Neonatal Cerebral Investigation

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Preface

The natural anxiety experienced by all new parents about the well-being and future of their child is increased when the baby is born small or ill, and is further heightened if there is any concern about the function of the brain. As clinicians involved in the care of newborns with neurological problems, and who are often asked to advise parents whose fetus is thought to have a neurological abnormality, we have considerable experience with the situations we describe in this book. Over the years we have sought advice from others, searched the literature, and consulted and read widely in order to solve clinical problems on a daily basis. This book represents a summary of the results of our knowledge and experience, and we have started with the clinical presentation of neonatal neurological disease rather than using a pathological or end-stage neuroimaging classification. We describe our approach to the problem and the way we interpret the results of the investigations we request, and hope others will find this approach useful as they strive to provide the best possible care to their vulnerable patients.

By the time this book is published it will be almost 30 years since the first ultrasound images of the neonatal brain were made at University College London Hospital and published in the *Lancet*. There have been huge advances since then, and the field has moved on considerably in the decade since the first edition of this book was published, as *Neonatal Cerebral Ultrasound* written by Janet M. Rennie. The wealth of detailed information that modern imaging produces has far exceeded the expectations which were envisaged in the early days of ultrasound imaging in the 1980s. Magnetic resonance imaging (MRI) is much more readily obtainable, and digital technology allows prolonged electroencephalogram (EEG) recordings to be made at the cotside. Ultrasound is still an important tool, but we have expanded the scope and the material to include the full range of investigations now available, and we have indicated when MRI and EEG are particularly helpful.

For convenience, we have adopted masculine pronouns when referring to babies, and feminine when referring to neonatologists. We hope that this will not offend anyone who reads the book.

JANET RENNIE, CORNELIA HAGMANN, NICOLA ROBERTSON

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Peter Silver never gave up hoping and believing that a second edition of *Neonatal Cerebral Ultrasound* would eventually appear, and since his departure from Cambridge University Press Deborah Russell and her team have been unfailingly enthusiastic and supportive. We thank Deborah for her patience and for remaining cheerful as each new deadline came and went without sight of any material, and for her tolerance as the count of words and figures steadily rose. Doreen Robertson has redrawn many of the figures, and we are very grateful to her for giving so freely of her time and skill.

The literature and knowledge base have exploded in the last 10 years, and we are eternally grateful to our contributors. Their expertise on specific topics is greater than our own, and we very much appreciate the time they gave up to help us in this enterprise. We have received much help and advice from Rox Gunny, our neuroradiologist, and her colleagues at Great Ormond Street Children's Hospital and the National Hospital for Neurology and Neurosurgery Queen Square; also Ronit Pressler, pediatric neurophysiologist at Great Ormond Street Children's Hospital. Dr Lyn Chitty, in fetal medicine, made very helpful comments on the appropriate parts of the text and lent us several images, for which we are grateful. Many of the images could not have been obtained without the help of our nursing staff, whose dedicated care ensures that we can perform MRI on even the sickest baby safely. We could not have made such rapid progress in imaging quality without the help of a superb NHS medical physics department, and we would like to thank all those involved.

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The cover photograph of Elliot Bowden, a very special baby to us all, is reproduced with grateful thanks to his parents. He represents many others, and we take this opportunity to extend our thanks to the parents of all our patients, who have allowed us to share their hopes and fears, to advise and inform them, and to walk with them on what is so often a difficult and stressful journey. In particular, we would like to acknowledge all those parents who have allowed us to enrol their babies into research studies over the years; without them, the advances which we report in this book would not have been possible.

We cannot finish the acknowledgements without thanking our partners: Ian Watts, Jürg Schlumpf, and Dominique Acolet. They have patiently endured many broken social engagements and evenings alone, and shouldered more than their share of household chores during the hours we have spent with our computers. We dedicate this book to them, with gratitude and much love.

Glossary and abbreviations

Acoustic impedance A fundamental property of tissue. Ultrasound is reflected at boundaries between tissues of different impedance

Acoustic shadow An area that is poorly visualized with ultrasound due to the fact that most of the beam energy has been reflected by a boundary above it

Adenosine diphosphate (ADP) Produced in energy reactions when ATP monodephosphorylates

Adenosine triphosphate (ATP) The key metabolite in biological energy reactions

Advanced method for accurate, robust, and efficient spectral fitting (AMARES) A magnetic resonance spectroscopy analysis technique based on time-domain data fitting

Aliasing Ambiguity resulting in an erroneous representation of the signal. Results from inadequate sampling, e.g., the fastest velocities appear in the reverse channel when all the flow is forward. In MRI, due to tissue outside the field of view

Anisotropy Anisotropy is the property of being directionally dependent, as opposed to *isotropy*, which means homogeneity in all directions

Apparent diffusion coefficient (ADC) An MRI parameter related to water diffusion properties. To obtain pure diffusion information a diffusion map can be calculated by combining at least two diffusion-weighted images that are differently sensitized to diffusion but remain identical with respect to the other parameters, spin density, T1, T2, TR, and TE. A parametric image containing these data is called an apparent diffusion coefficient (ADC) map

Attenuation Loss of energy from the ultrasound beam (leading to heating of tissue) during its passage

Axial resolution The ability to separate two targets at different depths along the axis of the beam

Bilirubin-induced neuronal dysfunction (BIND)

Blood oxygen level dependent (BOLD) Contrast mechanism based on blood oxygenation level frequently employed in functional MRI experiments

Cavitation The production and subsequent oscillation and collapse of bubbles in tissues subjected to high-intensity ultrasound

Cerebral metabolic rate (CMR)

Chemical shift imaging (CSI) In MRI a method for separately imaging water or fat: in MRS a multi-voxel localization technique

Chemical shift selective (CHESS) An MRS RF pulse sequence often used for water suppression

Choline (Cho) Commonly observed by MRS: includes membrane-related metabolites

Congenital heart disease (CHD)

Continuous wave (CW) Type of Doppler study in which ultrasound is transmitted and received continuously (in contrast to pulsed wave)

Creatine (Cr) Commonly observed by MRS: often co-existing with phosphocreatine in living tissue.

Demodulation Computerized process whereby frequency information is extracted from complex multifrequency signals – used in Doppler

Diffuse excessive high signal intensity (DEHSI) Qualitative MRI finding on T_2-weighted images: abnormally high signal intensity in white matter seen frequently in ex preterm infants at term-equivalent age

Diffusion-weighted imaging (DWI) MRI method demonstrating changes in tissue water transport; useful for demonstrating cerebral damage very early after an injury

Doppler effect A change in frequency of an ultrasound pulse reflected from moving tissue (e.g., fast flowing blood)

Duplex system The combination of range-gated Doppler velocity measurement with real-time imaging

Echo The portion of an ultrasound pulse that is reflected at a boundary and subsequently detected by the transducer

Echo time (TE) In an MRI or MRS spin-echo study the total time from excitation pulse to the echo

Exponential decay time constant of the observed FID (T_2*) Effective time constant for MRI magnetization decay

in the plane orthogonal to B_0 including local magnetic-field inhomogeneity effects: always $\leq T_2$

Extracorporeal membrane oxygenation (ECMO) An advanced intensive care technique available in very few centers, which involves oxygenation of the baby's blood outside the body

Fourier transform A mathematical technique which analyzes the different frequencies present in a signal

Fractional anisotropy (FA) Fractional anisotropy is calculated from the eigenvalues λ_1, λ_2, λ_3 of the diffusion tensor:

$$FA = \frac{\sqrt{3}}{\sqrt{2}} \frac{\sqrt{(\lambda_1 - \lambda)^2 + (\lambda_2 - \lambda)^2 + (\lambda_3 - \lambda)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

λ is the mean diffusivity (trace/3); and λ_1, λ_2, λ_3 diffusion tensor eigenvalues. FA is between 0 (perfect isotropic diffusion) and 1 (the hypothetical infinite cylinder – unidirectional) and subject intercomparable

Fraunhofer zone A region of an ultrasound beam furthest from a transducer where the beam becomes too broad to be useful for imaging

Free induction decay (FID) The exponentially decaying MRI RF signal from the flipped nuclear magnetization

Frequency Number of times per second that a change occurs; refers to the transducer vibration in ultrasound and precession rate of nuclear magnetization in MRI

Fresnel zone A region of an ultrasound beam nearest a transducer where the beam is narrowest and most useful for imaging

Germinal matrix–intraventricular hemorrhage (GMH-IVH) Bleeding that is isolated to the germinal matrix or associated with uncomplicated intraventricular hemorrhage – where there is blood in the ventricular cavity but no ventriculomegaly. This terminology clearly separates GMH-IVH from parenchymal lesions

Half-Fourier acquisition single shot turbo spin echo (HASTE) Very fast MRI technique based on the acquisition of a whole image following a single excitation. Often used when the organ of interest is subject to motion

Hypoplastic left heart syndrome (HLHS)

International Commission on Non-ionizing Radiation Protection (ICNIRP) International organization assessing risks and producing safety guidelines relevant to MRI

International Electrotechnical Commission (IEC) International body assessing risks and producing safety guidelines relevant to MRI

Inorganic phosphate (P_i) The orthophosphate in biological tissues: exists as the rapidly exchanging species HPO_4^{2-} and $H_2PO_4^-$

Intensity A measure of the strength of an ultrasound beam, equal to the energy (joules) traveling through the tissue per second per square meter of area (or watts per square meter)

Intracellular pH (pH_i) Estimable via MRS using many metabolite resonances (P_i often used)

Inversion recovery (IR) MRI technique providing T_1 contrast

Larmor frequency The frequency of precession of the nuclear magnetic vector about the static magnetic field; in other words the resonance frequency (in Hz) of a peak

Lateral resolution The ability to distinguish between two closely spaced objects located at the same depth

Lenticulostriate vasculopathy (LSV)

Linear array An ultrasound probe consisting of a large number (up to 300) of small transducers arranged in a row

Line density Number of scan lines per unit distance or degree of arc

Longitudinal or spin-lattice relaxation time constant (T_1) Time constant for MRI magnetization recovery parallel to B_0

Magnetic resonance angiography (MRA) MRI technique imaging the vascular system

Magnetic resonance imaging (MRI) Imaging modality using magnetic and RF fields and obtaining contrast via tissue-water characteristics

Magnetic resonance spectroscopy (MRS) Informs about tissue metabolite composition and other biophysical attributes including pH

Magnetic resonance spectroscopy imaging (MRSi) Multi-voxel MRS localization method

Magnetization transfer (MT) MRI method relying on transfer of nuclear magnetization to adjacent, otherwise unimaged, molecules

Medicines and Healthcare Products Regulatory Agency (MHRA) United Kingdom government-sponsored body providing MRI safety guidance

N-Acetyl aspartate (Naa) A predominantly neuronal metabolite

National Radiological Protection Board (NRPB) United Kingdom government-sponsored body providing MRI safety guidance

Net sample magnetization (M_o) The magnetization induced in a tissue sample by B_0 and utilized by MRI and MRS

Nuclear magnetic resonance (NMR) The phenomenon of a resonance signal detectable from certain isotopes when in a strong magnetic field

Number of phase encoding steps (N_{pe}) An MRI and MRSi parameter that is linked to spatial resolution in one of the dimensions

Noise An unwanted signal contaminating the signal of interest, which is usually random and will have a variety of causes

N-Methyl-D-aspartate (NMDA) An *amino acid* derivative that mimics the action of the *neurotransmitter glutamate* on NMDA receptors

Nucleotide triphosphate (NTP) Gives three prominent signals in phosphorus brain MRS: mainly attributable to ATP

Nyquist limit The maximum measurable Doppler shift frequency, equal to half the pulse repetition frequency

Outer volume suppressed image related in vivo spectroscopy (OSIRIS) MRS localization method: often used for phosphorus MRS

Phased array A compact linear array that produces a beam which is steered electronically, forming a sector scan image
Phosphocholine (PCho) Membrane-related metabolite
Phosphoethanolamine (PEt) Membrane-related metabolite: prominent in neonatal brain phosphorus MRS
Phosphocreatine (PCr) Detectable by phosphorus brain MRS: contributes to creatine signal in proton MRS
Phosphorus MRS (^{31}P MRS) MRS detecting metabolites containing phosphorus atoms
Piezoelectric A physical property of certain crystals which can generate sound waves when an electrical current is applied, and can generate a current when vibrated by a sound wave
Pixel A "picture element". Every electronic image is made up of a large array of (usually square) pixels
Point resolved spectroscopy (PRESS) MRS single-voxel localization method: often used for proton MRS
Polymerase chain reaction (PCR) Method of "amplifying" small amounts of cellular components in order to establish their identity. Used in the diagnosis of viral infection, for example
Pourcelot Index (PI) Doppler-derived measure calculated from flow velocity trace
Proton MRS (^{1}H MRS) MRS detecting metabolites containing hydrogen atoms
Pulsatility index (PuI or PI) Doppler-derived measure calculated from flow velocity trace
Pulse-echo principle The measurement of the time taken for pulses to arrive back from reflecting boundaries as a means of determining their distance
Pulse repetition frequency (PRF) The number of ultrasound pulses generated each second
Pulsed wave (PW) Used to refer to Doppler studies where the velocity information is obtained by analyzing data from "packets" or "pulses" of sound waves sent intermittently from the transducer, in contrast to continuous wave studies
Radiofrequency (RF) The oscillation frequency of the electromagnetic waves used by MRI
Real-time imaging The display of continuously updated images during a scan which will reveal any changes in the tissues immediately as they occur
Refraction A phenomenon that can cause an ultrasound pulse to change direction when it passes across a boundary between tissues with a different velocity of sound, resulting in a distorted ultrasound image
Repetition time (TR) In MRI or MRS the delay between consecutive RF pulse sequences
RF pulse magnetic field (B_1) The magnetic component of the RF pulses used in MRI
Scattering Random and/or variable reflection of ultrasound by smaller tissue structures which can contribute background noise to an image
Single ventricle (SV)
Spin echo (SE) The MRI signal obtained by refocussing the FID generated by an excitation RF pulse
Signal-to-noise ratio (SNR) Information quality improves as this increases
Spatial resolution A measure of the ability of a system to distinguish between two closely spaced objects
Speckle A random pattern of bright and dark spots which occur when echoes from small scattering structures interfere with each other when they arrive at the transducer at the same time
Spectral analysis The display of the frequencies contained within Doppler ultrasound signals
Static magnetic field (B_o) The main, homogeneous magnetic field of an MRI scanner
Stimulated echo acquisition mode (STEAM) MRS single-voxel localization method: often used for proton MRS
Sturge Weber Syndrome (SWS)
Subependymal pseudocyst (SEPC)
T_2 relaxometry MRI and MRS methods to measure tissue-water and metabolite T_2 values
T_1-weighted MRI contrast weighted according to longitudinal or spin-lattice relaxation
T_2-weighted MRI contrast weighted according to transverse or spin-spin relaxation
Tesla (T) Unit of magnetic field strength (1 T = 10 000 Gauss). For comparison, the Earth's magnetic field at its surface is between 20 and 70 μT.
Time-gain compensation (TGC) The electronic enhancement of signals obtained from deeper regions to compensate for loss of signal by attenuation
Transducer A (normally piezoelectric) device which converts electrical signals to sound energy, and vice versa
Transposition of the great arteries (TGA)
Transverse or spin-spin relaxation time constant (T_2) Time constant for MRI magnetization decay in the plane orthogonal to B_o
Twin-to-twin transfusion syndrome (TTTS) Syndrome that occurs in 15% of monochorionic twin pregnancies and results from the shunting of blood from one twin (the donor) to the other twin (the recipient). The donor becomes hypovolemic and oliguric whereas the recipient becomes hypervolemic and polyuric
Unconjugated bilirubin (UCB)
Uridine diphosphoglucuronyl transferase (UDPGT)
Volume of interest (VOI) The volume of tissue for analysis as represented on an image
Voxel Volume element, used in MRI and MRS to indicate the tissue contributing to an image pixel or an MR spectrum
Wall-thump filter Circuitry which eliminates low (<100 Hz) frequencies from Doppler signals produced by pulses reflected off the walls of blood vessels
Wavelength Distance between two consecutive peaks in an ultrasound or electromagnetic wave (abbreviated λ)