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Original article

Early detection of cerebral palsy in high-risk infants: translation of evidence into practice in an Australian hospital

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Short title: *Early detection of cerebral palsy*

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Abstract

Background and Aims: The early diagnosis of cerebral palsy allows children timely access to early intervention. In 2018, Monash Children's Hospital established an Early Neurodevelopment Clinic based upon evidence-based guidelines for the early diagnosis of cerebral palsy in high-risk infants. In this study, we aimed to characterise the infants presenting to the clinic and determine the rate of cerebral palsy diagnosis.

Methods: This study analysed data from infants attending the Early Neurodevelopment Clinic between May 2019 and April 2020. Infants at high-risk for cerebral palsy attended the clinic at three months corrected age. Neuroimaging reports were reviewed, and a Prechtl's General Movement Assessment and Hammersmith Infant Neurological Examination were performed. Infants were diagnosed as having typical development, delayed development, high-risk of cerebral palsy or cerebral palsy at the time of clinic attendance and referred on to the appropriate pathway.

Results: Ninety-six high-risk infants attended the clinic over the one year study period. Sixty-eight (71%) infants were extremely preterm or extremely low birth weight, and 28 (29%) were infants at born at older gestation with evidence of moderate to severe brain injury. Nine (9.6%) infants received a cerebral palsy diagnosis and 12 (12.5%) were considered high-risk of cerebral palsy. All infants with cerebral palsy or high-risk of cerebral palsy were referred to the Victorian Paediatric Rehabilitation Service.

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Conclusions: It is feasible to implement the early cerebral palsy diagnosis guidelines into a high-risk infant follow up clinic. Implementation of the guidelines allows for early diagnosis of cerebral palsy and appropriate referral of high-risk infants.

Key notes:

What is already known?
- Half of all infants with cerebral palsy have risk factors evident in the newborn period.
- Cerebral palsy can be identified in high-risk infants as early as 3-months corrected age.
- Cerebral palsy specific early intervention advances cognitive and motor development.

What this paper adds?
- This is the first Australian study to report on the implementation of early cerebral palsy diagnosis guidelines into a multidisciplinary outpatient clinic.
- Cerebral palsy was more commonly diagnosed in infants with evidence of moderate to severe brain injury than in extremely preterm or extremely low birth weight infants.

Keywords:
General movements, hammersmith infant neurological examination, neuroimaging, follow-up

Abbreviations:

CP	Cerebral palsy
GMA	General Movement Assessment
HINE	Hammersmith Infant Neurological Examination
MRI	Magnetic resonance imaging

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Introduction

Cerebral palsy (CP) is defined as "a group of permanent disorders of the development of movement and posture, causing activity limitation, attributed to non-progressive disturbances that occurred in the developing fetal or infant brain[1]." CP affects 1.4 per 1000 live births in Australia[2].

It was previously thought that CP could not be diagnosed before 12 months of age. However, in high-risk infants, signs of CP are visible early in life. The early diagnosis of CP enables access to appropriate early intervention to optimise motor function and better manage comorbidities. Early interventions within the first year of life in infants with or at high-risk of CP may have positive effects on cognitive and motor development and family wellbeing[3].

In 2017, a group of CP experts and other key stakeholders published a set of twelve recommendations for the early diagnosis of CP based upon a systematic review of high-quality evidence[4]. The guidelines recommend that infants are given the diagnosis of CP or an interim diagnosis of "high-risk of CP" as early as possible to ensure they receive timely access to appropriate therapies and support. The guidelines recommend that infants with known CP risk factors are assessed before five months of age using neuroimaging with magnetic resonance imaging (MRI), motor assessment with Prechtl's General Movement Assessment (GMA) and the Hammersmith Infant Neurological Examination (HINE).

Despite the strong evidence guiding the recommendations, there is little published literature on the implementation of these guidelines into clinical practice. Two studies within the United States have showed that implementation of the recommendations into high-risk infant follow up clinics is both feasible and practical[5, 6]. Real-world results from an Australian setting are important to analyse as the guidelines become more widely implemented.

In 2018, the Early Neurodevelopment Clinic was established at Monash Children's Hospital, Melbourne, Australia based upon the recommendations for the early diagnosis of CP. This analysis describes the utilisation of the clinic and the rate of CP diagnosis.

Methods

This study was conducted within the Early Neurodevelopment Clinic at Monash Children's Hospital, Melbourne, Australia. Monash Children's Hospital is one of two tertiary paediatric hospitals within Victoria and houses Monash Newborn, Victoria's largest Neonatal Intensive Care Unit. Monash

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Newborn admits more than 1500 babies each year[7]. In 2017, approximately 600 babies admitted to the unit were born less than 32 weeks, weighed less than 1500 grams at birth, required assisted ventilation for more than four hours, received major surgery, or received therapeutic hypothermia[8]. This project had ethics approval from the Monash Health Human Research Ethics Committee as a quality assurance project. It followed the guidelines set out in the National Statement of Ethical Conduct in Human Research (2007).

Clinic structure

The Early Neurodevelopment Clinic is held once a week within the Therapies department of Monash Children's Hospital. The unique location allows families access to allied health specialists, including physiotherapists, occupational therapists, and social work within a single appointment.

Two groups of infants were referred to the Early Neurodevelopment Clinic: infants born less than 29 weeks gestation or with a birthweight less than 1000 grams; and infants with evidence of moderate to severe brain injury who were born at any other gestation. A label of moderate to severe brain injury was considered if there was Papile grade three to four intraventricular haemorrhage[9], cystic periventricular leukomalacia, neonatal stroke, term hypoxic-ischaemic encephalopathy ($\geq$ 35 weeks gestation at birth), or other significant neurological conditions. The guideline indicates both these groups are high-risk for CP and should undergo comprehensive screening and assessment, using the most predictive tools outlined on the "newborn detectable risk" pathway of the guideline.

Infants attended the clinic at three months corrected age (12 – 14 weeks post-term age). A GMA and HINE were performed on all infants by both a neonatal consultant and physiotherapist trained in the assessments[10, 11]. Other allied health clinicians joined the consultation when required. The GMA was performed by observing infants for signs of fidgety movements[10, 12]. Infants were classified as having continuous fidgety movements, sporadic fidgety movements or absent fidgety movements, as per the test conventions. The HINE was completed using the standard proforma and scored from zero to 78, where a score less than 57 at 3-months indicates high risk for CP[11].

Neonatal cranial ultrasound and MRI brain reports (where available) were reviewed. Neonatal cranial ultrasounds were classified as abnormal by the presence of interventricular or cerebellar haemorrhage, persistent periventricular echogenicity over two or more ultrasounds, cystic changes or other significant pathology. Interventricular haemorrhage was graded using the Papile classification[9]. Any abnormality on MRI brain was considered abnormal. MRI findings were broadly

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categorised as normal, or showing maldevelopments, predominant white matter injury, predominant grey matter injury or miscellaneous pathology, as per the classification system by Himmelmann et al[13].

Infants were classified and diagnosed as having typical development, delayed development, high-risk of CP or CP at the time of clinic attendance based upon the above assessments. Physiotherapy follow-up occurred for infants with delayed development and infants with typical development but other concerns (either parent or clinician). Infants diagnosed as high-risk of CP or having CP were referred to the Victorian Paediatric Rehabilitation Service. Typically developing infants with no concerns were discharged to routine community care.

Data collection and analysis

Data was collected between the 12 months of May 2019 and April 2020 using electronic patient records.

Statistical analysis of the results was performed using IBM SPSS Statistics 25 (SPSS Inc, Chicago, USA). A Shapiro-Wilk test was performed on numerical data to determine the normality. Mean (SD) or median (IQR) was calculated for normally and non-normally distributed data, respectively. The number (%) was calculated for categorical variables.

Results

Between May 2019 to April 2020, 96 (98%) of 98 infants booked to the Early Neurodevelopment Clinic attended. Sixty-eight (70.8%) infants were born less than 29 weeks gestation or less than 1000 grams. Twenty-eight (29.2%) infants had evidence of moderate to severe brain injury and were born over 29 weeks gestation; eight (28.6%) had preterm brain injury, 13 (46.4%) had term hypoxic-ischaemic encephalopathy requiring therapeutic hypothermia, and seven (25.0%) had other neurological conditions (neonatal stroke, hydrocephalus, neonatal seizures or recurrent sleep apnoea).

Table 1 shows the characteristics of infants attending the Early Neurodevelopment Clinic and Table 2 summarises the assessment results and outcomes of the groups. All infants had neuroimaging performed before the clinic appointment. Cranial ultrasound was performed in 94 (97.9%) infants, and 48 (51.1%) had an abnormality present; 30 (31.9%) had grade 1 or 2 interventricular haemorrhage, seven (7.4%) had grade 3 or 4 interventricular haemorrhage, eight (8.5%) had

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evidence of white matter injury and three (3.2%) had other pathologies. MRI brain was performed in 75 (78.1%) infants and 49 (65.3%) had an abnormality present; 1 (1.3%) had maldevelopment, 33 (44%) had predominant white matter injury, 10 (13.3%) had predominant grey matter injury and 5 (6.7%) had miscellaneous pathology.

During the clinic appointment, a HINE and GMA were successfully performed on 92 (96%) and 94 (98%) infants respectively. The median (IQR) HINE of infants with typical development, delayed development, high-risk of CP or CP was 60.0 (56.3 – 63.0), 50.0 (45.0 – 52.0), 45.5 (40.8 – 47.5) and 34 (26.8 – 45) respectively. Of the seventeen infants who had "absent" fidgety movements, nine (53%) were diagnosed with CP, seven (41%) with high-risk of CP and one with developmental delay.

Two (3%) infants in the less than 29 week gestation or less than 1000g subgroup were diagnosed with CP and seven (10%) were given the diagnosis of high-risk of CP. In infants born less than 29 weeks gestation or with a birth weight less than 1000 grams, the prevalence of CP was 29 per 1000 neonatal survivors, and the prevalence of CP or high-risk of CP was 132 per 1000 neonatal survivors. Seven (25%) infants in the moderate to severe brain injury sub-group were diagnosed with CP, and five (18%) were given the diagnosis of high-risk of CP. Of the seven diagnosed with CP, six (85.7%) had term hypoxic-ischaemic encephalopathy. All 21 infants who received the diagnosis of high-risk of CP or CP were referred to the Victorian Paediatric Rehabilitation Service.

Discussion

To our knowledge, this is the first publication describing the implementation of early CP diagnosis guidelines in an Australian setting. This study shows that it is feasible to implement the guidelines into a high-risk infant follow up clinic. As a result of the Early Neurodevelopment Clinic, 21 high-risk infants were diagnosed with CP or high-risk of CP in 12 months. Importantly, this facilitated access to early intervention and support.

The attendance rate at the Early Neurodevelopment Clinic was high, and GMA, HINE and MRI were performed in the majority of infants. Telehealth appointments and crying infant states were barriers to performing the HINE and GMA in some infants. The guidelines by Novak et al.[4] recommend that all high-risk infants should have an MRI brain performed to allow for the early diagnosis of CP. Currently, Monash Newborn performs MRI brain scans at term equivalent age in preterm infants born less than 26 weeks gestation, those with significant preterm brain injury on cranial ultrasound,

or term infants with hypoxic-ischaemic encephalopathy undergoing therapeutic hypothermia, or another significant neurological event. All infants who did not have a term MRI brain had at least one cranial ultrasound while within the neonatal intensive care unit. Cranial ultrasounds have been shown to have a similar specificity to MRI for the diagnosis of CP but are less sensitive at detecting white matter changes at term[14].

Many infants had an abnormality detected on neuroimaging but few went on to be diagnosed with CP or high risk of CP. Low-grade interventricular haemorrhage (Papile grade 1 or 2) was the most common abnormality on cranial ultrasound. This has not been shown to increase the risk of CP when compared to a normal cranial ultrasound[15]. White matter injury was the most common abnormality detected on MRI brain. This is the most common finding on MRI brain in children diagnosed with CP and severe white matter injury is associated with worse motor impairment[16]. The Himmelmann et al.[13] MRI classification system used in this study does not take into consideration the severity of the white matter changes.

The median HINE scores of infants with typical development and infants diagnosed with CP were slightly lower than those reported by Romeo et al[17]. This may be attributed to our population having a lower median birth weight and gestational age, or may be the result from a small number of incomplete examinations due to COVID-19 necessitated telehealth.

Twenty-one percent of infants born less than 29 weeks gestation or less than 1000 grams had cramped synchronised movements observed at least once during admission to the neonatal intensive care unit. Few went on to have absent fidgety movements observed. Cramped synchronised movements have been shown to be highly predictive of absent fidgety movements and CP when observed consistently over the infantile period[18]. The predictive value is less when they are observed transiently or in the early preterm period.

Ninety-four percent of infants who had absent fidgety movements were diagnosed with CP or high risk of CP. This finding fits with previous knowledge that absent fidgety movements are highly predictive of CP in both the preterm and term infant[14].

The most recent report from Australia showed that from 2010 to 2012, the prevalence of CP was 50 per 1000 neonatal survivors born less than 1000 grams[2]. This is higher than the prevalence of CP reported by our study in the less than 29 weeks gestation or less than 1000 grams subgroup. The

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interim diagnosis of "high-risk of CP" may attribute to the prevalence being lower, as some infants in the high-risk group will likely go on to be diagnosed with CP.

This study showed a higher rate of CP diagnosis in term infants with hypoxic-ischaemic encephalopathy compared infants born less than 29 weeks gestation or less than 1000 grams and in preterm infants born between 29 and 36 weeks gestation with evidence of preterm brain injury. The rate of CP diagnosis in infants with term HIE was higher than the 17 – 19% reported by previous studies[19, 20]. This increased rate may be due to a small sample size.

Fourteen infants (14.6%) received postnatal corticosteroids to prevent or treat chronic lung disease. Twelve infants (85.7%) went on to develop chronic lung disease, and two (14.3%) infants went on to be diagnosed as high-risk of CP. Postnatal corticosteroid use has been associated with increased risk of CP, but the risk decreases in infants at high-risk of chronic lung disease[21]. As a majority of infants who received postnatal corticosteroids went on to develop chronic lung disease, we can assume that postnatal corticosteroids were given to a high-risk preterm infant group. We found that chronic lung disease occurred in 60.3% of infants born less than 29 weeks or with a birth weight less than 1000g. This rate is higher than that reported by the Australian and New Zealand Neonatal Registry for infants born less than 29 weeks gestation[8].

A formal diagnosis of CP or high-risk of CP is not essential for families to access necessary intervention and support within Australia, however it may make it easier for families to access services, particularly in regard to financial support (National Disability Insurance Schemes). The multidisciplinary nature of the Early Neurodevelopment Clinic links families with allied health specialists, such as social workers, which may further assists them in accessing these services.

Limitations

This small study examined the initial experience of the Early Neurodevelopment Clinic. As overall numbers were low, we are unable to perform statistical tests to ascertain differences between the groups. This study did not include data prior to the establishment of the Early Neurodevelopment Clinic. Therefore, we were unable to compare the rate of diagnosis or identify if the clinic decreased the average age of diagnosis. Due to finite resources, the Early Neurodevelopment Clinic had stricter eligibility criteria for screening than those recommended by the guidelines[4]. The clinic assesses referred infants with risk factors for CP identified in the newborn period. This group constitutes half

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of all children later diagnosed with CP[22]. The guidelines recommend that infants with no known CP risk factors but developmental concerns undergo an assessment for CP after five months of age[4]. How health services provide appropriate access to this population requires further consideration. Infants diagnosed with CP or high risk of CP at 3 months corrected age are required to have the diagnosis confirmed at a later stage. Further studies in this area may analyse the stability of the early CP diagnosis with age.

Conclusions

It is feasible to implement the early CP diagnosis guidelines into a high-risk infant follow up clinic within Australia. Providing a diagnosis of CP or high-risk of CP as early as three months corrected age through an Early Neurodevelopment Clinic resulted in families receiving early access to targeted early intervention and support.

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Table 1 - Demographics of Infants attending the Early Neurodevelopment Clinic

	<29 weeks/<1000 g (n= 68)	>29 weeks with evidence of brain injury (n=28)
Gestation at birth (weeks)	27.6 (3.3)	37 (5.8)
Birthweight (g)	879.5 (329.5)	2537 (1461)
Sex		
Male	39 (57.4)	16 (57.1)
Female	29 (42.6)	12 (42.9)
Mode of delivery		
Vaginal	23 (33.8)	16 (57.1)
Caesarean	45 (66.2)	12 (42.9)
Apgar Score		
1 minute (n=95)	5.5 (2.3)	4.5 (3.2)
5 minutes (n= 94)	7.3 (1.6)	6.3 (2.8)
Multiple birth	11 (16.2)	2 (7.1)
Surgery during neonatal period	3 (4.4)	3 (10.7)
Necrotising enterocolitis requiring surgery	2 (2.9)	0 (0)
Chronic lung disease†	41 (60.3)	4 (14.3)
Discharged on home oxygen	11 (16.2)	2 (7.1)
Retinopathy of prematurity requiring laser	5 (7.4)	0 (0)
Patent ductus arteriosus requiring treatment	17 (25)	0 (0)

Culture-proven sepsis	19 (27.9)	2 (7.1)
Postnatal corticosteroids	14 (20.6)	0 (0)
Hammersmith Neonatal Neurological Exam Score (n=68)	28 (4.5)	25 (6)
Generalised movements during neonatal period‡ (n= 92)		
Normal writhing	2 (3)	1 (4)
Poor repertoire	51 (76.1)	21 (84)
Cramped synchronised	14 (20.9)	3 (12)

Data represented as number (%), median (IQR) or mean (SD).

† Chronic lung disease is defined as the need for respiratory support past 36 weeks gestation.

‡ General movement assessment presented as worst score across neonatal period.

Table 2 – Outcomes from the Early Neurodevelopment Clinic

	<29 weeks/<1000 g (n= 68)	>29 weeks with evidence of brain injury (n=28)
Corrected gestational age at appointment (weeks)	13.6 (1.1)	13.1 (1.4)
Abnormality present on imaging		
Abnormality on MRI (n=75)	26 (54.2)	23 (85.2)
Abnormality on US (n=94)	36 (52.9)	12 (46.2)
Hammersmith Infant Neurological Exam† (n=92)	55 (11)	47.3 (14.6)
General Movement Assessment (n=94)		
Fidgety present (continuous)	55 (82.1)	15 (55.6)
Fidgety present (sporadic)	5 (7.5)	2 (7.4)
Fidgety absent	7 (10.4)	10 (37)
Neurodevelopmental Diagnosis		
Typical development	36 (52.9)	7 (25)
Developmental delay	23 (33.8)	9 (32.1)
High risk of Cerebral Palsy	7 (10.3)	5 (17.9)
Cerebral palsy	2 (2.9)	7 (25)
Need for ongoing follow up		
No follow up	20 (29.4)	1 (3.6)

Physiotherapy alone	40 (58.8)	14 (50)
Rehabilitation service	8 (11.8)	13 (46.4)

Data represented as number (%) and median (IQR).

† A small number of assessments were performed via telehealth due to COVID-19.

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Original article

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Conflicts of interest

No conflicts of interest to declare.

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