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Central nervous system involvement in arthrogryposis multiplex congenita: Overview of causes, diagnosis, and care

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Abstract

Arthrogryposis or AMC, arthrogryposis multiplex congenita, is defined as multiple congenital joint contractures in more than two joints and in different body areas. The common cause of all AMC is lack of movement in utero, which in turn can have different causes, one of which is CNS involvement. Intellectual disability/CNS involvement is found in approximately 25% of all AMC. AMC with CNS involvement includes a large number of genetic syndromes. So far, more than 400 genes have been identified as linked to AMC, with and without CNS involvement. A number of neonatally lethal syndromes and syndromes resulting in severe disability due to CNS malfunction belong to this group of syndromes. There are several X-linked disorders with AMC, which are primarily related to intellectual disability. A number of neuromuscular disorders may include AMC and CNS/brain involvement. Careful clinical evaluation by a geneticist and a pediatrician/pediatric neurologist is the first step in making a specific diagnosis. Further investigations may include MRI of the brain and spinal cord, electroencephalogram, blood chemistry for muscle enzymes, other organ investigations (ophtalmology, cardiology, gastrointestinal, and genitourinary systems). Nerve conduction studies, electromyogram, and muscle pathology may be of help when there is associated peripheral nervous system involvement. But most importantly, genetic investigations with targeted or rather whole exome or genome sequencing should be performed. A correct diagnosis is important in planning adequate treatment, in genetic counselling and also for future understanding of pathogenic mechanisms and possible new treatments. A multidiciplinary team is needed both in investigation and treatment.

KEYWORDS

arthrogryposis multiplex congenita, neonatally lethal AMC syndromes, central nervous system involvement, multi-organ involvement, intellectual disability

1 | INTRODUCTION

Arthrogryposis multiplex congenita, AMC, is defined as congenital contractures in at least two joint levels and in multiple body areas (Dahan-Oliel et al., 2019; Hall & Reed, 1982). Its occurrence in around 1/3,000–5,000 live births (Darin, Kimber, Kroksmark, & Tulinius, 2002; Lowry et al, 2010). And there are now more than 400 known syndromes with arthrogryposis (Hall, 2014). The common background in all AMC is reduced fetal mobility, which in turn can have many causes—pathology in the central nervous system including the brain and anterior horn cells, neuromuscular junction, peripheral nerves, muscle, connective tissue, teratogens, maternal illness, and limitation of space in utero. One way to classify the many different syndromes is to distinguish three main groups: only limb involvement, limb involvement plus other organ systems, and limb involvement plus central nervous system (CNS) involvement (Hall, 2014). The latter group

includes severe forms, including neonatally lethal forms, and syndromes with intellectual disability of varying severity plus other organ system involvement, leading to severe functional disability. The prevalence of syndromes with intellectual disability with or without structural brain anomalies among all cases with AMC varies between 25 and 30% (Darin et al., 2002; Hall, 1997).

Classification and diagnosis of patients with AMC can be difficult. More than 400 known genes that cause AMC can be divided in at least 26 different categories and associated with different pathways, and there are modifying factors that are still unclear (Hall 2016). Where brain involvement is the cause of decreased fetal mobility and AMC, the clinical presentation is often severe. Make a correct diagnosis has several issues. In prenatal diagnosis it is a very important information for parents if there is CNS involvement, as that usually implies a poor prognosis in terms of function and autonomy, and even lethality, and may affect decisions about continuing the pregnancy. In neonatally lethal forms it is important for the parents to know the cause, for genetic counseling and, if possible, for prenatal diagnosis in following pregnancies. In the child with arthrogryposis and brain involvement, a specific diagnosis makes it possible to make a prognosis for future development, and plan treatment and support accordingly—and in the future, medical treatment for some of these disorders may be possible.

In this article, we will describe some examples of the many syndromes with arthrogryposis and brain involvement. We will also mention some important points in investigation/workup of the child with AMC and CNS involvement, and discuss treatment and care.

2 | INVESTIGATIONS

A multidisciplinary approach is paramount in investigating a child with AMC and CNS involvement. Most of these syndromes have a genetic cause. Family history, possible maternal illness, history of pregnancy and delivery should be asked about. A careful clinical examination is the first step in order to direct the genetic investigation and to perform a comprehensive organ investigation. Joint involvement, including jaws and spine, and documentation of type of involvement is important. Flexion or extension of affected joints, tightly fixed or flexible contractures, hypermobile joints, luxation or subluxation; spinal malpositioning, kyphosis or scoliosis; impaired mouth opening, are all important signs to look for and document. Associated findings including facial characteristics and dysmorphic signs should be registered. Photographs of the child are of great value both for diagnosis and follow-up, and in the older child or adult patient photos from the neonatal period are often very helpful for diagnostic purposes. X-rays of affected joints and limbs are usually performed as part of the orthopedic workup. Often, not only skeletal and neuromuscular but also other organ systems are involved, such as cardiovascular, respiratory, gastrointestinal, genitourinary, ophthalmological, and oto-rhino-laryngeal, depending on the underlying cause. A careful neurological evaluation needs to be done: muscle tone and muscle strength should be evaluated, as well as neonatal reflexes, deep tendon reflexes, and cranial nerve functions. Dysmorphic signs, seizures, decreased alertness in the child, and delayed general development may be early signs of CNS involvement.

MRI of the central nervous system and electroencephalogram (EEG) are first tier investigations for respectively, CNS structural and functional anomalies. If it is unclear whether there is central or peripheral nervous system involvement, especially during the first months of life, or if there is a suspicion of associated peripheral nervous system or muscle involvement, neurophysiology studies with electromyogram (EMG), nerve conduction studies (NCS), and muscle pathology might be relevant. In order to rule out associated organ malformations and potential comorbidities, cardiac and abdominal ultrasonography should be performed. Creatine kinase (CK) levels and routine blood and urine chemistry to search for functional organ anomalies for instance of the liver or kidney can be of diagnostic value. On the contrary, more complex metabolic investigations should only be performed if there is a high clinical suspicion since metabolic causes of AMC with CNS involvement remain rare. Evaluation and investigation of cognitive function should always be asked for when there are signs of CNS involvement, and in intellectual disability hearing and vision should be assessed, as well as neuroophtalmological examination.

Chromosomal analysis or CGH array is still the first step in genetic investigation today. When there is a clinical suspicion of a single gene syndrome, targeted gene or gene panel analysis may give the correct diagnosis. In many cases where the diagnosis is unclear, however, whole exome and in the near future whole genome analysis will be the best alternative for genetic diagnosis (Todd et al., 2015, Bayram et al., 2016, Dieterich, Le Tanno, Kimber, Hall, & Giampietro, 2019).

AMC can be diagnosed prenatally with ultrasound investigation (Skaria, Dahl, & Ahmed, 2019). Prenatal diagnosis is important both for parental counseling and to enable planning of a safe delivery. Cesarean section may be indicated if the joint contractures are severe, as there will otherwise be a risk for fracturing of bones during delivery. Investigation with fetal MRI may also give further information regarding possible CNS involvement/brain and other anomalies (Nemec et al., 2011).

3 | CLINICAL SYNDROMES AND GENETICS

Although neuromuscular disorders represent the most frequent cause of syndromes with AMC (Bayram et al., 2016; Beecroft et al., 2018; Darin et al., 2002), disorders affecting the central nervous system are at least as numerous in terms of pathophysiological mechanisms involved and genes implied and vary tremendously among each other from a phenotypical point of view. Interestingly and making the diagnostic procedure even more complex, brain anomalies and intellectual disabilities can be found associated with some neuromuscular diseases with AMC. Here, we want to emphasize the most frequent causes and clinical manifestations of AMC with CNS involvement with the aim to guide the diagnosis and proper management (Figure 1, Figure 2).

Some extrinsic causes in CNS-linked AMC have been identified, especially congenital infections. Today the most frequent viral infection causing AMC and CNS anomalies is maternal Zika virus infection

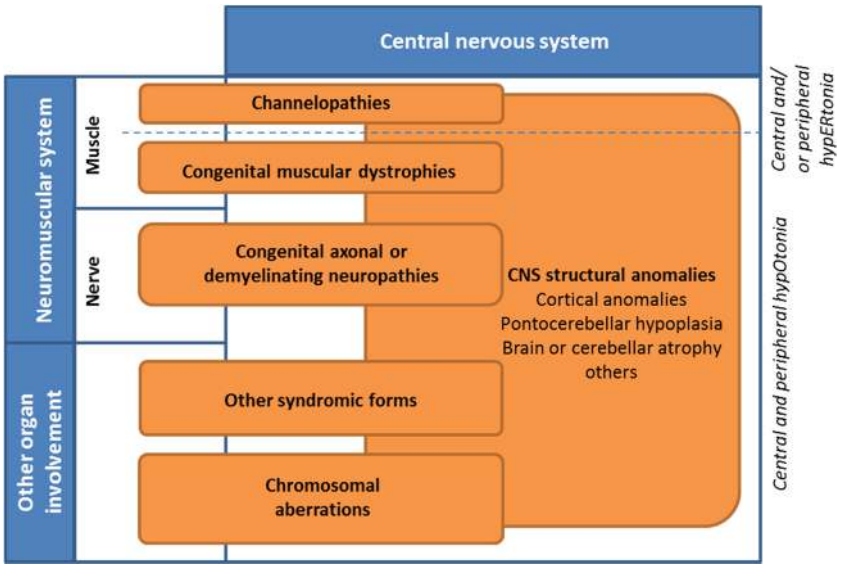
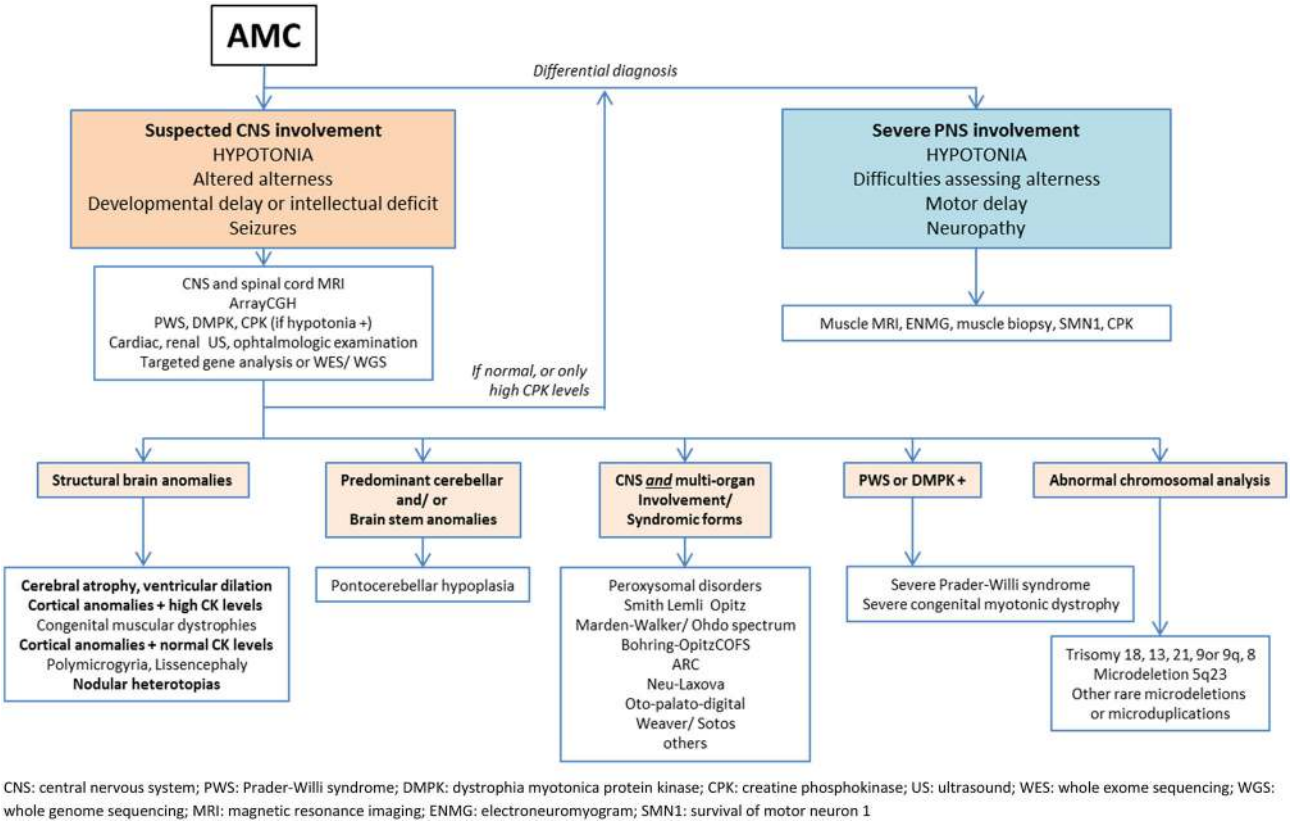


FIGURE 1 Schematic illustration of the main entities of AMC with central nervous system involvement according to the associated anatomical structures involved and the presence of hypertonia and/ or hypotonia



CNS: central nervous system; PWS: Prader-Willi syndrome; DMPK: dystrophia myotonica protein kinase; CPK: creatine phosphokinase; US: ultrasound; WES: whole exome sequencing; WGS: whole genome sequencing; MRI: magnetic resonance imaging; ENMG: electroneuromyogram; SMN1: survival of motor neuron 1

FIGURE 2 Proposition of a diagnostic aid for patients with AMC and suspected central nervous system involvement

during pregnancy (C Lage et al, 2019; Carvalho et al., 2019). Up to 30% of all newborns present with AMC, with bilateral or unilateral hip, knee, hand and/or feet involvement. Microcephaly is constantly associated in these cases. Congenital infections by other viruses, such as the cytomegalovirus (Perlman & Argyle, 1992), varicella zoster virus (Huang, Lin, Chiu, & Hung, 2001), and rubella virus (Hall & Reed, 1982) have also been reported but seem to be very rare in terms of number of affected patients.

As for chromosomal aberrations, by far the most frequent cause associated with AMC is trisomy 18 or Edward syndrome (Hoff, Loane, Gilhus, Rasmussen, & Daltveit, 2011). Multiples joint contractures occur as either club feet or rocker-bottom feet, with clenched fists and overriding fingers, with therefore predominantly distal joint involvement. The diagnosis should be suspected if there are cardiac and to a lesser extend brain malformations, as well as associated growth restriction, and be confirmed by leucocyte karyotype or CGH

array. More than 90% of all cases are straight forward trisomies, whereas mosaicism and translocations or aneuploidies involving chromosome 18 constitute the remaining causes (Rosa, Rosa, Zen, Graziadio, & Paskulin, 2013). Other chromosomal aberrations include trisomies 13 and 21, recurrent translocations of chromosome 9q and 8, and microdeletions especially involving 5q23 (Ansari et al., 2014; Hoff et al., 2011; Riccardi, 1977; Zelante, Notarangelo, Croce, Piemontese, & Gasparini, 1994).

The occurrence of AMC seems to be a very rare event in Prader–Willi syndrome and has per se only been described in two patients (Bigi et al., 2008; Denizot, Boscher, Le Vaillant, Rozé, & Gras Le Guen, 2004). Isolated adducted thumbs have more frequently been described though (Klinge, Scott, & de Sousa, 2001; Oiglane-Shlik et al., 2006) or isolated small hollow feet with malpositioned toes (L'Herminé et al., 2003). The occurrence of diminished movement in late second or third trimester may explain why joint contractures do not appear more frequently in PWS (Gross, Rabinowitz, Gross-Tsur, Hirsch, & Eldar-Geva, 2015; Insoft, Hurvitz, Estrella, & Krishnamoorthy, 1999; Oiglane-Shlik et al., 2006).

Congenital myotonic dystrophy is another frequent cause of fetal hypo- or akinesia presenting usually at birth with respiratory insufficiency, severe generalized hypotonia, facial diplegia and diminished deep tendon reflexes without fasciculations. The diagnosis is often suspected because of a family history of classic myotonic dystrophy and/or typical clinical signs in the mother (facial appearance, myotonia, neuropsychological signs) and prenatal polyhydramnios. Of note, myotonia is usually not evident in the newborn or child, but should be searched for in the mother (Roig, Balliu, Navarro, Brugera, & Losada, 1994). Joint contractures regularly involve the feet (club feet, pes equinus, pes planovalgus), but may also be present at multiple joint levels such as the hips, knees, shoulders and elbows, even without distal limb contractures (González de Dios et al., 1999; Martinello, Piazza, Pastorello, Angelini, & Trevisan, 1999; Schilling, Forst, Forst, & Fujak, 2013). Up to 20% of patients with congenital myotonic dystrophies have been reported with AMC (Schilling et al., 2013). Imaging findings on brain MRI are not specific but the diagnosis is readily done by molecular genetic analysis looking for a pathological CTG expansion in the DMPK gene.

Recently germline mutations in genes encoding essential components of the nodes of Ranvier and paranodes have been associated with severe peripheral and central axoglial diseases presenting with hypokinesia and arthrogryposis: CNTNAP1 (Laquérriere et al., 2014; Lakhani et al., 2017), CNTN1 (Compton et al., 2008), GLDN (Maluenda et al., 2016; Wambach et al., 2017), and LGI4 (Xue et al., 2017). CNTNAP1 mutations have been documented in patients with peripheral nerve hypomyelination and central leucodystrophy, with or without AMC. Structural brain anomalies have been observed: brain atrophy, corpus callosum dysgenesis, and ventricular dilation (Table 1). Only one consanguineous family has been described so far with a homozygous pathogenic variant in CNTN1. Detailed investigations of the CNS were not possible due to the severe phenotype and respiratory insufficiency and early death. There was no response to external stimuli which could be interpreted as CNS involvement. Nevertheless CNTN1 is known to be implicated in neurogenesis during cortical development and in the peripheral nervous system (PNS) alike (Bizzoca et al., 2012; Falk, Bonnon, Girault, & Faivre-Sarrailh, 2002). LGI4 mutations have only been identified in nine patients from four families (Xue et al., 2017). PNS involvement was evident but no structural brain anomalies were seen in MRI imaging in one surviving patient, who had also global developmental delay. Gliomedin, encoded by GLDN was initially found in patients with a lethal congenital contracture phenotype (Maluenda et al., 2016). More recently, patients surviving past the neonatal period have been published (Wambach et al., 2017). No brain anomalies in two surviving patients could be found on MRI but they presented both with either borderline intellectual functioning in late adolescence (17 years) or delayed language development at 2 years. Both proximal and distal joints were involved, but frequently with extended knees, and predominant lower limb involvement.

CNS involvement in congenital muscular dystrophies is associated with secondary alpha-dystroglycanopathies with a very wide range of phenotypic presentations, ranging from the most severe form as Walker–Warburg syndrome (absence of psychomotor acquisitions, severe eye, brain, brain stem involvement with cobblestone lissencephaly, and pontocerebellar hypoplasia), via the less severe muscle-eye-brain disease (pachygyria, polymicrogyria, PCH), to intermediate phenotypes with mild or rare eye and variable CNS anomalies (Sparks et al, 2012; Romero et al, 2018). Joint contractures appear in the most severely affected patients (Astrea et al., 2018; Fukuyama, Osawa, & Suzuki, 1981) (Table 1).

AMC is a clinical finding in pontocerebellar hypoplasia (PCH) type 1 where there is spinal cord involvement and in the more severe form of pontocerebellar hypoplasia PCH4, respectively linked to TSEN54, EXOSC3, RARS2, VRK1, and TSEN54 pathogenic variants (Eggens, Barth, & Baas, 2014 Genereviews; Rudnik-Schöneborn et al., 2013). More recently, PCH9 due to AMPD2 and PCH12 due to COASY mutations have been identified. Patients with these types of PCH also present with multiples contractures at birth possibly linked to either peripheral hypertonia or spinal cord involvement (van Dijk et al., 2018; Kortüm et al., 2018; Table 1).

Peripheral and even central hypertonia has also been observed in what we called "channelopathies." These are due to either homozygous or compound heterozygous loss of function mutations of the sodium dependent glycine transporter 1 encoded by SLC6A9, or heterozygous gain of function mutations of the sodium leak channel nonselective (NALCN) gene (Kurolap et al, 2016; Chong et al, 2015; Aoyagi et al, 2015). The phenotype due to NALCN mutations has been referred to as CLIFHADD syndrome (congenital contractures of the limbs and face, hypotonia, and developmental delay).

Mutations in some genes controlling the human cortical development have also been associated with AMC: KIF5C (Poirier et al, 2013), DYNC1H1 (Das et al, 2018), TUBB2B (Laquérriere et al, 2016) in case of lissencephaly, FLNA (Lah et al, 2016) and NEDDL4 (Elbracht et al, 2018) with periventricular heterotopia, and PI4KA (Pagnamenta et al, 2015) and BICD2 (Laquérriere et al., 2014; Ravenscroft et al, 2016) with polymicrogyria. No abnormal brain or spinal malformations have been documented in patients with TRIP4 mutations, but six out of

TABLE 1 Overview of the anatomical central nervous system (CNS), peripheral nervous system (PNS) and frequent clinical anomalies encountered in genetic and non-genetic AMC causes with CNS involvement

Clinical entities	Congenital infections		Other					Channelopathies		Congenital central and peripheral hypomyelination				Malformations of cortical development									Pontocerebellar hypoplasia						Congenital muscular dystrophy						
Gene or cause of AMC	ZIKV	CMV	Trisomy 18	PWS	Congenital MD	*ZC4H2*	*MAGEL2*	*SLC6A9*	*NALCN*	*CNTNAP1*	*CNTN1*[a]	*LGI4*	*GLDN*	*NEDD4L*	*FLNA*	*TUBB2B*	*KIF5C*	*BICD2*	*DYNC1H1*	*PI4KA*	*TRIP4*[b]	*ASCC1*	*TSEN54*	*EXOSC3*	*VRK1*	*RARS2*	*AMPD2*	*COASY*	*FKTN*	*POMT1*	*POMT2*	*POMGNT1*	*LARGE1*	*FKRP*	*GMPPB*
Global DD or ID when non lethal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brain atrophy	+		+		+	+	+	+	+	+							+																		
Ventricular dilation					+	+		+		+																	+		+	+	+	+	+	+	
Corpus callosum anomalies				+			+	+	+						+	+		+									+			+					
Cortical malformations		+												+	+	+	+	+	+			+	+						+	+	+	+	+	+	+
Nodular heterotopia			+											+	+				+																
Pontocerebellar hypoplasia			+						+[c]							+			+				+	+	+	+	+	+	+	+	+	+	+	+	
Central hypomyelination										+																									
Muscular dystrophy																													+	+	+	+	+	+	+
Moto neuron disease						+						+						+	+		+		+	+	+	+		+							
Neurogenic muscle atrophy										+		+	+									+		+											
Peripheral hypomyelination										+		+	+																						
Axial hypotonia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral hypertonia			+					+	+														+	+	+	+	+	+							
Epilepsy									+	+		+			+	+	+		+								+					+			
Microcephaly	+					+		+	+								+		+				+	+			+	+		+	+				+

Abbreviations: AMC, arthrogryposis multiplex congenita; Congenital MD, congenital myotonic dystrophy; CMV, cytomegalovirus; DD, developmental delay; ID, intellectual deficiency; PWS, Prader-Willi syndrome; ZIKV, Zika virus.

[a]No brain MRI performed so far in published patients.

[b]No brain anomalies on brain MRI in published patients.

[c]Cerebellar atrophy only.

eight presented with learning difficulties (Davignon et al, 2016; Knierim et al, 2016), and mutations in another subunit of the Activating Signal Cointegrator 1 complex, ASCC1, have also been documented in patients with AMC, developmental delay and abnormal cortical gyration (Knierim et al, 2016; Table 1).

Syndromic forms of AMC and multi-organ involvement are very often associated with CNS anomalies. Some examples are Pena Shokeir syndrome/fetal akinesia deformation sequence with intrauterine growth retardation, pulmonary hypoplasia, short gut syndrome, cryptorchidism, and brain malformations (Adam, Coetzee, & Honey, 2018); Miller Dieker syndrome which may include congenital heart defect, microcephaly and brain malformations, typically lissencephaly, renal involvement (cystic or pelvic kidney), cleft palate, duodenal atresia, and more (Köhler et al, 1995); Zellweger syndrome/ Cerebrohepatorenal syndrome, a severe peroxisomal disorder with involvement of many organ systems (brain, liver, kidneys, but also eyes, heart, lungs, gut, genitalia, adrenal glands) (Klouwer et al, 2015). Recently, KIAA1109 variants have been described in a severe disorder of brain development and arthrogryposis, Alkuraya–Kucinskas syndrome, overlapping with Aase Smith syndrome (Gueneau et al, 2018). X-linked arthrogryposis syndromes are frequently associated with intellectual disability (Hunter et al., 2015).

Many of the syndromes with AMC, CNS-involvement and multi-organ involvement may be lethal in the neonatal period. In an epidemiological study from Finland 1987–2002, a total of 214 cases of arthrogryposis were identified in live born infants, stillbirths and terminated pregnancies, and lethal arthrogryposis syndromes, especially LCCS, Lethal Congenital Contracture Syndrome, were found in 141, giving an incidence of just under 1/7,000 (Pakkasjärvi et al., 2006).

4 | MULTIDICIPLINARY CARE AND TREATMENT

A multidisciplinary team management is necessary. At best, this should be carried out totally or in conjunction with a tertiary referral center because of the rarity of these conditions and the special needs in diagnosis and management of these patients. In all individuals with arthrogryposis, physical therapy, splinting and orthotics, and orthopedic treatment/surgery are the mainstays of treatment. Early physical therapy to mobilize stiff joints and activate muscle function is important (Kroksmark, Kimber, Jerre, Beckung, & Tulinius, 2006). Children with arthrogryposis may have difficulties in mouth opening, sucking, and swallowing, and may have major feeding problems in infancy. Some children may need gastric tube feeding. When brain involvement is present, seizures are a common problem and epilepsy may need to be investigated and treated. Problems regarding vision and hearing must be addressed. Functional evaluation and follow-up is important, both regarding cognitive development and motor development. In the child with arthrogryposis and brain involvement/developmental delay, cognitive evaluation by a psychologist should be done at appropriate ages, to be able to plan adequate schooling and psychosocial support. Motor development and function should be evaluated and followed by physiotherapist and occupational therapist in addition to treatment and planning of appropriate physical aids, training and activities. Involvement of a speech therapist may be needed for speech and feeding problems, a dietician may be needed for nutritional problems. The orthopedic surgeon and neonatologist/pediatrician will naturally be involved. Genetic evaluation and investigation is necessary. But other specialists, for example, cardiologist, ophthalmologist, neurologist, and others may also need to be involved. Endocrine and/or metabolic problems may be present and need treatment.

5 | CONCLUSIONS

There is an extreme diversity in the causes and clinical presentations of AMC associated with anomalies of the central nervous system. Often, AMC represents the most severe end of the phenotype related to a specific gene or cause, which means that AMC is not always a constant feature in these diseases. Furthermore, and despite their diversity, the clinical signs and CNS imaging findings most often lack specificity. At best, some associated signs may either be in favor of or make less probable one or several disease groups. As a consequence, and unless we find more robust genotype–phenotype associations, making a precise diagnosis remains challenging. More and more causes also imply involvement of both the central and the peripheral nervous systems, for example, DYNC1H1, BICD2, ZC4H2, or MAGEL2. In some cases, AMC seems to be linked rather to the peripheral nervous system involvement than to the CNS anomalies. Severe forms of CNS involvement in patients with DYNC1H1 mutations may present with spastic tetraparesis but without AMC (Poirier et al, 2013), whereas congenital joint contracture are a frequent finding in severe forms with peripheral nervous system involvement and presenting as spinal muscular atrophy lower extremity predominant/ SMALED1 (Harms et al, 2012).The clinician should therefore follow a systematic clinical and paraclinical evaluation of these patients. These data will also help in interpreting and confirming the molecular diagnosis on WES or WGS or CGHarray.

Much still needs to be learned about the causes and possible treatments of these often severe syndromes with arthrogryposis, brain involvement, intellectual disability and often also other organ involvement. Careful clinical evaluation is essential in investigating the child with arthrogryposis and brain involvement, as well as targeted investigation of organ systems, blood and urine chemistry, depending on the clinical signs and symptoms. Whole-genome sequencing is often the best way to identify the genetic cause when the diagnosis is unclear in conjunction with a detailed clinical evaluation. Because of the rarity and the special needs of these children and adults, a multidisciplinary approach is paramount both in investigation and in management.

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