Care Excellence (NICE) Guideline on diagnosing, assessing and managing CP[17] underlined the importance of investigating the prevalence of ASD and ADHD in children and young people with CP. According to the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5), the diagnosis of ASD relies on persisting deficits of social communication and interaction and restricted and repetitive behaviors, interests, activities, while ADHD is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity interfering with functioning or development.[18] ASD and ADHD are common NDDs in the pediatric population with a prevalence of 1% and 5%, respectively.[18] Recent studies on epidemiological, clinical, neuroimaging and biological risk factors showed high rates of comorbidity and support several overlapping traits between ASD and ADHD.[19–21] Furthermore, given the link between mental and physical health, detection and

management of specific comorbid diagnoses such as ASD and ADHD could improve planning for service and treatment of people with CP. The main aim of this systematic review was to explore the relationship between CP, ASD and ADHD and to investigate how these disorders overlap. This review starts with a discussion of the incidence and prevalence of CP and ASD and then presents research findings focusing on the incidence and prevalence of CP and ADHD.

2. Methods

2.1. Study selection and data collection

PRISMA guidelines were followed.[22] The search strategy included research databases such as PubMed, Scopus, Web of Science, EBSCOhost and other potentially relevant internet sources such as Google®. All database searches were performed on January 6th, 2018 using a combination of the following free-text terms: "cerebral palsy" AND "autism" OR "ASD" OR "pervasive development disorder" AND "Attention Deficit Hyperactivity Disorder" OR "ADHD".

After this initial literature search, each single study title and abstract was screened by the first author. All references with duplicate data were excluded. Based on eligibility criteria, two reviewers (FC and RS) independently screened an abstract of available citations to identify potentially eligible studies. The full text of all potentially relevant studies was subsequently retrieved and further examined for eligibility. All references included in the papers identified as relevant from the database search were also examined for possible inclusion in this review. Data were extracted independently by two authors (FC and RS) and disagreements were resolved by negotiation with a third author (AT). Agreement as to whether or not the study met the inclusion criteria was 100%.

2.2. Eligibility criteria

All the studies included in this review met the following five criteria: They 1) investigated the prevalence of ASD in CP or vice versa; 2) investigated the prevalence of ADHD in CP or vice versa; 3) enrolled children, adolescents and young adults (18–35 years); 4) were published in English; and 5) were published in peer-reviewed journals. No restrictions were placed on the date of publication. Review articles and single clinical reports were excluded.

2.3. Data extraction

Studies meeting the inclusion criteria were summarized in terms of: I) type of study; II) number of participants (sample size); III) diagnosis-related groups; III) country of data collection; IV) participants' age; V) diagnostic criteria and assessment tools; VI) rates of comorbidity.

3. Results

We identified 2542 studies on CP and ASD (PubMed n = 817, Scopus n = 840, Web of Science n = 738, EBSCOhost n = 120, and other sources n = 27) and 998 studies on CP and ADHD (PubMed n = 425, Scopus n = 265, Web of Science n = 184, EBSCOhost n = 108, and other sources n = 17). The screening phase involved the examination of titles and abstracts of all identified studies. 2411 studies (CP and ASD n = 1639; CP and ADHD n = 772) were excluded as they were not deemed suitable. After adjusting for duplicates, 533 studies on CP and ASD and 135 studies on CP and ADHD were screened to identify potentially eligible studies. 47 studies (CP and ASD n = 28; CP and ADHD n = 19) were selected for the eligibility phase. Out of these, 12 studies on CP and ASD and 7 studies on CP and ADHD were excluded as they did not provide sufficient data on ASD or ADHD in children or young people with CP. Following this, 16 empirical studies on CP and ASD and 12 empirical studies on CP and ADHD fully met the previously stipulated eligibility criteria for inclusion in the systematic review process. The PRISMA flow diagram (Fig. 1) provides more detailed information on the study selection process.

3.1. Study characteristics

The main methodological features and general characteristics of all reviewed studies are summarized in Tables 1 and 2.

3.2. Countries of data collection

Studies on the co-occurrence of CP and ASD were conducted in the United Kingdom (n = 4), Sweden (n = 7); Turkey (n = 2); Finland (n = 1); United States of America (n = 3), Iceland (n = 1) and France (n = 1).

Studies on the co-occurrence of CP and ADHD were carried out in the United States of America (n = 3), United Kingdom (n = 1); Israel (n = 3); England (n = 1), Sweden (n = 1), Northern Ireland (n = 1), France (n = 1), Ireland, Italy (n = 1), Denmark (n = 2), Iceland (n = 1), Canada (n = 1), and Norway (n = 1).

3.3. Characteristics of participants

The reviewed studies included 5050 participants with a primary diagnosis of CP or ASD, and none of them included participants with a primary diagnosis of ADHD. Studies focusing on ASD in children or young people with CP involved 2770 children or young people (age range: 0–19 years) with CP, of whom 240 (8.7%) met the criteria for ASD. Studies focusing on the co-occurrence of CP in populations with ASD or Pervasive Developmental Disorders (PDDs) involved 485 children or adolescents (age range: 2–18 years) with ASD, 23 (4.7%) of whom met the criteria for CP.

Studies evaluating the co-occurrence of CP and ADHD involved 1795 children or adolescents (age range: 1.8–20 years) with CP, 399 (22%) of whom met the criteria for ADHD.

3.4. Diagnostic criteria and assessment tools

NDDs can potentially be assessed both categorically and dimensionally. We found a multiplicity of assessment tools for ASD or ADHD in children and young people with CP. Thirteen studies used a categorical approach based on the DSM (n = 12) or the International Classification of Diseases (ICD; n = 2) to define ASD (n = 10) or ADHD (n = 4). One of these

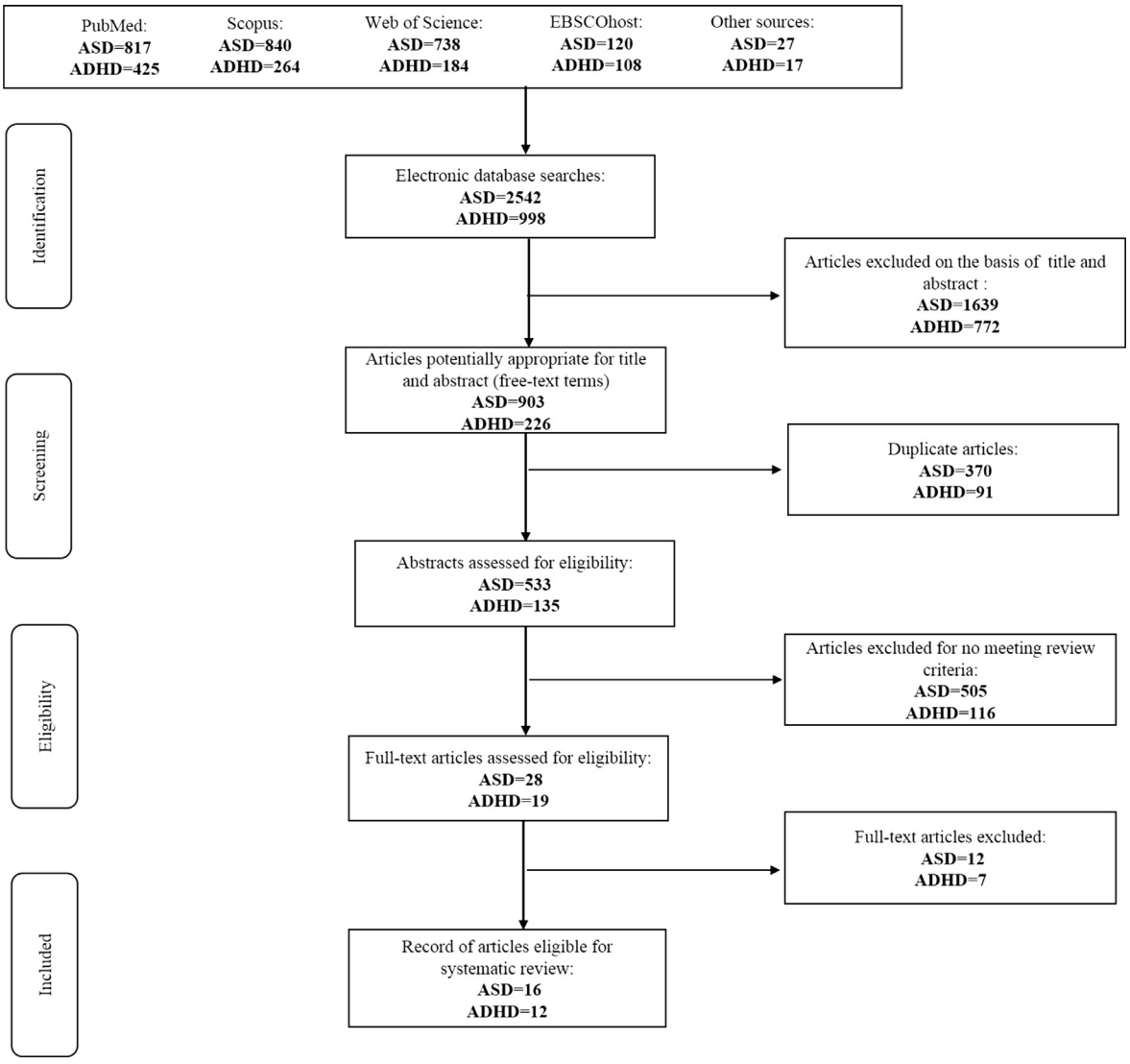

Fig. 1 – The PRISMA flow diagram provides more detailed information regarding the selection process of studies.

studies used both DSM and ICD. The gold standards for the diagnosis of ASD were used in five studies, four of which used the Autism Diagnostic Interview – Revised (ADI-R)[23] and one used the Autism Diagnostic Observation Schedule (ADOS).[24] Eight studies used a dimensional approach to the diagnosis of ASD. The Autism Behavior Checklist (ABC)[25] was used in five studies, the Childhood Autism Rating Scale (CARS)[26] was used in three studies and the Strength and Difficulties Questionnaire (SDQ),[27] the Social Communication Questionnaire (SCQ),[28] and the Questionnaire measures of psychiatric caseness[29] were used in three studies separately.

Six studies used a dimensional approach to the diagnosis of ADHD. The Conners' Rating Scale (CRS)[30] was used in three studies, the SDQ was used in two studies, and the Child Behavior Checklist (CBCL)[31] and the Teacher's Report Form (TRF)[32] were used in one study. The Behavior Problem Index (BPI),[33] the Rutter questionnaires,[34] the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)[35] and the Test of Everyday Attention for Children (TEA-Ch)[36] were used in four studies separately.

The functional levels measured by GMFCS were provided in eight studies (CP and ASD n = 4; CP and ADHD n = 4), while only one study measured fine motor function in children with CP by MACS.

3.5. *Comorbidity of CP and ASD*

Sixteen studies were eligible for inclusion. The literature review revealed two groups of studies on the co-occurrence of CP and ASD. The first group comprises twelve studies focusing on ASD in children or young people with CP. In 1996, Goodman & Graham found that 4 (3%) out of 149 hemiplegic children had ASD and suggested that this rate was ten times higher than in the general population.[29] One hundred seventy-seven children were screened for autistic-type symptoms by Nordin and Gillberg and ASD was found in 4 (10.5%) of the 38 children with CP.[37] Of these, two children had an autistic disorder, one had an autistic-like condition and one had PDD-NOS. Ek et al. recruited 29 Swedish children diagnosed with blindness due to bilateral retinopathy of prematurity (ROP) stage 5 (i.e. total

Table 1 – Summary of the epidemiologic evidence on CP and ASD.

Authors	Year of publication	Type of study	Number of participants (N)	Diagnosis-related groups	Country	Age	Diagnostic criteria and assessment tools	Prevalence of ASD or CP n (%)
Goodman and Graham	1996	cross-sectional	149	CP	UK	6–10 years	Questionnaire measures of psychiatric caseness	4 (3%)
Nordin & Gillberg	1996	epidemiological	38	CP	Sweden	school-age	ABC, CARS, DSM-III-R	4 (10.5%)
Fombonne et al.	1997	epidemiological	174	Autism	UK	6–16 years	ADI-R	5 (2.9%)
Ek et al.	1998	population-based	27	Autistic Disorder + blindness	Sweden	7–17 years	CARS, DSM-IV	8 (29.6%)
Chakrabarti & Fombonne	2001	cross-sectional	97	PDD	UK	2.5–6.5 years	ADI-R	2 (2%)
Steffenburg & Gillberg	2003	population-based	37	CP	Sweden	8–16 years	ABC, CARS, ADI, DSM-III-R	6 (16.2%)
Kielinen et al.	2004	population-based study	187	Autistic Disorder	Turkey	4–18 years	DSM-IV	8 (4.3%)
Lindquist et al.	2006	population-based study	18	CP + hydrocephalus	Sweden	5–12 years	CARS	6 (33%)
Mukaddes et al.	2007	case–control	30	CP + visually impaired	Turkey	7–18 years	ABC, CARS, DSM-IV	10 (33%)
Carlsson et al.	2008	population-based study	34	CP + epilepsy	Sweden	8–12 years	SDQ	5 (14%)
Kilincaslan & Mukaddes	2008	case–control	126	CP	Finland	3–18 years	ABC, CARS, DSM-IV	19 (15%)
Himmelmann and Uvebrand	2011	population-based	186	CP	Sweden	4–8 years	DSM-IV, GMFCS	9 (4.8%)
Kirby et al.	2011	population-based	476	CP	USA	8 year	GMFCS, DSM-IV-TR	39 (8.2%)
Christensen et al.	2013	population-based	451	CP	USA	9 year	GMFCS, DSM-IV-TR	31 (6.9)
Delobel-ayoub et al.	2017	population-based	1225	CP	Iceland, Sweden, France, UK	0–19 years	ICD-10-R; GMFCS	107 (8.7%)
Hirschberger et al.	2018	multicenter, prospective cohort follow-up	93	CP	USA	10 years	SCQ, ADI-R, ADOS-2	8 (20%)

Cerebral Palsy (CP), Autism spectrum disorders (ASD), Pervasive Development Disorder (PDD), Autism Behavior Checklist (ABC), childhood Autism Rating Scale (CARS), diagnostic and statistical manual of mental disorders (DSM), Autism Diagnostic Interview (ADI), Strength and Difficulties Questionnaire(SDQ), Autism Diagnostic Observation Schedule-2 (ADOS-2), Social Communication Questionnaire (SCQ), Gross Motor Function Classification System (GMFCS), International Classification of Diseases (ICD).

Table 2 – Summary of the epidemiologic evidence on CP and ADHD.

Authors	Year of publication	Type of study	Number of participants (N)	Diagnosis-related groups	Country	AGE	Diagnostic criteria and assessment tools	Prevalence of ADHD or CP n (%)
McDermott et al.	1996	population-based	47	CP	USA	4–17 years	Behavior Problem Index	12 (25.5%)
Goodman	1998	prospective	328	hemiplegia	UK	2.5–4.9 years	CTRS; Rutter questionnaires	–
Gross-Tsur et al.	2002	prospective, double-blind, placebo controlled, crossover	116	CP + ADHD	Israel	3.9–20.0 years	CRS; DSM-IV	29 (33%)
Schenker et al.	2005	cross-sectional study	148	CP	Israel	6.1–13.6 years	GMFCS	28 (19%)
Symons et al.	2007	double-blind, placebo-controlled, randomized, single-case	3	CP + ADHD	USA	8–11 years	DSM-IV	3 (100%)
Parkes et al.	2008	crosssectional multi-centre survey	818	CP	England, Sweden, Northern Ireland, France, Ireland, Denmark, Italy	8–12 years	SDQ	253 (31%)
Bottcher et al.	2009	population-based	33	CP	Denmark	9.11–13.6 years	TEA-Ch	–
Sigurdardottir et al.	2010	case–control	36	CP	Iceland	4–6 years	CBCL, TRF	3 (6%)
Shank et al.	2010	case–control	33	CP	USA	8–16 years	CPRS-R, GMFCS	–
Brossard-Racine et al.	2011	cross-sectional	76	CP	Canada	6–12 years	SDQ	23 (30.3%)
Bjorgaas et al.	2012	population-based	67	CP	Norway	8–12 years	ICD-10, GMFCS, Kiddie-SADS, DSM-IV, MACS	28 (18%)
Gabis et al.	2015	Population-based	90	CP	Israel	1.8–15.4 years	GMFCS	20 (22.5%)

Cerebral palsy (CP), attention-deficit/hyperactivity disorder (ADHD), Gross Motor Function Classification System (GMFCS), Child Behavior Checklist (CBCL), Teacher's Report Form(TRF), Conners' Rating Scale (CRS), Conners Parent Rating Scales – Revised (CPRS-R), Strengths and Difficulties Questionnaire (SDQ), Test of Everyday Attention for Children (TEA-Ch), Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), diagnostic and statistical manual of mental disorders (DSM), Conners teacher rating-scale (CTRS), Manual Abilities Classification System (MACS).

retinal detachment). 15 children (8 boys, 7 girls) had an autistic disorder, however only 8 children (29.6%) met two of the DSM-IV criteria for this disorder.[38] Steffenburg et al. examined 98 children with active epilepsy and learning disability and reported that 6 (16.2%) children with concurrent CP had a diagnosis of ASD.[39] A population-based study comprised 67 children with hydrocephalus, 18 of whom with CP.[40] Among children with additional impairments in the form of CP, 6 (33%) subjects out of 18 had autism. This was significantly more common than in the 3 children with autism among the 49 (6%) without these additional impairments. Carlsson et al. described and compared behavioral problems in a group of children with CP, with and without epilepsy.[41] Five out of the 34 children (14%) enrolled had autism, all in the epilepsy group, suggesting that behavioral problems (incl. autism) are common in CP, and this is even more so when epilepsy is present. In 2009, Kilincaslan & Mukaddes assessed the prevalence of autistic disorder and PDD-NOS in a group of 126 children with CP, with 19 (15%) children diagnosed with autism (11% autistic disorder and 4% PDD-NOS).[42] PDD was more common in children with tetraplegic, mixed, and hemiplegic CP as well as in children with epilepsy, learning disability, and low level of speech. In a functional neuroimaging study, Himmelmann & Uvebrant found that nine out of 186 children with CP had a diagnosis of autism or ASD (n = 3 with an intelligence quotient in the lower normal range, n = 1 with a mild learning disability, and n = 5 with a severe learning disability). In children diagnosed with autism, the authors found periventricular white-matter lesions in 3 subjects, cortical/subcortical and basal ganglia lesions in 2 subjects, a malformation in one child, and normal imaging in three subjects.[43] The Autism and Developmental Disabilities Monitoring (ADDM) Network published two studies to monitor CP prevalence in different USA regions and evaluate sociodemographic correlates and characteristics of children with CP. Based on these two reports, it is possible to estimate the rates of comorbid ASD in children with CP. In Kirby et al.'s study, 39 (8.2%) out of 476 children with CP were diagnosed with ASD.[44] They found that ASD co-occurred in 24 (6.2%) children with spastic subtype, 7 (6.4%) of whom with unilateral subtype and 17 (6.2%) with bilateral subtype, and in 4 (14.8%) children with non-spastic subtype as well as 11 (17.7%) children with other subtypes (spastic-ataxic, spastic-dyskinetic, and cerebral palsy not otherwise specified). The authors concluded that comorbid ASD was present in approximately 8% of children with CP across all sites. They also found that, as walking ability decreased, the proportion of children with a comorbid ASD also declined – from 12.9% among children who walked independently to 3.4% among those with limited or no walking ability. In the second report of the ADDM Network, Christensen et al. found that 31 (6.9%) of the 451 children with CP were diagnosed with ASD.[45] ASD co-occurred in 21 (6%) children with spastic subtype, 7 (5.5%) of whom with unilateral subtype and 14 (6.3%) with bilateral subtype, and in 7 children (18.4%) with non-spastic subtype and 3 children (4.7%) with mixed/not otherwise specified subtype (the authors included: spastic-ataxic, spastic-dyskinetic, and cerebral palsy not otherwise specified).[45] Recently, Delobel-Ayoub et al. evaluated the prevalence of comorbid ASD among children with CP and described their characteristics.[46] A total of 1225 children with CP were included in the study, 107 (8.7%) of whom had an associated diagnosis of ASD. 6.4% of children with CP without intellectual disability presented with comorbid ASD, a proportion obviously higher than in the general population. The authors concluded that children with CP appear to be at greater risk of ASD than the general population, independently of their intellectual level. A recent study by Hirschberger et al. investigated the prevalence of neurodevelopmental impairments in children aged 10 who were born extremely preterm.[47] A total of 93 out of 849 children (11%) had CP, 8 (20%) of whom presented with comorbid ASD. At age ten years, children who had been diagnosed with CP at age two years had a +1.71 risk of having ASD compared with children without CP.

The second group comprises four studies focusing on comorbid CP in populations with autistic disorder or PDDs. In an epidemiological survey on 325,347 children including 174 subjects diagnosed with autism, Forbonne et al. found a 2.9% rate for CP among children with autism, suggesting that the rate of CP in children with autism was higher than the population rate but twice as low as that in the comparison group (children without autism suffered from a range of different medical and developmental problems as well as intellectual deficits).[48] Subsequently, in a group of 97 children, Chakrabarti & Fombonne found two females (2%) with CP diagnosed with PPD and autism, respectively.[49] A population-based study by Kielinen et al. investigated associated medical disorders and disabilities in 187 children with autistic disorder.[50] The rate of CP –4.3% (eight subjects out of 187)– is almost 10 times the population rate of 5.7 per 1000 in northern Finland (von Wendt et al., 1985b). In addition, this study reported comorbid ASD in 4 (2.1%) children with diplegia, 2 (1.1%) with triplegia and 2 (1.1%) with tetraplegia. Finally, a case–control study compared 227 children with visual impairments and 30 children with visual impairments plus ASD.[51] Mukaddes et al. found that the two groups differed significantly in terms of CP (13% vs. 33%), concluding that subjects with blindness plus autism have a greater neurological impairment such as intellectual level and cerebral palsy.

Full details of these studies are shown in Table 1.

3.6. *Comorbidity of CP and ADHD*

We found twelve studies evaluating the comorbidity between CP and ADHD. Our review of the literature revealed three groups of studies on the co-occurrence of ADHD and CP.

The first group of studies investigated the prevalence of ADHD symptoms in CP populations. In a population-based research, McDermott el al. measured behavioral problems in children with CP in a non-clinical setting.[52] They reported that 12 (25.5%) children with CP out of a group of 47 children presented with hyperactive problems including concentration difficulty, forgetfulness, and impulsive behavior. Motor and cognitive or behavioral problems were examined in 148 children with CP.[53] The most frequently co-occurring neuropsychiatric impairments were ADHD (19%) and learning disorders (46%). To describe psychological symptoms in children with CP aged 8–12-years, Parkes et al. conducted a cross-sectional multi-centre survey[54] using a dimensional approach to evaluate emotional and behavioral problems. The authors used

the parent form of the SDQ and found that approximately 31% of children with CP (N = 818) showed hyperactivity disorders. Sigurdardottir et al. assessed emotional and behavioral problems in 33 pre-school children with congenital CP by the CBCL.[55] Two of these children presented with ADHD. In children with CP, attention problems and withdrawal were the most problematic symptoms both at home and at preschool. In a cross-sectional study, Brossard-Racine et al. explored behavioral problems in school-aged children with CP (N = 76) and identified modifiable factors associated with problematic behavior.[56] Hyperactivity-inattention problems affected 30.3% of them. In this group, 18 children (23.7%) fell in the hyperactivity abnormal range and 5 (6.6%) in the hyperactivity borderline range. Furthermore, the authors suggested that the presence of hyperactivity problems in children with CP is predictive of later peer-related problems. Recently, in a population-based study, Bjorgaas et al. assessed the rate of psychiatric disorders using a diagnostic interview.[57] Among the 56 children identified with GMFCS level I–IV, 32 subjects (57%) met the criteria for a child psychiatric disorder. Specifically, 28 children met the criteria for ADHD/ADD. These children had a GMFCS level III–IV and a MACS level III–V. In another study, Gabis et al. investigated the association between functional level and mental comorbidity in a large cohort of children with CP[58] by stratifying a sample of 90 children by GMFCS level and CP subtype. ADHD was prevalent in 22.5% of the children. Among children with ADHD, three (50%) children were categorized into GMFCS Level I, 3 children (30%) into GMFCS Level II, 4 children (33%) into GMFCS Level III, 7 children (44%) into GMFCS Level IV, and 6 children (14%) into GMFCS Level V. In addition, ADHD was found to co-occur in 11 (12.9) children with quadriplegia, 4 (4.8%) children with hemiplegia, 3 (3.5%) children with athetoid CP, and 4 (4.8%) children with spastic diplegia.

Studies in the second group evaluated the effect of methylphenidate on ADHD in children with CP. Goodman found that hyperactivity was particularly predictive of continuing psychiatric problems in school-age children (N = 240) with hemiplegia[59] and suggested that use of stimulants could prevent the emergence of other psychiatric problems. Two studies explored the use of methylphenidate for ADHD in children with CP. In a prospective, cross-over, double-blind study, Gross-Tsur et al. treated twenty-nine patients with CP and ADHD (33% on 116 subjects) with methylphenidate or placebo, each for 4 weeks.[60] The effect of methylphenidate on attentional skills were evaluated using parent and teacher reports. The study showed the efficacy of methylphenidate in children with dual diagnosis of CP and ADHD, at least in the short term. Symons et al. evaluated methylphenidate administration in 3 school-aged children with CP and comorbid ADHD symptoms and found that low-dose vs. high-dose methylphenidate resulted in clinically significant reductions in directly observed stereotyped and disruptive behavior.[61]

Studies belonging to the third group assume that children with CP present with impairments in attention and executive function similar to ADHD children. Bottcher et al. tested attention and executive functions with standardized neuropsychological measures in a group of children with unilateral (n = 15) or bilateral (n = 18) spastic CP, highlighting that children with CP had particular difficulties on measures of sustained and divided attention, while no significant differences on attention tasks were found between participants with unilateral and bilateral spastic CP.[62] Shank et al. hypothesized that children with CP and control peers would show positive correlations between visual inspection time (IT) task duration thresholds and parent/guardian ratings of ADHD symptom severity.[63] Children with CP exhibited significantly slower IT, with more symptoms of inattention and hyperactivity than the control group. However, while correlations between IT durations and reported ADHD symptoms were significant in the control group, no such finding were observed in the CP group.

Studies included in this section are summarized in Table 2.

4. Discussion

The purpose of this systematic review was to establish the incidence and prevalence of comorbid NDDs in the CP population. According to the NICE Guideline on diagnosing, assessing and managing CP (Shaunak & Kelly, 2017), we focused on ASD and ADHD, as these NDDs are interrelated and may share pathological mechanisms and clinical features.[19,20,64,65]

The ASD prevalence estimates in CP vary widely from 2% to 30%. This may in part be due to the variety of the populations studied. We found a higher prevalence of ASD (from 29% to 33%) in studies where CP was associated with other medical conditions such as visual impairment, retinopathy of prematurity, and hydrocephalus, which suggests that these additional medical conditions increased the risk of ASD. Studies focusing on comorbid CP in populations with ASD revealed a prevalence from 2.9% to 4.3%. Similarly, the prevalence of ASD in populations with CP varies from approximately 3%–16%, suggesting a higher frequency of ASD in children with CP compared with the estimated prevalence (ca. 1.5%–2%) in the ASD population.[66] Regarding the comorbidity between CP and ADHD, we found that ADHD prevalence in CP ranged from 19% to 35%. A recent meta-analysis on ADHD prevalence in children up to 18 years of age found an overall pooled estimate of 7.2%.[67] These findings suggest that ADHD seems to be more common in children with CP than in the general population.

Taken together, the studies discussed in this review point out that children and young people with CP are clearly at increased risk of ASD and ADHD. However, differences in prevalence rates between studies could be due to the different diagnostic tools used. Traditionally, the question of whether ASD and ADHD are best classified using categorical or dimensional approaches is a contentious one and has profound implications for clinical practice and scientific enquiry alike. Both categorical and dimensional solutions appear to be valuable and this varies according to the disorder considered.[68] However, many neurodevelopmental conditions are better described as dimensional rather than categorical disorders.[69] This has been suggested for both ASD and ADHD, as dimensional approaches can be used to identify discrete subgroups of individuals within each disorder. Thus, in the current review, we reported the empirical literature into studies taking a categorical and dimensional

approach to evaluate the comorbidity between CP and ASD or ADHD.

Although diagnostic procedures for ASD have improved, diagnosing this disorder in children with CP remains a complex issue. Probably the gold standards for diagnosis such as the ADOS and ADI-R are not suitable for some children with CP. Assessing communication impairments in CP is difficult owing to common oral-motor disorders.[42] Besides, diagnostic measures for ASD include complex motor tasks that are not suitable to the motor skills of children with CP. Most studies relied on DSM or ICD criteria for the diagnosis of ASD, whereas only three studies used DSM criteria for ADHD diagnosis. Most studies used a dimensional approach to evaluate attention or behavioral problems associated with ADHD. Some studies employed the revised CRS-R, which is considered the gold standard for assessing ADHD, others evaluated ADHD symptoms using tools tapping emotional and behavioral aspects such as the SDQ or CBCL. Compared with the DSM- or ICD-based categorical approach, these dimensional tools tend to generate higher prevalence rates for ADHD.[70] It should be noted that the SDQ and the CBCL are not diagnostic measures for ADHD but only reflect parental or teachers' perceptions of a child's specific disruptive behaviors. Parent and teacher reports on a screening questionnaire cannot replace clinical validation of a diagnosis. Furthermore, these dimensional tests (CRS-R, SDQ, and CBCL) include a significant number of questions irrelevant to the level of motor activity and behavior of children or adults with CP. Therefore, there are still diagnostic challenges to overcome in order to successfully implement a screening approach for other NDDs in people with CP. Early identification of ASD or ADHD symptoms through a dimensional approach in children with CP could help clinicians improve management decisions and lead to targeted treatment and therefore better outcomes. In addition, our review highlights the paucity of published studies on the occurrence of ASD and ADHD in children with different CP subtypes or functional abilities. Only two studies reported that ASD was more frequent in children with non-spastic CP, particularly hypotonic CP.[44,45] No studies report the prevalence of ASD based on functional levels measured by GMFCS, CFCS and MACS. Regarding the comorbidity between CP and ADHD, only two recent studies evaluated the prevalence of ADHD symptoms in children with CP based on GMFCS functional levels: One study reported ADHD symptoms, and comorbid ADHD was found to be more frequent in children with quadriplegia.[58] The other study reported a prevalence of ADHD in children with GMFCS level III–IV and MACS level III–V, while no differences in ADHD symptom prevalence were found in children with different CP subtypes.[57] This would be a fruitful area for further research, in order to establish whether occurrence of other NDDs in CP varies according to CP subtypes or functional abilities. In fact, the precise quantification of comorbidity between ASD or ADHD in children or young people with CP could help determine the effectiveness of medical and physical therapeutic interventions.

Some studies indicate some overlap of cognitive deficits between ADHD and CP.[62,63] Attention and executive functions seem to be more commonly affected in children with CP or ADHD than typically developing children. Improving attention and executive functions such as working memory may be beneficial for both patients and their families, reduce the need for special education and improve social and daily life functioning.[71] Nevertheless, there is a lack of evidence-based knowledge regarding cognitive function and the effects of cognitive interventions in CP.

The studies included in our review also addressed the effects of stimulant therapy in children with CP and ADHD. Methylphenidate showed to be beneficial in ADHD, even when associated with other neurologic disorders such as intellectual disabilities, fragile X syndrome, autism spectrum disorder, and epilepsy.[60] However, pharmacological treatments targeting ADHD symptoms in CP have received little attention. Two studies reported that methylphenidate is effective in children with dual diagnosis of CP and ADHD[60,61] and emphasized that low-dose (0.3 mg/kg/dose) methylphenidate was associated with clinical significant reductions of ADHD symptoms in children with CP, at least in the short term. However, caution is recommended as findings cannot be generalized given the small sample size.

5. Conclusion and future directions

Based on our systematic review, people with CP are clearly at increased risk of other NDDs such as ASD or ADHD. The complexity of the CP condition is a challenge when diagnosing ASD or ADHD. Children with CP should specifically be screened for both these conditions; however, future psychometric studies are needed to promote the development of measures suitable for individuals with CP, particularly when sensory impairments and motor deficits limit use of gestures such as pointing, that may complicate differential diagnosis. Measures tapping ASD or ADHD symptoms need to be valid, reliable, sensitive, and able to detect change over time, and they also need to be appropriate for use in CP. Characteristics associated to ASD or ADHD such as social communication, attention, executive function and behavior problems may be overlooked or thought of as being part of the disorder. Therefore, ASD or ADHD may go undiagnosed in individuals with CP. In order to avoid this risk, health care professionals need to be more informed and knowledgeable about the symptoms of ASD or ADHD. Assessing the presence of these conditions would improve the significant cost of healthcare, therapies, and overall daily live for families with children affected by CP. A comorbidity between NDD and a disabling condition such as CP could be either a pathology, an impairment, a functional limitation, or an additional disability. Further studies are needed to ensure that appropriate services are in place to provide parents and carers with information on the diagnosis and management of CP and that this information is tailored to their individual needs and learning styles.

Unfortunately, no attempts were made to understand the common pathogenic mechanisms linking CP, ASD and ADHD. One may argue that the brain lesion itself causes an increased prevalence of ASD and ADHD in CP people, pointing to a direct brain behavior link, and it would be reasonable to assume that CP may be a risk factor for other NDDs. Thus, a possible hypothesis could be that the CP-related brain damage or malformation could affect the same brain areas involved in the etiopathogenetic mechanisms of ASD or ADHD. However, it is well known that CP may occur in the absence of clear and

definitive lesions on the current neuroimaging techniques.[72] So far, it would be reasonable to assume that a neural connectivity impairment rather than a localized deficit is involved in the pathophysiological process of NDDs. This could also apply to CP individuals, in whom aberrant brain connectivity was demonstrated not only at the injury's site, but also in the normally-appearing perilesional cortex.[73] In addition, the associations between excessive risks of a wide range of ASD and ADHD in the CP population reveal the presence of unmeasured shared causes. Such shared causes may be of genetic or environmental nature, or a combination of the two factors. However, genetic risk factors for CP and other neurodevelopmental conditions present with considerable heterogeneity and complexity. Researchers have demonstrated a number of quite heterogeneous genetic variants and have documented causal relationships between different NDDs through advanced methods.[74–76] These findings corroborate the hypothesis of a common underlying disturbance for comorbid CP, ASD and ADHD. Further research is needed to determine the extent of genetic or neuroimaging overlap between individuals with CP and ASD and ADHD.

In conclusion, improved characterization of behavioral phenomenology and comorbidity complexes might be taken as starting point for the development of emerging methods of brain imaging and genetics, and ultimately lead to the development of optimized treatment approaches to ease the burden of children and young people with CP and their caregivers who struggle daily with these devastating conditions.

Conflict of Interest

I confirm that there is no financial or others conflict of interest that may be related to the authors.

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