Research in Developmental Disabilities 45–46 (2015) 178–187

Contents lists available at ScienceDirect

Research in Developmental Disabilities

Relationship between characteristics on magnetic resonance imaging and motor outcomes in children with cerebral palsy and white matter injury

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ARTICLE INFO

Article history:
Received 10 February 2015
Received in revised form 26 July 2015
Accepted 28 July 2015
Available online 8 August 2015

Keywords:
Cerebral palsy
Magnetic resonance imaging
White matter injury
Periventricular leukomalacia
Intraventricular haemorrhage

ABSTRACT

In a population cohort of children with white matter injury (WMI) and cerebral palsy (CP), we aimed to describe the magnetic resonance imaging (MRI) characteristics, identify key structure–function relationships, and classify the severity of WMI in a clinically relevant way. Stratified on MRI laterality/symmetry, variables indicating the extent and location of cerebral abnormalities for 272 children with CP and WMI on chronic-phase MRI were related to gross motor function and motor topography using univariable and multivariable approaches. We found that symmetrical involvement, severe WM loss in the hemispheres and corpus callosum, and cerebellar involvement were the strongest predictors of poor gross motor function, but the final model explained only a small proportion of the variability. Bilateral, extensive WM loss was more likely to result in quadriplegia, whereas volume loss in the posterior-mid WM more frequently resulted in diplegia. The extent and location of MRI abnormalities differed according to laterality/symmetry; asymmetry was associated with less extensive hemispheric involvement than symmetrical WMI, and unilateral lesions were more focal and located more anteriorly. In summary, laterality/symmetry of WMI, possibly reflecting different pathogenic mechanisms, together with extent of WM loss and cerebellar abnormality predicted gross motor function in CP, but to a limited extent.

1. Introduction

Cerebral palsy (CP) is the term used to describe individuals with a movement disorder resulting from non-progressive disturbance to the developing brain (Rosenbaum, Paneth, Leviton, Goldstein, & Bax, 2007). On neuroimaging, various patterns of brain disturbance can be identified and classified in mutually exclusive categories that reflect the timing of the disturbance and the likely pathogenic mechanism (Himmelmann & Uvebrant, 2014; Krageloh-Mann, Horber, Petruch, Weber, & de la Cruz, 2013; Reid et al., 2014a; Robinson et al., 2008; Towsley, Shevell, & Dagenais, 2011). White matter injury

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http://dx.doi.org/10.1016/j.ridd.2015.07.030
0891-4222/

(WMI), typical of children born preterm, is consistently reported as the most common pattern in CP, with up to 50% of children with CP classified to this pattern (Reid et al., 2014a; Reid, Dagia, Ditchfield, Carlin, & Reddihough, 2014b). Most neuroimaging classifications of WMI include periventricular leukomalacia (PVL), intraventricular haemorrhage (IVH), and periventricular haemorrhagic infarction (PVHI) (Krageloh-Mann & Horber, 2007). PVL traditionally refers to necrosis of white matter dorsal and lateral to the external angles of the lateral ventricles, with either cyst formation or glial scarring (Volpe, 2008). Less severe, diffuse injury that occurs peripherally is increasing being seen without the focal necrosis. Haemorrhage, on the other hand, commonly originates from the richly vascularised germinal matrix cells that line the walls of the lateral ventricles, between the head of the caudate nucleus and the thalamus. In most cases, blood enters the lateral ventricles and spreads throughout the ventricular system (IVH). PVHI is thought to be secondary to periventricular white matter venous congestion and subsequent infarction, caused by high-grade IVH (Volpe, 2008).

Compared to other abnormal MRI patterns in CP, children with WMI typically have spastic diplegia or hemiplegia and are ambulant (Arnfield, Guzzetta, & Boyd, 2013; Bax, Tydeman, & Flodmark, 2006; Robinson et al., 2008; Towsley et al., 2011). Evidence from a small number of studies indicates that the location of white matter (WM) lesions is related to motor outcome (Bax et al., 2006; Staudt, Niemann, Grodd, & Krägeloh-Mann, 2000; Staudt, Pavlova, Bohm, Grodd, & Krageloh-Mann, 2003). Comparatively less, however, is understood about severity of WMI, the best method of classifying severity, and the relationship between severity and clinical outcomes. Although scoring systems have been developed to rate neonatal brain injury in infants born preterm and to predict the subsequent risk of adverse neurodevelopmental outcome (Inder, Wells, Mogridge, Spencer, & Volpe, 2003; Kidokoro, Neil, & Inder, 2013; Miller et al., 2005; Nguyen The Tich et al., 2009; Sie et al., 2005; Woodward, Anderson, Austin, Howard, & Inder, 2006), these systems tend to rely on features that are unique to the immature neonatal brain (Shiran et al., 2014), and were not designed to discriminate characteristics of WMI in children with ongoing motor impairment.

In response to the lack of scoring systems for the severity of brain abnormality in children with CP, two new systems have recently been proposed. One is a semi quantitative method that uses a graphical template of the brain hemispheres onto which the lesion is transposed, and a scoring system for quantitative analysis of the lesion characteristics (Fiori et al., 2014). The construct validity of the new system is now being tested through determination of the size of correlations between lesion scores and clinical outcomes in specific CP subgroups. Low to moderate correlations have been observed between hemispheric scores and measures of upper limb function in children with unilateral CP and periventricular white matter lesions (Fiori et al., 2015). The other new severity rating scale is also intended for all pathogenic patterns and comprises scores for the number of lobes affected and for abnormalities within the white matter, grey matter, and major white matter tracts based on assessment of anatomic MRI (Shiran et al., 2014). Thus far, total scores have shown only weak correlation with GMFCS levels in children with hemiplegia, but good correlation with measures of upper limb function.

We have taken a different, but complementary, approach to the issue of scoring severity of abnormalities on neuroimaging in CP. On the basis of their MRI, the children in our large 1999–2008 population cohort have already been assigned to one of six broad patterns that reflect the presumed pathogenesis and timing of injury (Reid et al., 2014a), in this case a WMI pattern. We planned to describe the range of clinical outcomes resulting from WMI and determine which characteristics, individually or in combination, best predicted clinical outcomes such as level of gross motor function. These analyses would then be used to inform a severity classification for WMI that could be used in conjunction with the MRI classification already in use in Europe and Australia. The few previous studies that have explored structure–function relationships in CP have typically been performed in groups defined by clinical subtype (Cioni, 1997; Cioni et al., 1999; Holmefur et al., 2013; Krageloh-Mann et al., 1995; Kułak et al., 2007; Shiran et al., 2014; Yokochi et al., 1991), are have not been used solely to subclassify WMI severity in all CP subtypes. The studies that have been based on imaging pattern have still restricted inclusion to specific CP subtypes (Lee et al., 2011; Staudt et al., 2000, 2003).

In the absence of data on structure–function relationships that are specific to WMI and inclusive of all CP subtypes, the aims of this study were (1) to further characterise WMI in a large population CP cohort irrespective of clinical subtype, (2) to determine which MRI characteristics have the strongest associations with motor outcomes, and (3) based on the strength of identified associations, to develop a severity classification for WMI that discriminates children with different levels of functional ability. The ability to classify severity of WMI using conventional structural MRI not only has prognostic value for children whose first MRI is performed in the chronic phase of injury, but can provide clinicians with an additional tool for counselling families about imaging results and their relationship to clinical outcome. A meaningful WMI severity classification will also be important for ongoing research into causal pathways and preventive strategies within pathologically similar subgroups, and will facilitate comparison between geographic cohorts.

2. Method

The study was conducted at the Melbourne Children's campus, Australia. The Royal Children's Hospital Human Research Ethics Committee approved the study protocol and waiver of consent.

2.1. Study cohort

Eligible participants were identified from the Victorian Cerebral Palsy Register, a population registry established in 1987 to capture data on persons born or living in the Australian state of Victoria from 1970 who conform to the recognised