Reorganisation of the sensorimotor cortex following early unilateral brain damage

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1- to describe the presence and severity of hemiplegic CP on the basis of neonatal MRI findings and correlate the involvement of different structures (basal ganglia, posterior limb of the internal capsule and hemisphere) with the size of the lesion2…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital and peripartum neurological conditions
Study type	Observational invasive

Summary

ID

NL-OMON41354

Source
ToetsingOnline

Brief title
Cortical reorganisation following early brain injury

Condition

- Congenital and peripartum neurological conditions
- Neonatal and perinatal conditions
- Vascular haemorrhagic disorders

Synonym
neonatal stroke

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: WKZ Onderzoeksfonds

Intervention

Keyword: hemiplegia, infarct, plasticity, stroke

Outcome measures

Primary outcome

Outcome measures

Primary outcome measure: nature of reorganisation, defined as *intra-hemispheric reorganisation* or *inter-hemispheric reorganisation* and relation between reorganisation and *functional outcome*, assessed with gross- and fine motor developmental status (see methods).

Secondary outcome

not applicable

Study description

Background summary

Hemiplegic cerebral palsy is the most common form of cerebral palsy (CP) with a prevalence of 1:3000 livebirths.1 Perinatal arterial ischemic stroke (PAIS) is responsible for more than 70% of moderate to severe hemiplegic CP.2 Malformations or unilateral parenchymal haemorrhage (PH) and unilateral periventricular leukomalacia (PVL) in preterm infants are responsible for the remaining 30%. While the diagnosis of brain injury in preterm infants is mostly made using routine neurosonography, PAIS is often considered to be present when full-term infants present with (hemi)convulsions within the first 24-48 hours after birth. The diagnosis is subsequently confirmed with neonatal MRI, rather than neurosonography. Not all children with unilateral brain injury will however go on to develop hemiplegic CP. This seems to depend on the size, but especially the site of the lesion. Neuroimaging, cranial ultrasound and especially MRI have been shown to be extremely helpful for early prediction of subsequent motor outcome.3,4,5,6 The number of important structures that are involved (basal ganglia, internal capsule and cerebral cortices) have been shown to accurately predict subsequent development of hemiplegic CP.7 More

recently our group has shown that abnormal signal intensity on diffusion weighted imaging (DWI) in the descending corticospinal tracts will even more precisely predict hemiplegic CP, within days of occurrence of the insult.6 Hemiplegic motor signs tend to be recognised after the first six months up to two years, with delayed onset in those with milder hemiplegic CP. Although the main lesion determines subsequent motor outcome, smaller lesions may be present in the contralateral hemisphere (15-25% on neonatal MRI). In 64% of the 22 children studied by Mercuri et al.8 some degree of functional impairment of the non-hemiplegic hand was found. It was of interest that the severity of the impairment on the non-hemiplegic side was not significantly related to the severity of impairment in the hemiplegic hand but it was due to milder abnormalities of the hemisphere contralateral to the side of the PAIS/PH, as can nowadays be better visualised using high quality MRI-DWI performed in the neonatal period.
To address the issue of potential involvement of both hemispheres, we will assess integrity of both hemispheres using a variety of structural and functional methods evaluating the gray matter volume, the integrity of the white matter and the resulting pattern of reorganisation.
Reorganisation of the sensorimotor system has recently been studied in small groups of children and adolescents with a variety of underlying problems. These studies have shed light on differences between the reorganisation of somatosensory and motor pathways. While reorganisation of the somatosensory system usually takes place in the ipsilesional hemisphere, reorganisation of the primary motor function may occur in the contralesional hemisphere as a result of preservation of ipsilateral corticospinal projections.9,10,11,12,13 Interhemispheric dissociation between motor and sensory representation can therefore be seen. The difference between motor- and sensory representation may be due to the fact that spino-thalamic sensory fibres only reach the cortical level after the first weeks after birth.14 The thalamo-cortical fibres therefore still bypass the lesion, which occurred before the thalamo-cortical fibres have fully developed. While contralesional reorganisation could be considered to be a result of brain plasticity, ipsilesional reorganisation has been shown to be more effective in the preservation of motor function than contralesional reorganisation.
Preterm infants with unilateral PH and full-term infants with PAIS, born between 1990-2005 and who were admitted to the level III neonatal intensive care unit at the Wilhelmina Children*s Hospital/University Medical Centre Utrecht will be eligible for the study. Both infants with and without development of hemiplegic cerebral palsy will be invited to participate. Altogether 62 infants with PH and 69 full-term infants with PAIS who are now eight years or above will be approached and invited to participate in the study. These children have at least been seen in our follow-up clinic till an age of 5 years.

Study objective

1- to describe the presence and severity of hemiplegic CP on the basis of

neonatal MRI findings and correlate the involvement of different structures (basal ganglia, posterior limb of the internal capsule and hemisphere) with the size of the lesion
2- to correlate the structural characteristics of a lesion with the pattern of subsequent sensorimotor reorganisation.

Study design

Methods
Functional and structural magnetic resonance imaging (fMRI) data will be acquired on a 3-Tesla Philips scanner (Best, the Netherlands) in block designs. Active movement will consist of repetitive opening and closing of the hand; passive movement will consist of the same movement performed by the examiner. Both hands will be assessed separately and in random order. During the active hand movement they will be asked to exert, or not exert pressure. During the passive movement task, the children are asked to relax, while the examiner opens and closes their hand at a 1 Hz frequency. Postprocessing of fMRI data and statistical analysis of the functional images will be performed using SPM2 (Statistical Parametric Mapping, Wellcome Department of Neuroscience, London, UK). The pattern of brain activation (ipsi- and contralateral primary sensorimotor cortex (SMC), supplementary motor area (SMA), and lateral premotor cortex (PMC) will be studied to assess the degree of reorganization.
Gray matter density will be assessed using an automated voxel based structural analysis (VBM, SPM2) using structural brain MRI. A cost-function approach will ensure adequate hemisphere alignment, which will be followed by a voxel based comparison of patients in groups A & B. A correlation analysis between the performance on motor recovery and gray matter density will be performed. In order to further ensure the authenticity of gray matter analyses and exclude the possibility of differences between the groups being accounted by deformation, deformations maps will extracted and the Jacobian determinants of the normalization for every subject will be calculated. Using a two-sample t-test we will then compare gray matter volumes for groups A & B. All analyses will be corrected for multiple comparisons using a False Discovery Rate (Genovese et al., 2002) with the threshold for statistical significance set at $p<0.05$.
Diffusion Tensor Imaging (DTI) Diffusion images for thirty-two directions of diffusion will also acquired using EPI. The diffusion images for each direction will be realigned (SPM99/SPM2), and only the averaged image for each direction is used to determine the diffusion tensor for each voxel and subsequent fibre tracking. These procedures will be performed using DTI-Studio software

Navigated transcranial magnetic stimulation (TMS) will also be performed to study ipsilesional or contralesional reorganisation (Guzzetta et al. 2007, Staudt et al. 2004,2006). The TMS coil will be navigated to the individual fMRI-activation maxima within the preselected regions of interest.

Guzzetta A, Bonanni P, Biagi L, Tosetti M, Montanaro D, Guerrini R, Cioni

G.Reorganisation of the somatosensory system after early brain damage. Clin Neurophysiol. 2007;118:1110-21
Staudt M, Gerloff C, Grodd W et al reorganisation in congenital hemiparesis acquired at different gestational ages. Neurology 2004, 56:854-63
Staudt M, Braun C, Gerloff C, Erb M et al. Developing somatosensory projections bypass periventricular brain lesions. Neurology 2006; 67:522-5

Assessment of gross motor function and hand function
Gross Motor developmental status will be classified by the Gross Motor Function Classification System (GMFCS) [Palisano 1997] and measured by the Gross Motor Function Measure (GMFM) [Russell 1993].Fine Motor developmental status will be classified by the Manual Ability Classification System (MACS) [Eliasson 2006] and measured by the Assisting hand Assessment (AHA) [Krumlinde] for bilateral activities (both affected and unaffected side) and the Abilhand for children for unilateral assessment (affected side) [Arnould 2004]
GMFCS:
Palisano R., Rosenbaum P., Walter S., Russell D., Wood E., Baluppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997; 39: 214-223.
GMFM:
Russell D.J., Rosenbaum P.L., Gowland C., Hardy S., Lane M., Plews N., McGavin H., Cadman D., Jarvis S. Manual for the Gross Motor Function Measure (second edition). Hamilton, ON: McMaster University; 1993.
MACS:
Eliasson AC, Krumlinde-Sundholm L, Rosblad B, Beckung E, Arner M, Ohrvall AM, Rosenbaum P. The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. Dev Med Child Neurol. 2006 Jul;48(7):549-54.
AHA:
Krumlinde-Sundholm L, Holmefur M, Kottorp A, Eliasson AC. The Assisting Hand Assessment: current evidence of validity, reliability, and responsiveness to change. Dev Med Child Neurol. 2007 Apr;49(4):259-64.
Abilhand:
Arnould C., Penta M., Renders A., Thonnard J.L. ABILHAND-Kids: A measure of manual ability in children with cerebral palsy. Neurology 2004; 63: 1045-52.

A selection of Neuropsychological tests will be done by the department of Neuropsychology:
- The Raven-C-NL (Intelligence)
- Thomal (Mnestic functions)
- Beery VMI 5th edition (graphic constructions)
- Bourdon-Vos test (attention/concentration)
- Trail Making, Balloon piercing, Sorting Task (executive functions)
- Reaction speed (npsyreact)

Study burden and risks

Magnetic resonance imaging (MRI) is performed for clinical purposes in many, if not all, follow-up centers for many years. Over the last 15 years, we have accumulated considerable collective expertise in MRI techniques, and its associated practical issues in children aged between 8-10 years in previous studies. We have used the MRI prototype scanner in the department of Psychiatry to help the children get accustomed to the technique. We allow children to bring their favourite CD to listen to and they can bring one of their parents into the MRI room, whom they can see when looking in a mirror which is above their head. The researcher will be with the child all day, which will also help in not getting anxious about being in the MR scanner. There will not be a risk for undergoing any of the tests mentioned in previous sections. It may be of benefit to obtain detailed information about the brain lesion which can be of use for the further rehabilitation process. For the children who did not develop a hemiplegia but are also invited to take part in the present study (group relatedness), other problems may be brought to light, which may help in explaining certain problems which are experience at school and this may be of help in improving the situation at school.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

A) preterm infants with a gestational age < 37 weeks admitted to the level III neonatal intensive care unit of the Wilhelmina Children*s Hospital, UMC Utrecht, between 1990 and 2000 with (1) a unilateral PH which subsequently did or did not result in hemiplegic cerebral palsy, and (2) an MRI during the neonatal period and often also at 24 months of age. Group (B): term infants >=37 weeks gestation admitted to our level III neonatal intensive care unit with 1) neonatal encephalopathy and/or seizures and diagnosed to have PAIS which subsequently did or did not result in hemiplegic cerebral palsy, and (2) an MRI during the neonatal period and often also at 24 months of age. Starting from the first of january 2011 we will also include children with CP due to a PAIS who were referred to the VU medical centre in Amsterdam. They will be studied in the UMCU. Furthermore we will continue including children who fulfill the inclusion criteria as mentioned earlier, but also included children at the age of six years and older.
In 2015, an additional five patients will be included. These patients were previously too young to be included, but have now reached the age of six years or older.

Exclusion criteria

Preterm infants with lesions affecting both hemispheres, like periventricular leukomalacia. Fullterm infants with lesions affecting both hemispheres, such as injury to the central grey nuclei or watershed injury, occurring in infants with hypoxic-ischemic encephalopathy Infants with congenital anomalies, chromosomal disorders, or infections of the central nervous system are also not eligible for the study.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-05-2009
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	09-12-2008
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-03-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-12-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL24121.041.08