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SCOPING REVIEW

Incidence of hip problems in developmental central hypotonia: A scoping review

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Abstract

Aim: To describe what is known about hip problems in individuals with developmental central hypotonia.

Method: Searches were conducted in five databases to October 2023. Down syndrome was excluded from this analysis of less well-known genetic diagnoses. At least two reviewers independently screened titles, abstracts, read full-text articles, and extracted data.

Results: Of 89 full-text articles, 79 met inclusion criteria. Studies included 544 individuals aged 1 month to 63 years with Kabuki, 49, XXXXY, Prader–Willi, PURA, Koolen de Vries, Emanuel, TRPM3, Wolf–Hirschhorn, and other rare syndromes. Most diagnoses may be associated with a combination of differences in hip structure or stability that are evident at birth, or develop in early infancy, with increasing hip dysplasia and subluxation over time. Joint or ligamentous laxity was most reported along with hypotonia and hypermobility as risk factors. Limited data were identified about conservative or surgical intervention and outcomes in these populations.

Interpretation: Children with significant hypotonia, with or without a confirmed genetic diagnosis, are at increased risk of hip problems that may be missed with standard neonatal screening. Ultrasound is recommended between 6 weeks and 6 months, and annual orthopaedic review with regular radiographs for older children and adults with significant and persistent hypotonia.

The terminology of paediatric hip problems can be confusing and has changed over time because of better understanding. Congenital dislocation of the hip (CDH) was the original term for infants who had unstable hips at birth and developed fixed dislocations if they were not treated at a young age. However, because there is no congenital malformation with this diagnosis, the terminology has been changed to developmental dysplasia of the hip (DDH), to recognize that the problem develops late in pregnancy or at birth or in early infancy because of multiple related factors.[1] DDH describes a range of hip problems including hip instability, acetabular dysplasia, femoral dysplasia, hip subluxation (femoral head is partly displaced), and complete hip dislocation (femoral head is fully displaced from the acetabulum),[2] and is generally used with children who do not have developmental neuromotor disabilities.[3] Teratological dislocation of the hip indicates severe changes to the hip and a fixed dislocation apparent at the time of birth.[4] This term is outdated and should be described more specifically, such as hip dislocation in a child with arthrogryposis. Neuromuscular hip dysplasia is the term used for children with cerebral palsy (CP) and other neurodevelopmental conditions.[5]

CP is an umbrella description for disorders of movement and posture caused by non-progressive brain injuries before, during, or shortly after birth, and includes genetic, environmental, and other causes.[6] In the 1990s, multiple studies

Abbreviations: AHD, acquired hip dysplasia; CDH, congenital dislocation of the hip; DDH, developmental dysplasia of the hip; PWS, Prader–Willi syndrome.

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demonstrated that hip dysplasia develops primarily between the ages of 2 to 5 years in children with CP who had normal hips at birth. This neuromuscular hip dysplasia occurs with a higher risk in children with the most severe neurological impairment, as described using the Gross Motor Function Classification System (GMFCS),[7] regardless of whether they have increased muscle tone (hypertonia) or low muscle tone (hypotonia).[8–10] However, beyond finding that the incidence was not different, there are no published data showing the natural history comparison between high-tone hips and low-tone hips.

The past decade has seen an explosion in interest, evidence, and application of hip surveillance programmes for children with CP. The publication of the first 10-year follow-up programme from the Cerebral Palsy Follow-Up Program in Sweden[11] demonstrated how regular radiographs, clinical assessments, timely surgical intervention, and a total postural management programme could eradicate hip dislocation, decrease contractures, deformity, and associated pain, and decrease the need for additional surgeries. These findings were supported in the 20-year follow-up,[12] and hip surveillance programmes have now been implemented around the world,[13–15] although they are still limited in the USA.[5]

Hypotonia or low muscle tone is not well defined or understood.[16] It includes the ability to maintain position against gravity (active postural tone), as well as reduced resistance to passive movement.[17] Hypotonia may result from central (supraspinal/suprasegmental) or peripheral (segmental or motor unit) causes. Peripheral origins include damage to the peripheral nerves (e.g. neuropathies), muscle (e.g. myopathies or muscular dystrophies), anterior horn cell (e.g. spinal muscular atrophy), or neuromuscular junction (e.g. myasthenias).[18]

Developmental central hypotonia describes children with non-progressive hypotonia, originating in the central nervous system. This includes CP-like conditions (where hypotonia is the sole motor type), congenital hypotonia of unknown origin, and genetic disorders where hypotonia is a prominent feature.[19] Children who present with non-degenerative central hypotonia from genetic, metabolic, or unknown causes are included under the umbrella of CP in some locations.[20] However, a survey of CP registries indicates that fewer than half include children presenting with the sole motor type of hypotonia.[21] As a result, many children with developmental central hypotonia may be excluded from hip surveillance programmes, particularly if a formal CP diagnosis is a requirement.

Central hypotonia with hypermobile joints is a feature of many genetic disorders including Down, Prader–Willi, and other syndromes.[22] The American Academy of Cerebral Palsy and Developmental Medicine Central Hypotonia Care Pathway recommends hip surveillance for this population.[23] However, the present methods for hip surveillance, surgical intervention, and postural management for hip health are all based on established best practices for children with CP, who more typically present with spasticity or dystonia.[24] In contrast, it has been proposed that hip problems occur in children with hypotonia because of lack of muscle force keeping the hip in joint, and that the resulting lack of pressure contributes to insufficient depth growth of the acetabulum.[24] Since little is known about hip health for individuals with hypotonia, we set out to complete a scoping review of the literature.[25–27]

What this paper adds

- Incidence of hip problems is significantly increased for individuals with hypotonia associated with multiple rare genetic diagnoses.
- Regular hip surveillance for children and adults with significant and persistent hypotonia is recommended.
- Individuals with developmental central hypotonia should be included in databases to follow the natural history of hip problems.

This study sought to explore what is known about hip problems in individuals with developmental central hypotonia. Down syndrome is most prominently reported, while the literature on hip health for other diagnostic groups, meeting criteria for developmental central hypotonia, is sparse and tends to be more descriptive. To adequately map the literature on these less commonly reported conditions, studies including individuals with Down syndrome were excluded following the literature search and will be addressed in a separate paper.

The specific questions guiding this review were as follows. (1) What diagnoses are associated with developmental central hypotonia and hip problems? (2) What is the natural history, prevalence, and incidence of hip problems in reported diagnoses? (3) What specific hip problems have been reported? (4) At what ages do hip problems occur? (5) What are the risk factors for these hip problems? (6) What surgical and other interventions have been reported to prevent or treat hip problems? (7) What outcomes have been reported for these interventions?

METHOD

Methodologies for the conduct and reporting of scoping reviews have evolved over time. The conduct of this study was informed by earlier guidance,[25–27] and was in line with the latest guidelines[28] from the JBI. Reporting follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) statement.[29]

Search strategy

An electronic database search was undertaken in conjunction with librarians at Västmanlands Hospital, Västerås,

Sweden. PubMed, CINAHL Plus, AMED, and Scopus were searched for relevant studies from database inception to February 2023. The following search terms were included. (1) Population: hypotonia or hypotonic or hypoton* (with * representing wild-card) or Down syndrome or trisomy 21 AND hip dysplasia or hip dislocation or hip instability or hip laxity or hip migration or hip. No age limits were specified, to follow the progression of hip health over the lifespan. (2) Intervention: not specified—but could include surgery, splinting, positioning, physiotherapy, or no intervention. (3) Comparison: not specified. (4) Outcome: not specified—but could include all International Classification of Functioning, Disability and Health domains, natural history, and/or descriptive or prevalence data on any aspect of hip health.

No limits were placed on design methodology, language, or publication status. The electronic database search strategy was published on the Open Science Framework with the protocol on 23rd August 2023 and may be retrieved online (https://doi.org/10.17605/OSF.IO/2WN6R).

This initial comprehensive search was downloaded into Rayyan (www.rayyan.ai) to allow independent review and identification of articles to be read full-text. Identified references were exported into a Microsoft Excel sheet where reasons for inclusion or exclusion, following full-text review, were documented. The Cochrane library and PEDro were searched for the terms hip and hypotonia. Keyword searches (hip AND x diagnosis) were then conducted using Google Scholar in October 2023 for articles relevant to diagnostic conditions identified in the initial electronic search. The search strategy and results of the iterative keyword Google Scholar searches are documented in Appendix S1. Following full-text review, reference lists of included articles were hand-searched for additional relevant citations.

Eligibility criteria

At least two of three authors (ERB, GSP, RWL) independently reviewed titles and abstracts retrieved in the search, and those to be reviewed full-text were agreed through discussion. Articles were read full-text if the abstract or title indicated inclusion of individuals with central hypotonia and hip problems (hip instability, dysplasia, migration, subluxation, or dislocation). Articles either included diagnoses where hypotonia was a known feature, or the title or abstract specifically mentioned hypotonia and hip issues. All types of study were considered: intervention studies (describing surgical cohorts, splinting, or casting interventions), descriptive evidence, reviews, commentaries, surveys, or qualitative studies.

An iterative process was undertaken given the exploratory nature of this scoping review. Some less well-known diagnoses associated with hypotonia and hip problems were identified in the initial full-text review in Rayyan. Any additional articles including these diagnoses were then reconsidered for full-text review. In the Google Scholar search, keywords were used, for example hip and Emanuel syndrome, hip and PURA syndrome, etc. The first 10 references were considered for each diagnosis, and read full-text if the title, abstract, or highlighted text identified hip dysplasia, subluxation, or dislocation, or if the article reviewed clinical features of a cohort that might provide prevalence or natural history data related to hip problems. For Prader–Willi syndrome (PWS), most of the first 10 references were duplicates of those identified in the initial database search so an additional page of 10 references were searched.

Studies not meeting population criteria included diagnoses (1) where hypotonia is degenerative and not central in origin, for example spinal muscular atrophy, muscular dystrophies, or myopathies; (2) where joint hypermobility, ligamentous laxity, and hip issues are related to a connective tissue disorder, for example Ehlers Danlos syndrome, Costello syndrome, cutis laxa disorders; (3) where multiple muscle and joint issues are teratological or congenital, for example arthrogryposis, IMAGe syndrome, and other rare genetic disorders; (4) where the hip issues relate to arthritic joint conditions as seen in various forms of dwarfism and in older adults; or (5) other degenerative diagnoses such as leukodystrophies, and genetic or metabolic disorders where the child is unlikely to survive beyond infancy.

In addition, we excluded studies discussing CDH or DDH in infants not meeting population inclusion criteria and mixed population studies that did not include more than 50% of individuals meeting population inclusion criteria. Studies related to hip arthroplasty/total hip replacement, bone mineral density, gait analysis, hip muscle strength, or range of motion, and studies related to radiological or ultrasonic technique, or modelling, were also excluded.

Data extraction

At least two reviewers independently extracted data from included studies using a study-specific data extraction form, detailed in the protocol. Data extracted and tables created were discussed, checked, and reviewed by all authors to identify key points to be highlighted in the review.

Analysis

Tables were created to summarize results for each condition. Visual analysis (using Microsoft Excel for Mac, version 16.66.1) mapped and illustrated data across studies, diagnoses, geographical locations, and over time. Where individual cases were reported, age at onset and specific interventions were counted for each case. Terms used to describe hip problems in each study were counted, with several studies using more than one term or description. Raw numbers were converted to percentages where this was helpful to allow comparison between diagnoses because of the skewed number of cases or reports. Evidence quality and risk-of-bias ratings were not appropriate owing to the descriptive nature of this scoping review, and the heterogeneous studies included.[26]

RESULTS

In the primary comprehensive database search 1372 references were identified. A further 152 references were identified by searching on Google Scholar and seven articles through hand-searching or contacting known researchers. Once duplicates were removed, 1488 articles remained and titles and abstracts were reviewed by at least two authors for any mention of an issue related to hip health in an individual described as presenting with hypotonia. Following title and abstract review, 89 articles were read full-text by at least two authors, and 79 met inclusion criteria. See Figure S1 for the flow diagram illustrating study search results. Appendix S2 provides the list of excluded articles with reasons.

Seven included studies were developed by an international panel of authors. Remaining studies originated from various countries in Europe, North and South America, Asia, North Africa, Asia, and the Middle East. See Figure 1 for a map illustrating origins of included studies. Although language was not restricted at any stage of the search or screening process, all included studies were published in English language journals.

Included studies described individuals with a variety of diagnoses. Twenty studies were related to Kabuki (also known as Niikawa–Kuroki) syndrome,[30–49] 11 related to 49, XXXXY (Fraccaro) syndrome or variants,[50–60] nine related to PWS,[61–69] seven described PURA-related syndromes,[70–76] six related to Koolen de Vries syndrome,[77–82] five each reported TRPM3-related,[83–87] Wolf–Hirschhorn,[88–92] and Emanuel (4p-) syndromes.[93–97] The remaining 11 articles discussed other rare conditions including adenosine kinase deficiency,[98] Okamoto,[99,100] Lowe,[101,102] and Joubert[103] syndromes, as well as deletions on the long arms of chromosome 18 (18q-)[104–106] and chromosome 4 (4q-),[107] and one study included children with developmental central hypotonia most of whom were undiagnosed.[108] See Figure 2 for an illustration of relative proportions of individuals in each diagnostic group who were described or reported in included studies.

A variety of different study types were included: cohort, case series, and case studies often reported age range and some details on identified cases, as did some reviews. As a result, some details on hip problems, age at onset, and/or intervention were available for 544 individuals aged 1 month to 63 years. Other reviews and descriptive or expert opinion articles provided some prevalence/incidence data and/or broad suggestions for identification, screening, intervention, and management. Peer-reviewed studies published in the past 10 years reported no conflict of interest, or that funders had no influence on the study. This information was not provided for book chapters or older studies, but conflict of interest does not appear to be a major concern or influence for the studies included in this review. See Table S1 for details of all included studies.

A variety of terms were used to describe hip problems, making it challenging to compare diagnoses, or to ensure that authors were describing the same hip problem. A number of articles used several different terms in their study, resulting in 123 total reports of hip problems over the 79 studies. Although CDH or DDH should indicate that the hip dysplasia is not associated with a developmental neuromotor disability, 27 out of 123 (22%) reports used the term congenital or CDH, and 13 out of 123 (11%) used the term developmental or DDH. The remaining reports included the terms hip subluxation, hip dysplasia, or hip subluxation, and occasionally hip luxation. No studies used the term neuromuscular hip dysplasia; however, one described hip dysplasia, progressive subluxation, and dislocation as neuropathic.[76]

There was limited distinction in many studies between dislocation, dysplasia, or subluxation that were present at birth or in early infancy, and hip problems that developed or were acquired over time. Of 544 cases reported overall,

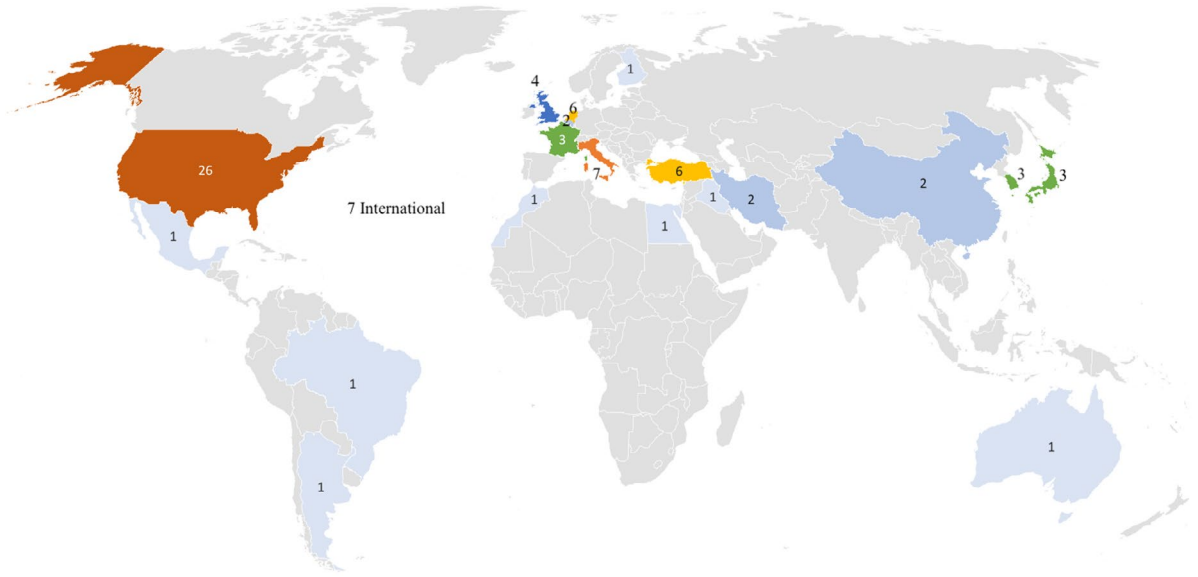

FIGURE 1 Map illustrating origins of studies included in this review.

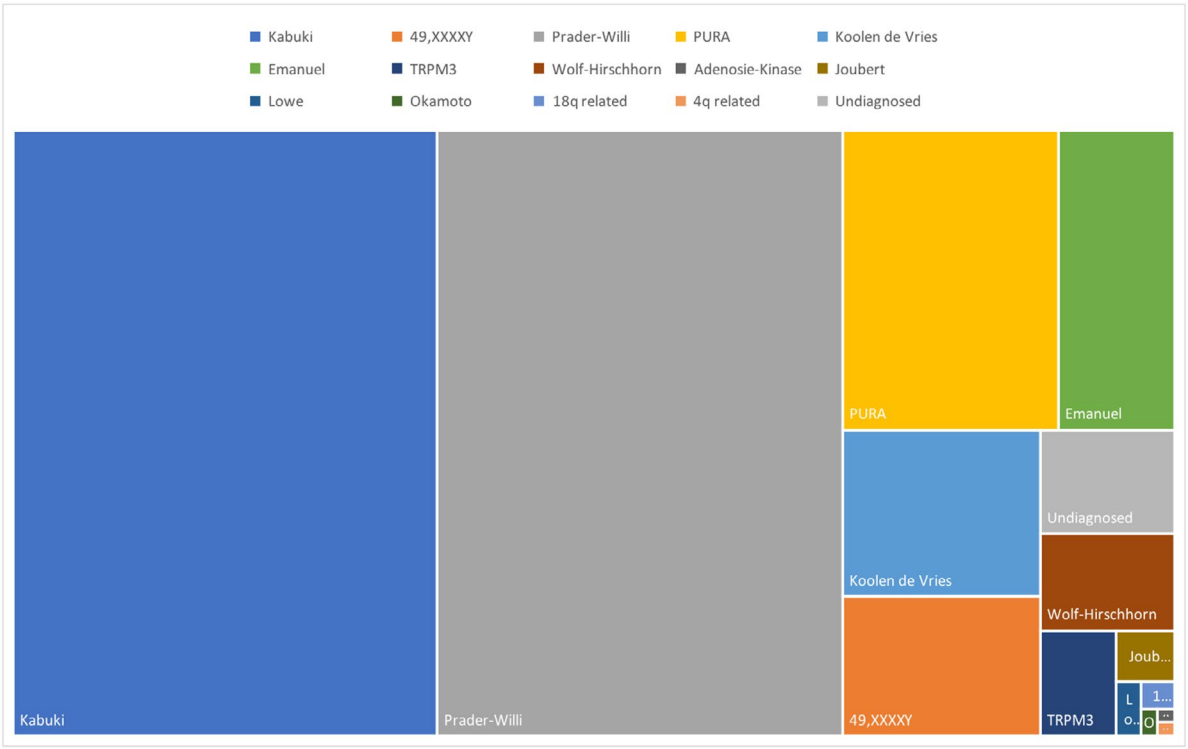

FIGURE 2 Tree chart illustrating relative proportions of cases reported for each diagnosis in included studies.

the age or approximate timing at onset was unclear in 442 cases (81%). Hip dysplasia was the most identified hip health problem (52 out of 123; 42%) followed by hip dislocation (46 out of 123; 38%), while hip subluxation was least described at 25 out of 123 (20%) reports. Only 15 out of 79 studies discussed risk factors for hip problems, with several proposing more than one risk factor. Joint or ligamentous laxity was the most highly reported risk factor (eight studies) followed by hypermobility and hypotonia, each suggested in five studies (Figure 3).

In addition, it was not always clear whether authors were describing only acetabular dysplasia, or whether femoral head dysplasia was also present. Few studies reported typical radiographic measures for hip dysplasia such as acetabular index or centre edge angle, or for hip subluxation or lateral displacement such as migration percentage. Several diagnoses (Kabuki, PWS, and 49, XXXXY) were reported to have a combination of congenital and developmental factors related to their hip problems.[37,39,51,63] This implies that differences in hip architecture and/or stability were present in early infancy and that hip dysplasia also increased over time. However, the bone structure is not necessarily abnormal due to a genetic cause and should not be described as congenital because even early changes are probably functionally based, as the body's response to abnormal motor function.[65,109]

Figure 4a illustrates differences in reports of hip problems from different geographical regions. As would be anticipated, the greatest numbers of reports originated from North America (USA and Canada) and Europe (Belgium, Finland, France, Italy, the Netherlands, and the UK). Only one study, using the term CDH, was reported from Australia and New Zealand.[48] As a percentage of reports, hip dislocation was reported most from the Greater Middle East (Iran, Iraq, Egypt, Morocco, and Turkey) followed by East Asia (China, Japan, and Korea). Hip dislocation or dysplasia were most highly reported across all regions while, as a percentage of reports, hip subluxation was reported more from international, North American, or Central/South American (Argentina, Brazil, and Mexico) studies.

Figure 4b illustrates reporting of different types of hip problem across time by decade, and both percentage of reports and actual numbers of reports are shown for each period. The years 1970 to 1989 (two decades) were combined because of the small number of reports, and reports from the year 2020 onwards include only 4 years of data, making trends harder to interpret. Although the number of reports has significantly risen since 2000, there appears to be a decreasing trend in reports of hip dislocation, and an increasing trend in reports of hip dysplasia from 1990 to 2019 which may relate to changes in terminology use.

Twenty-two of 79 studies reported various types of surgical, splinting, or casting intervention;[35–37,39,40,51,52,58,59,62–64,67,74,76,83,86,89,99,100,104,108] however, of these, only eight provided clear detail on the intervention and outcomes for included cases.[35–37,39,63,64,89,108] Overall, pelvic osteotomies were the most reported surgeries, followed by open or closed reductions with or without traction and/or casting. No studies were identified reporting either conservative or surgical interventions for Koolen de Vries or Emanuel syndromes. One review recommended

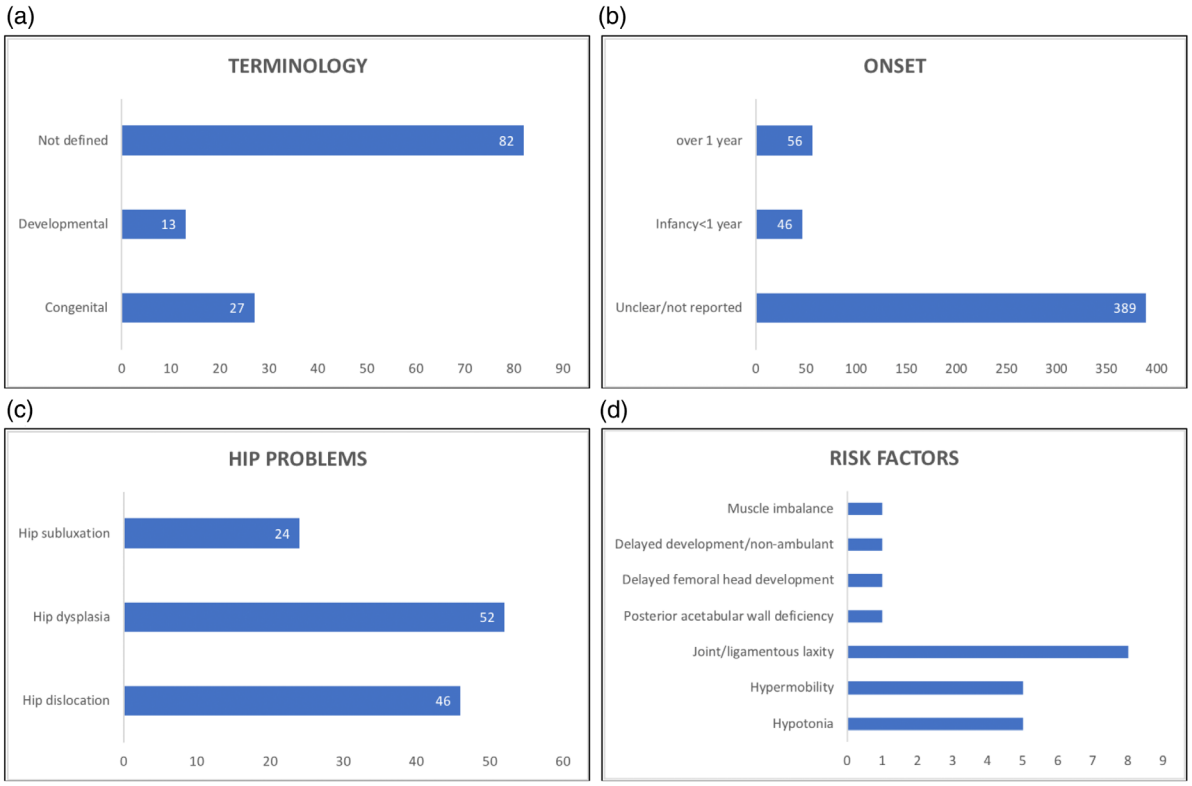

FIGURE 3 (a) Terms used to indicate timing of hip problems in included studies. (b) Age at onset reported in individual cases. (c) Hip problems reported across all included studies. (d) Risk factors for hip problems reported.

femoral osteotomies for children with PURA syndrome, but did not report details for any cases.[76]

Successful, more conservative treatment (including splinting, casting, traction, open/closed reduction, and/or soft-tissue releases) was reported for 13 children while 13 others required additional pelvic and/or femoral osteotomies. Successful osteotomies resulting in concentrically located, pain-free hips without instability or clicks were reported for 21 children, while 10 required surgical revision due to re-dislocation or fractures. Owing to limited details and lack of extended follow-up, it is unknown whether these children required further surgeries in the future. See Figure 4c,d for a summary of interventions and outcomes across studies. Details may be found in Table S1.

Diagnosis-specific results

Results specific to each identified diagnosis follow, and are presented in order of number of studies identified, from greatest to least reported. Detailed results may be found in Table S1.

Kabuki syndrome

Fifteen articles provided primarily hip problem incidence/prevalence data,[30–34,38,41–49] while the other five articles described surgical and other interventions in 15 children.[35–37,39,40] Hip health problems were reported in 10%[44] to 12%[46] of infants, and ranging from 18%[49] to 40%[45] in studies including older children and adults. The onset of hip problems was reported from birth/infancy,[31,44] as well as later in childhood, suggesting there is a combination of acquired or progressive hip dysplasia, as well as differences in hip structure present from infancy.[37,39] Ligamentous laxity, joint hypermobility, and hypotonia are suggested as risk factors for early dislocation,[31,42,44] and for either subluxation or hip dislocation after walking age.[37]

Primary studies suggest that non-surgical treatment (e.g. a Pavlik harness) may be effective in some infants, but that osteotomies may be required for those with persistent acetabular dysplasia.[35] Acetabular osteotomies have been reported from as young as 16 months[39] to 5.7 years.[37] Posterior acetabular wall deficiency may be a factor, and a report of a child re-dislocating at 11 years suggests that incomplete periacetabular osteotomy combined with capsular plication may be preferred for this population.[37] Standard neonatal screening may not detect dislocation in all infants with Kabuki syndrome, and/or the hip instability may increase over the first 2 years.[39]

Fraccaro syndrome/49, XXXXY and variants

One review[56] and 10 primary studies[50–55,57–60] described the incidence of hip issues in 28 out of 120 cases ranging in age from 3 months to 28 years. Most studies were single case reports,[50,52–54,59] or small case series.[58,60] Two large

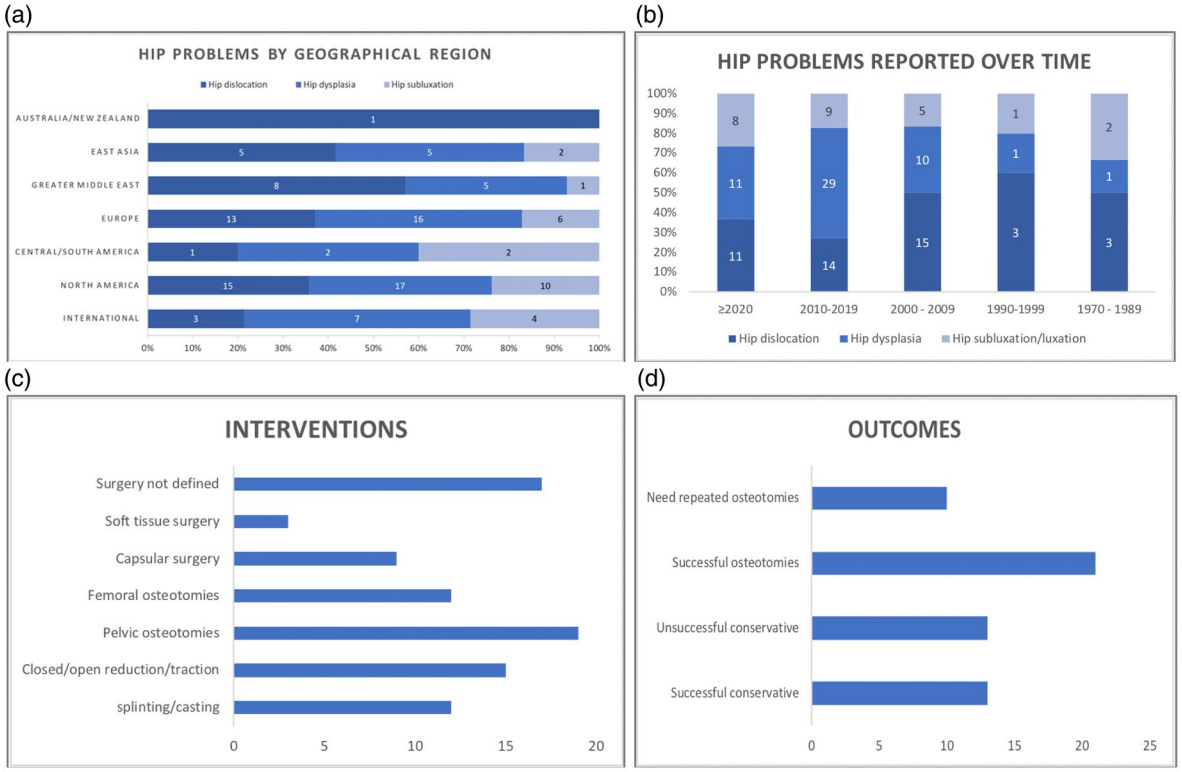

FIGURE 4 (a) Hip problems reported from different geographical regions. Bar length indicates percentage of reports for that region while numbers indicate actual number of reports. (b) Hip problems reported over time. Bar height indicates percentage of reports for that period while numbers indicate actual numbers of reports. (c) Interventions reported for individual cases reported in studies. (c) Comparison of successful versus unsuccessful (required further surgical intervention) femoral/acetabular osteotomies, or more conservative treatment (includes splinting, casting, open/closed reduction, traction, and/or soft-tissue releases).

international cohort studies[51,55] and a US cohort[57] reported hip dysplasia in 16 out of 111 (14%).

The most recent international cohort and review study[51] identified an increased incidence of hip issues in included countries outside the USA (Australia, Brazil, Canada, Honduras, Italy, Mexico, and Spain). Hip problems were found to increase with age: 3.2% in under 5 years, 10.7% in 5- to 9-year-olds, and 17.1% in individuals over 10 years.[51] Risk factors are suggested to be delayed development of the femoral head,[51] and joint laxity with hypotonia. Hip surgery (not defined) was reported in one infant and in four individuals over the age of 10 years.

PWS

Eight primary source studies[62–68] and one review[61] described the natural history of hip health and interventions in individuals with PWS. Six studies involved retrospective chart review of 511 children and adults ranging in age from 3 months to 66 years.[62,63,65–68] One case report[64] described a child with PWS requiring surgery for hip dislocation at age 2 years, and a survey study included 565 members of the Prader-Willi Syndrome Association USA who were mainly family members of individuals with PWS.[69]

Survey authors[69] suggested that high body mass index in combination with ligamentous laxity and hypotonia may be risk factors, while another study[66] found no link between age or body mass index and those with hip problems. Prenatal hypotonia and associated increased rate of version podalic delivery was also suggested as a risk factor.[65] Individuals with PWS may present with unusually excessive or asymmetrical hip range of motion, but no association with hip dysplasia was found in one study.[68]

It is unclear whether dysplasia is always present at birth, but newborn infant screening is not effective in picking up hip dysplasia without instability, and ultrasound is recommended.[61,63,65] Hip dysplasia is reported to occur in 8%[68] to 30%[63] with 1.4%[62] to 11.25%[63] requiring intervention. Types of surgery reported include proximal femoral varus derotation osteotomies,[67] acetabular osteotomies,[62–64,67] capsular surgery,[63,64] and soft-tissue tenotomies.[63] In the most recent study, with the youngest participants,[62] hip dysplasia was found to improve with age for those treated with growth hormone, and surveillance without early intervention was recommended as only 1 out of 72 required acetabuloplasty. Ongoing surveillance is essential because many orthopaedic problems may be masked by obesity,[68] and mild dysplasia can progress to hip subluxation at older ages.[63] Eren et al.[64] recommended the extended use of casting in hip extension, abduction, and neutral rotation following surgery for

individuals with intellectual disability and obesity to prevent issues with skin healing.

PURA syndrome

Three cohort studies included 206 individuals aged 5 months to 48 years.[71,74,75] A single case report of an infant who passed away at 2 months was compared with 72 previously reported cases,[72] and a comprehensive gene review[76] included data from 71 previously reported cases. In addition, a case series[70] reported on four children (newborn infant to 7 years) where two had hip subluxation, and another single case report[73] also provided a literature review. Onset in infancy was reported for one child at age 1 month,[70] but remaining studies describe hip dysplasia as developing over time. Incidence/prevalence may range from 11%[74] to 28%[75] and hypotonia was identified beyond infancy in 79.9%.[71] Chronic truncal hypotonia, joint laxity, and delayed motor development/non-ambulant status are risk factors for hip subluxation or dislocation,[72,75,76] and hip reconstruction with varus derotation osteotomies is recommended, although dislocation may recur because of joint laxity.[76]

Koolen de Vries syndrome

One review,[80] two cohort studies,[77,82] a case series,[78] and two case reports comparing an individual adult with nine[81] or 26[79] adults from the literature described the prevalence/incidence of hip dysplasia, hip subluxation, or dislocation in this population. Cohort studies included 107 individuals aged 7 months to 50.1 years, while the adult-only case reports and comparisons included 37 individuals aged 18 to 63 years. One study reported hip dislocation in 2 out of 26 adults from the literature (8%), but not in the case described,[79] while the other did not identify any reports of hip dislocation in either their case (a 63-year-old) or nine other adults from the literature.[81] In cohorts including children, hip dislocation or dysplasia was reported in 7.4%[77] to 12.5%.[78]

Age at onset is unclear, and most cases appear to be present in infancy, but some reports suggest acquired subluxation or dislocation.[81] Hypotonia is present in 96% in infancy, and in 83%[77] to 88%[79] at older ages. Joint hypermobility is also highly reported in children (85%),[78] although it appears to decrease with age, and has been suggested as a risk factor for hip dislocation.[81] Scoliosis is prevalent in individuals with Koolen de Vries syndrome and a higher incidence of hip dysplasia was noted in individuals who also developed scoliosis.[77] Physical therapy is recommended for monitoring contractures, scoliosis, and hip issues, along with standard orthopaedic care.[80]

Emanuel syndrome

A North American survey study reported on 67 individuals aged 9 months to 33 years,[97] and a single case report from Turkey compared their case with 83 cases reported in the literature.[95] In addition, we identified a single case report from Mexico,[93] a comprehensive gene review,[94] and a descriptive review.[96] Hip subluxation or dislocation was reported in 47% of cases,[96,97] although age at onset was unclear. One case report indicated that the child was born with bilateral hip dysplasia,[93] but another review suggested that hip dysplasia may develop over time.[96] The comprehensive review reported that all individuals had significant centrally based hypotonia, congenital hip dislocation, or that subluxation was common, and recommended orthopaedic monitoring with X-rays for hip dysplasia.[94]

TRPM3-related neurodevelopmental disorder

Three international cohort studies included 25 individuals aged 5 months to 45 years,[83,85,87] and one of these compared their series of seven children (mean age 3.6 years) with nine other published cases.[85] In addition, a single case report from France[86] and a comprehensive gene review[84] were identified. Hip dysplasia or subluxation were reported in 25%[84] or 26%[85] of cases, while hypotonia was present in 75%.[85] The case report suggested that joint defects are part of the clinical signs of this syndrome,[86] with some reports of onset from birth or infancy.[83] However, the comprehensive review suggested that orthopaedic issues such as scoliosis, contractures, and hip dislocation may develop over time, meriting ongoing physical therapy monitoring.

Wolf–Hirschhorn syndrome

Primary studies included a small cohort of 10 children aged 1 month to 5 years,[88] a small case series of three children (6 years, 7 years, and 15.5 years),[89] and a case report of a 20-month-old child.[90] An older case report provided a review of 43 previously published cases,[92] and a guideline was also identified.[91] Two of 10 children in the small cohort had bilateral hip dislocation.[88] Buddhdev et al. reported on issues with bone quality, leading to non-union or fracture following hip surgeries including varus derotation osteotomies and acetabuloplasty, and recommend not removing hardware.[89] Annual hip surveillance is recommended,[89] with early assessment and treatment.[91]

Other rare disorders

The largest study in this category was a retrospective cohort including 63 children with developmental central hypotonia. Most (50 out of 63) were undiagnosed, and remaining children were diagnosed with various rare chromosomal abnormalities, syndromic hypotonia (including two with Joubert syndrome), or cerebral dysgenesis. Of these 63 children, hip radiographs were reviewed for 53, and follow-up radiographs (at least 1 year later) were available for

33. A migration percentage above 33% was more commonly found in children older than 8 years. Increased migration percentage was also associated with higher GMFCS levels, although most (48 out of 63) were classified in GMFCS levels I to III. Migration percentage did not progress over time in more than two-thirds of children who had more than one radiograph (23 out of 33), although four children (three in GMFCS level IV, one in GMFCS level III) with migration percentages more than 50% required surgery.[108] Surprisingly, only one other report included children with Joubert syndrome.[103] The authors described 11 children aged 1 month to 11 years, all with hypotonia, and 2 out of 11 were described as having CDH.

One study described six individuals with Lowe syndrome aged 4 to 20 years with hypotonia and joint hypermobility. One was born with dislocated hips, while two others developed hip subluxation with increasing age.[101] A comprehensive gene review suggested that joint hypermobility may lead to dislocation and recommended annual orthopaedic surveillance.[102] Two reports seemed to describe the same child with Okamoto syndrome at age 6 months,[100] and at 8 years of age.[99] Bilateral hip dislocation was noted in the neonatal period and treated with a Pavlik harness, but hips were still dislocated at 3 months.[100] Four hip surgeries (not described) appear to have been completed in China, and the authors suggested that at 8 years of age repeated osteotomies may have been required.[99]

One report described the first child with adenosine kinase deficiency (of 18 published cases) who was diagnosed with bilateral hip dysplasia and hip subluxation at 4 years of age.[98] The remaining studies were case reports reporting hip dysplasia, subluxation, or dislocation in infants with deletions related to chromosome 18q,[104–106] or chromosome 4q.[107] These reports all suggested onset at birth or early infancy, and no information on risk factors or treatment beyond use of an abduction splint in the first few months was provided.[104]

Hip problems across diagnoses

Figure 5 illustrates differences in reported onset of hip problems by cases, and the terms used to describe hip problems across diagnoses. For PURA[70,72,75,76] and Wolf–Hirschhorn syndromes,[89,90] a significant proportion of cases were identified at older ages, and increased hip migration percentages in children older than 8 years of age were measured for children with rare diagnoses.[108] For many children with developmental central hypotonia there may be a combination of hip dysplasia that is present in early infancy, as well as increasing instability over time. Hip dislocation was the most highly reported term for individuals with Kabuki and Wolf–Hirschhorn syndromes. Hip subluxation was reported in more than 20% of cases for PURA,[70,76] Emanuel,[94,97] Wolf–Hirschhorn[89] syndromes, and TRPM3-related disorders,[83,84] and was the only term used to describe hip problems in children with a variety of diagnosed and undiagnosed conditions.[108]

Joint or ligamentous laxity was the risk factor reported most overall, particularly for Kabuki[32,35–37] and PURA syndromes.[72,75,76] Posterior acetabular wall deficiency was reported only for Kabuki syndrome,[37,39] while delayed femoral head development was only suggested for 49, XXXXY syndrome,[51] and muscle imbalance was suggested in relation to the cohort of rare conditions.[108] Most detail on interventions was identified for Kabuki syndrome and PWS, with all types of conservative and surgical intervention being reported. Capsular surgery was only described for these diagnoses.[36,37,39,63,64] Four children had hip subluxation with migration percentages above 50% in the cohort of rare conditions, and both periacetabular and femoral varus osteotomies were completed.[108] Femoral osteotomies were also reported for children with Kabuki syndrome,[35] PWS,[63,67] and Wolf–Hirschhorn syndrome,[89] although they were recommended for PURA syndrome.[76]

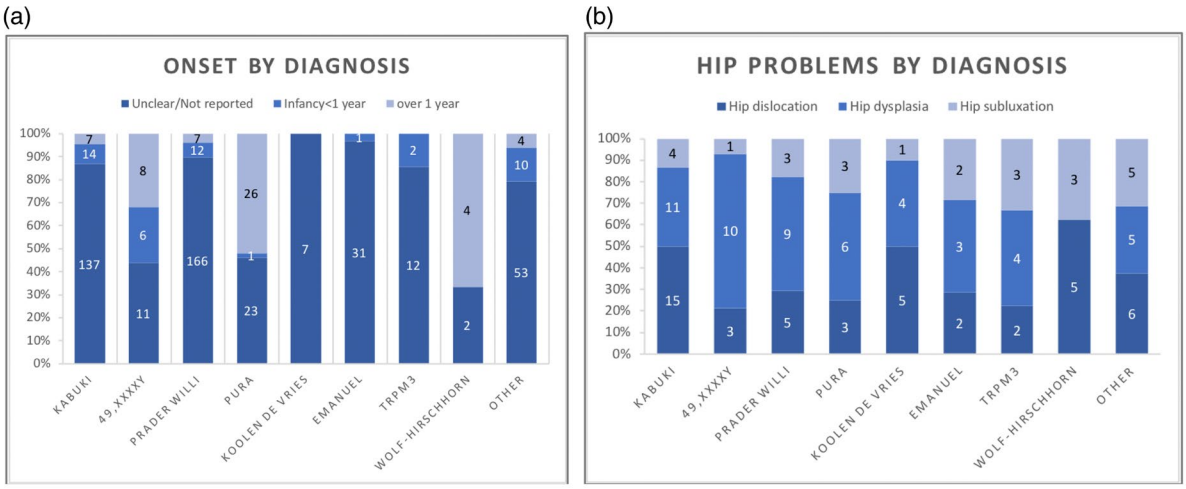

FIGURE 5 (a) Onset reported across diagnoses, by percentage for each diagnosis and by numbers of cases. (b) Hip problems reported across diagnoses, by percentage of reports for each diagnosis and actual numbers of reports.

Recommendations for X-ray frequency and hip/orthopaedic surveillance

Fourteen included studies specifically recommended hip or orthopaedic surveillance for individuals with Kabuki,[31,47] 49, XXXXY,[51,58] PWS,[62,63,66,67,69] PURA,[74,76] Emanuel,[94] Wolf–Hirschhorn,[89] and Lowe syndromes.[102] While hip ultrasound was recommended before 6 months for PWS,[63,65] for Kabuki and 49, XXXXY syndromes authors suggested that hip issues may be identified earlier than the genetic diagnosis is confirmed.[39,56] Among studies that suggested a schedule for surveillance, yearly radiographs and follow-up was the most common recommendation.[67,89,102] One author recommended radiographs at 1 year, 2 years, 5 years, 10 years, and 15 years for PWS,[63] while another recommended yearly radiographs in adulthood.[67] Although many children with developmental central hypotonia may have limited or slow progression of hip problems, some develop hip subluxation without pain or loss of hip abduction range of motion. These individuals will not be identified by clinical assessment so radiographs should be completed at least every 2 to 4 years.[108]

DISCUSSION

This review mapped the literature in relation to hip problems in children and adults with developmental central hypotonia, and included studies related to Kabuki, 49, XXXXY, PWS, PURA, Koolen de Vries, Emanuel, TRPM3, Wolf–Hirschhorn, Joubert, and other rare syndromes. Hypotonia was reported in almost all infants and young children with these diagnoses, and persists into adulthood for a large number of individuals with reported rates ranging from 30%[32] to 88%[79] with the next lowest rate at older ages being 65%.[97] The incidence/prevalence of hip problems was reported between 12%[51] and 35%[30] depending on diagnosis, which is significantly higher than the general population where rates of 1% to 1.5% are reported, or 5 per 1000 in male infants and 13 per 1000 in female infants.[2]

Joint or ligamentous laxity was the most reported risk factor for hip dysplasia in this review followed by hypotonia and hypermobility. However, one study reviewing the status of adults with Koolen de Vries syndrome found that the individuals who were reported to have had dislocated hips (age not reported) were still hypotonic in adulthood, but did not still have hypermobile joints.[79] A retrospective cohort study[62] found that children with PWS who were treated from an early age with growth hormone were less likely to have hip dysplasia as they got older. Another study found that children with Kabuki syndrome exhibited decreased hypermobility (60% reduced to 6%) and improved motor control following 2 years of treatment with growth hormone. The mechanism of growth hormone treatment on hypermobility in these syndromes is not yet understood, but it is thought that it may increase muscle stiffness or promote muscle growth and development.[42] Distinguishing hypermobility, ligamentous and joint laxity, and hypotonia is challenging, and while these are frequently seen together, their exact relationship is unknown.[110,111]

Only a few included studies clearly described the onset of hip problems, with some cases presenting at birth or in early infancy, and others presenting at older ages. However, most included diagnoses appeared to be associated with a combination of some differences in hip structure or function (dysplasia or instability) that were evident from infancy in addition to increasing or acquired hip dysplasia (AHD) over time. This contrasts with AHD in children with CP, who typically have normal hip structure and stability at birth.[112]

Little can be concluded about conservative or surgical intervention for children with developmental central hypotonia because of the small number of cases reported, the heterogenous nature of the interventions and studies, and the limited follow-up. For some infants, use of a Pavlik harness or abduction casting was reported to be effective. This contrasts with children with CP and spasticity or hypertonia, where the use of botulinum neurotoxin and casting or bracing has been shown to be ineffective in reducing hip subluxation and is not recommended.[113] For children with hypotonia and persistent or progressive dysplasia, acetabular osteotomies were most reported in this review, followed by closed or open reductions with or without casting. Femoral de-rotation osteotomies were less common, except in diagnoses where hip problems appear to fit the profile of AHD. This reinforces that acetabular dysplasia is a more common feature, and may be apparent first in children with developmental central hypotonia. Again, this contrasts with children with CP where soft-tissue surgeries may be the first approach, followed by femoral de-rotation osteotomies, while pelvic osteotomies are less common, and more typical for older or more severe cases.[12,15]

It is difficult to draw any conclusions about the incidence of hip problems over time because of the retrospective nature of most included studies, the limited number of larger studies, and the lack of consistent terminology and descriptors used. The trend towards decreased reporting of hip dislocations could indicate better recognition and management, but also may merely illustrate a change in terminology. For example, the term CDH may have been used in earlier studies for all young children with unstable hips, regardless of whether they were actually dislocated or not. Additionally, increased use of genetic testing has probably increased recognition of children with milder forms of these genetic phenotypes and may be the reason for apparently higher incidences of hip problems in older studies compared with later ones.

Owing to the evident confusion of terminology in the literature and in common use, more standard descriptions are required. We would propose that all hip dysplasia identified in infants under 6 months be called DDH, and this may be secondary to their diagnosis, for example DDH-Kabuki, DDH-PWS, DDH-hypotonia (for children who do not yet have a specific diagnosis), etc. Children who are screened in some way and are reported to have

normal hips in infancy, but develop hip dysplasia later, may be termed to have AHD secondary to their primary diagnosis. Therefore, one would have AHD-CP, AHD-spinal muscular atrophy, AHD-Kabuki, etc. Over time this terminology would allow developing data on the need for screening, expected natural history, and response to treatment.

Children with developmental central hypotonia, with or without a confirmed genetic diagnosis, are at increased risk of hip problems, which may be missed with standard neonatal screening. Some countries (such as Austria and Germany) have universal screening for DDH with ultrasound, while many others use clinical screening, with selective hip ultrasound for those with risk factors between the ages of 6 weeks and 6 months. There remains debate about which is the best and most effective approach, which risk factors merit early ultrasound, and the varied protocols for timing of clinical screening and ultrasound.[114] Since infants with significant hypotonia, regardless of diagnosis, have increased risk of hip problems, we would suggest that hypotonia in an infant should be an indication for hip ultrasound between the ages of 6 weeks and 6 months, and referral to orthopaedics for evaluation of any concerns. Annual orthopaedic review with regular radiographs should be started from 12 months for children with hypotonia, and continue for as long as risk factors such as hypotonia, delayed motor development, or non-weightbearing/non-ambulant status are present.

Studies report that many children with developmental central hypotonia and hip dysplasia who were thought to be treated successfully using conservative methods, redislocated or developed increasing hip instability once they began to walk. This reinforces the need for ongoing hip surveillance during the first few years of life. For older children and adults with significant and persistent hypotonia, annual surveillance should be continued, and X-rays and orthopaedic review should be triggered for other individuals with these 'at-risk' diagnoses who demonstrate changes in gait pattern, range of motion, or leg length.

Longitudinal research is needed to understand the natural history of hip dysplasia and subluxation in individuals with developmental central hypotonia. Migration percentages greater than 30% or 33% are the cut-off scores commonly used in hip surveillance programmes for referral to orthopaedics for consideration of preventive intervention.[10] The cohort study of 53 children with developmental central hypotonia identified that a migration percentage greater than 33% was most common in children older than 8 years of age,[108] in contrast to children with CP and spasticity where a migration percentage greater than 30% or 33% is more common between 3 years and 5 years of age.[112] However, there are insufficient longitudinal data at this time to determine whether a migration percentage above 30% predicts future displacement in children with hypotonia.

Higher GMFCS levels are associated with increased hip problems in children with CP.[8–10] Some preliminary data in this review suggest that non-ambulant children with developmental central hypotonia may experience more severe hip problems, requiring intervention. However, ambulatory status was only reported for a very few children in this review, making it difficult to draw any strong conclusions. Most children with developmental central hypotonia appear to be ambulant but some develop hip instability after they begin walking. Most included studies provided insufficient functional details on the natural history and spectrum of motor abilities associated with these rare syndromes. Consistent terminology and functional descriptors are needed to be able to provide an analysis of differences in hip status between children who are functional ambulators and those who are primarily wheelchair users.

There is debate in the literature about the use of GMFCS levels to classify children not diagnosed with CP.[115] However, many children with developmental central hypotonia do meet clinical criteria for a CP diagnosis,[20] and there are insufficient numbers to develop separate diagnosis-specific classifications. The benefits of expanding the definition of CP to include all who have neurodevelopmental disorders and motor disability is increasingly proposed, to enhance access to appropriate care and intervention.[116] While many children with developmental central hypotonia may be considered 'CP-like' (rather than CP), and timing and presentation of hip issues may differ somewhat from children with AHD-CP, we would advocate that they should not be excluded from hip surveillance programmes because of lack of a CP diagnosis. Future research should include consistent functional descriptors such as the GMFCS to confirm or refute any association between hip problems and ambulatory status or GMFCS/functional motor abilities.

This review identified at least eight genetic diagnoses or syndromes, in addition to single reports on several other rare diagnoses underlying the clinical presentation of developmental central hypotonia. Significantly increased incidence of hip problems was identified in all these diagnoses as well as in a cohort of largely undiagnosed children with developmental central hypotonia. This suggests that attention to hip status should be paid for all infants presenting with hypotonia, regardless of specific diagnosis, and that periodic follow-up or hip surveillance over time is warranted. Some differences in the profile and progression of hip problems compared with children with CP have been identified in this review, and the link with ambulatory status is unclear. More research is required to establish the most appropriate hip surveillance protocols for children and adults with developmental central hypotonia.

Owing to the exploratory and descriptive nature of this review, no strong conclusions can be drawn. The included studies are highly heterogenous, and for many conditions only a few articles, or reports of a small number of cases, were identified. In addition, it is unclear how many unique reported cases were included, as various articles included or reported on other cases or cohorts from the literature. It is not clear how these studies overlapped in their inclusion, therefore influencing results and conclusions. The search was broad ranging, and librarian assistance was sought to ensure a thorough search; however, despite this, many

irrelevant citations were retrieved, while some relevant citations were retrieved through simple keyword searches. As with any review, it is possible that we missed relevant citations in grey literature or in other languages. This is the first review to attempt to comprehensively map the literature in this area, and we retrieved a wider range of articles on these rare conditions than anticipated. The search was not restricted in terms of design, age range, or languages and with the iterative and exploratory searching process we are confident that our search is relatively complete.

CONCLUSION

Children and adults with developmental central hypotonia are at increased risk of hip dysplasia, subluxation, and dislocation compared with the general population. This review included a range of genetic diagnoses, where hypotonia is a prominent feature in almost all infants, and continues for a significant proportion into adulthood. Early recognition and conservative intervention may be effective for some of these infants, although genetic diagnoses may not be confirmed until older ages. Proactive screening and hip ultrasound between the ages of 6 weeks and 6 months should therefore be considered for all infants with significant hypotonia, with or without a confirmed genetic diagnosis. Although children with developmental central hypotonia appear to have a higher incidence of acetabular dysplasia in infancy than children with CP, they also present with increasing instability over time. These individuals warrant inclusion in hip surveillance programmes, although there are some differences between the presentation, timing, and progression of hip problems in children with hypotonia compared with the typical protocols for children with CP. For individuals with significant hypotonia, hip surveillance may need to continue through the adolescent years into adulthood, as there are reports of late-onset hip instability in some diagnoses. There is a need for consistent definition and reporting of hip problems in the literature to adequately map the natural history, intervention, and outcomes of children and adults with developmental central hypotonia.

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CONFLICT OF INTEREST STATEMENT

Ginny S. Paleg has worked as an educational consultant for Prime Engineering, a manufacturer of supported standing and stepping devices. She is not an employee, and owns no stock. Prime Engineering provided no funding for this study, and had no influence on study conduct or reporting. Roslyn W. Livingstone, M. Wade Shrader, Freeman Miller and Elisabet Rodby-Bousquet have no interests which might be perceived as posing a conflict or bias.

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SUPPORTING INFORMATION

The following additional material may be found online:
Appendix S1: Primary search strategy and follow-up exploratory search documentation.
Appendix S2: Excluded full-text articles with reasons.
Figure S1: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA) flow diagram illustrating the search.
Table S1: Included studies.

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