Fetal Asphyxia: A Case Study of Translational Research

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Abstract

Translational research is a high priority for the Canadian Institutes of Health Research and the National Institutes of Health in the United States. The history of the significance of fetal asphyxia as a cause of brain damage and cerebral palsy reflects the challenge for translational research. An antepartum and intrapartum cause of cerebral palsy was proposed in the 19th century. Our current understanding that fetal asphyxia beyond a certain threshold will cause brain damage is built on the foundation of laboratory studies conducted over the last 50 years. However, many questions remain to be answered. Clinical studies have confirmed a similar response of the human fetus to fetal asphyxia in vivo. Translation of this knowledge into patient care during the intrapartum period has been achieved to some degree.

The emphasis on translational research relates to the political, public, and professional desire to improve patient care. The challenges for translational research have been highlighted in recent publications and are evident in fetal asphyxia. The goals of translational research will only be achieved with a continuing commitment to both laboratory and clinical research.

Résumé

La recherche translationnelle est un domaine qui est fort important aux yeux des Instituts de recherche en santé du Canada et des *National Institutes of Health* américains. L'histoire de l'importance de l'asphyxie fœtale à titre de cause de lésion cérébrale et d'infirmité motrice cérébrale reflète le défi que doit relever la recherche translationnelle. Une cause antepartum et intrapartum d'infirmité motrice cérébrale a été proposée au 19e siècle. Notre compréhension actuelle du fait que l'asphyxie fœtale sera à l'origine, au-delà d'un certain seuil, de lésions cérébrales repose sur des études de laboratoire menées au cours des 50 dernières années. Cependant, de nombreuses questions demeurent sans réponse. Des études cliniques ont confirmé la présence *in vivo* d'une réaction similaire du fœtus humain à l'asphyxie fœtale. La traduction de ces résultats en soins pouvant être offerts aux patientes au cours de la période intrapartum a été accomplie à un certain degré.

L'accent mis sur la recherche translationnelle est associé aux souhaits politiques, publics et professionnels d'assister à une amélioration des soins offerts aux patientes. Les défis que doit relever la recherche translationnelle ont été soulignés par de récentes publications et sont manifestes dans le cas de l'asphyxie fœtale. Les objectifs de la recherche translationnelle ne seront atteints que par l'intermédiaire d'un engagement continu envers la recherche clinique et en laboratoire.

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INTRODUCTION

An operational definition of translational research proposed by the Translational Research Working Group at the National Institutes of Health in the United States was "research that transforms scientific discoveries arising in the lab, clinic or population into new clinical tools and applications that reduce the incidence, morbidity and mortality of disease."[1] At the present time, this is a high priority research initiative. Canada's Health Minister has officially launched the National Strategy for Patient Oriented Research as a transformative initiative that will greatly enhance the support of translational research in Canada.[2]

The National Institutes of Health has established the National Center for Advancing Translational Sciences. The mission of this centre is to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. The reason for doing so is that there are many time-consuming bottlenecks in the pipeline between a scientific discovery and development of new ways to improve human health.[3]

The critical path begins with defining the question, and then initiating laboratory and clinical research and applying the findings to patient care. The long history from

identifying the possible significance of fetal asphyxia as a cause of brain damage and spastic paralysis to applying this knowledge in patient care represents an example of the challenge for translational research.

CLINICAL FACTORS ASSOCIATED WITH SPASTIC PARALYSIS

William Little was born in 1810, began medical studies in 1828 in London Hospital, was admitted to membership of the College of Surgeons in 1833, and became a licentiate of the College of Physicians in 1837. In 1834, he went to the University of Berlin to research clubbed feet. His doctoral thesis was a monograph on tenotomy. He returned to London and became the Senior Physician to the London Hospital, founder of the Royal Orthopaedic Hospital, and visiting physician to the Asylum of Idiots, where in 1837 he introduced the technique of tenotomy for clubbed feet, many in children with infantile paralysis.

His research related to birth injuries resulting from difficult pregnancies and labours. A first publication was in 1843, and in 1862 he produced a definitive publication "On the Influence of Abnormal Parturition, Difficult Labours, Premature Birth and Asphyxia Neonatorum . . ."[4] This report was based on a careful study of 200 cases of spastic paralysis. He concluded:

> . . . that premature birth, difficult labours, mechanical injury during parturition to head and neck, where life had been saved, convulsions following birth, were apt to be succeeded by a determinate affection of the limbs of the child, which I designated spastic rigidity of the limbs of newborn children, spastic rigidity from asphyxia neonatorum.

Thus, initially, cerebral palsy was known as Little's disease.

Sigmund Freud, born in 1856, attended medical school in Vienna and was subsequently considered to be a brilliant neurologist and neurophysiologist. In 1897 he wrote a monograph on cerebral palsy that was recognized as the definitive description of this entity for the next 50 years.[5] Regarding Little's factors, he highlighted the observation that most children experiencing a difficult birth escape unharmed. Two explanations were proposed:

1. the intensity and quantity of the affecting factor must reach beyond a threshold value, or
2. the etiology of the effect is not a simple one.

He highlighted congenital events during pregnancy and concluded:

> Infantile paralysis could be due to a series of etiological conditions with purely congenital cases constituting one extreme with one of Little's factors assuming growing importance to the other end and in other cases an unusual intensity of one of Little's factors would make contribution of a congenital condition superfluous.[5]

The debate continued over the next 50 years. In 1958, writing on the causation of cerebral palsy in *Recent Advances in Cerebral Palsy,* Illingsworth said, "Numerous papers have been written about the etiology of cerebral palsy, but the more one reads of them the more likely is one to feel confused as to the conclusions." He concluded that anoxia is probably the most important single causative factor, but that other factors are involved.[6]

LABORATORY STUDIES

In 1956, when introducing a symposium on neurological and psychological deficits of asphyxia neonatorum, Dr Bailey (director of the National Institute of Neurological Diseases and Blindness) said

> Medical research in regard to cerebral palsy and other neurological disabilities has been relatively neglected. For a truly comprehensive attack on this problem we must focus a sharper scientific search for greater knowledge of those adverse biological factors which operate in the perinatal period. The proper point of departure in such a search is in controlled animal observations.[7]

Our current understanding of the significance of fetal asphyxia is built on the foundation of laboratory research conducted over the last 50 years. Beginning with acute studies of the exteriorized fetal monkey, and continuing in sheep with studies using fetal lambs chronically instrumented in utero, asphyxia has been examined using a number of different models for the induction of fetal asphyxia including maternal hypoxemia, reduced utero-placental blood flow, cord occlusion, and umbilical embolization, while the effect of cerebral ischemia has been examined by carotid artery occlusion. Studies were designed to examine the effect of a single continuous total asphyxia exposure, a single continuous partial asphyxia exposure, and recurrent asphyxia.

The studies of a single continuous asphyxia exposure established a threshold of 10 minutes of total asphyxia beyond which brain damage may occur.[8] When brain damage actually occurs will vary with gestational age. The distribution of neuropathology affects the cerebral

The prevalence and significance of intrapartum fetal asphyxia as expressed by a metabolic acidosis at delivery

Umbilical artery base deficit	Incidence	Moderate or severe newborn complications
> 12 mmol/L	20/1000 births	10%
> 16 mmol/L	5/1000 births	40%

hemisphere, basal ganglia, and thalamus.[9,10] A single continuous exposure to partial asphyxia has demonstrated that the development of a significant metabolic acidosis leading to fetal compromise may occur after 60 minutes of exposure. The brain damage that occurs is principally in the cerebral hemispheres.[11,12] Fetal asphyxia may occur as a recurrent event. These studies indicate that an episode of asphyxia that would not independently lead to brain damage may with repeated exposures have a cumulative effect. The neuropathology occurs principally in the striatum.[13]

A striking feature of these studies of fetal asphyxia has been the variable outcome, ranging from no brain damage in many, and brain damage in some, to death in a few cases. This is consistent with the proposal by Sigmund Freud that the cause of the brain damage may not be a simple one.[5]

The consistent finding before brain damage occurs has been a severe metabolic acidosis and hypotension. The concept of fetal cardiovascular compensation resulted from studies of the cardiovascular response to fetal asphyxia. The initial response of the fetus to an asphyxial exposure is an increase in arterial pressure due to increased systemic vascular resistance. There is a redistribution of cardiac output, with centralization of the circulation and increased blood flow to the brain, heart, and adrenals.[14] This cardiovascular response maintains cerebral oxygen metabolism by a combination of increased cerebral blood flow and oxygen extraction.[15] If the asphyxial exposure persists, a threshold of cardiovascular decompensation will occur with hypoxemia and severe metabolic acidosis. Initially this is associated with a shutdown of energy-using processes, but if it is sustained, brain damage due to decreased cerebral oxygen consumption will occur. Another variable was identified in studies of coliform endotoxemia due to lipopolysaccharides in conjunction with proinflammatory cytokines.[16] Although coliform endotoxemia does not increase metabolic acidosis, it may enhance susceptibility to subsequent hypoxic-ischemic brain damage by compromising fetal cardiovascular compensation, with profound reductions in placental blood flow and cerebral oxygen delivery.

The complexity of the subject has been further highlighted by studies of neuronal death. The mechanisms leading to neuronal death include energy failure, excitatory amino acids, glutamate, free oxygen radicals, and growth factors. Studies of hypoxic-ischemic neuronal loss have demonstrated that many neurons do not die during the asphyxial insult itself, but rather the insult initiates processes that operate over time after the event.[17]

CLINICAL RESEARCH

The ability to conduct clinical studies of fetal asphyxia began with the micro blood gas electrode instrument. This instrument was the result of a number of contributors including Ole Siggard-Anderson's acid base nomogram, the Radiometer Company pH electrode in 1952, Richard Stow's carbon dioxide electrode in 1954, and Leland Clark's oxygen electrode in 1956.[18,19] In 1959, we received one of the first Radiometer blood gas machines in North America in our laboratory.

In 1993 a task force of the World Federation of Neurology Group proposed the following definition of fetal asphyxia: "Fetal asphyxia is a condition of impaired blood gas exchange leading to progressive hypoxemia and hypercapnia with a significant metabolic acidosis." An umbilical artery base deficit > 12 mmol/L was established as the threshold of metabolic acidosis beyond which moderate or severe newborn complications may occur [20]

The prevalence of intrapartum fetal asphyxia with a significant metabolic acidosis at delivery is summarized in the Table. Fetal asphyxia with a metabolic acidosis expressed by an umbilical artery base deficit > 12 mmol/L occurs in approximately 2% of deliveries and in many cases is not associated with moderate or severe newborn complications.[21]

For predictive purposes, fetal asphyxia has been classified as mild, moderate, and severe on the basis of significant metabolic acidosis at delivery and the severity of the subsequent neonatal encephalopathy. The significance of intrapartum fetal asphyxia as determined in follow-up studies of children led to a number of conclusions:

1. Fetal asphyxia with a metabolic acidosis (base deficit) beyond 12 mmol/L may occur with subsequent normal motor and cognitive development.

2. There is no evidence of an association between mild fetal asphyxia and major deficits, and long-term follow-up has demonstrated no association with minor disabilities later in childhood.[22]

3. Moderate or severe fetal asphyxia may be associated with major deficits in both term and preterm newborns.[23]

The occurrence of antepartum fetal asphyxia has been confirmed; however, the significance of such asphyxia to an individual fetus remains to be determined. Epidemiological studies of cerebral palsy have implied that most of the brain damage occurs in the antenatal period.[24] Postmortem studies of infants who die during or immediately following delivery have demonstrated that brain damage has occurred in the antenatal period.[25] These cases with neuropathology represent examples of recurrent asphyxia. In a study of preterm pregnancies with evidence of asphyxia at delivery, at least 40% of the asphyxia in the preterm pregnancies occurred in the antepartum period.[26] Newborn asphyxia may also occur. The preterm newborn with respiratory complications may experience a number of physiologic derangements including hypoxemia and hypotension. A study of 130 preterm newborns (< 34 weeks' gestational age) demonstrated that sustained hypoxemia and hypotension in the newborn are important factors in the development of brain damage.[27]

TRANSLATION OF LABORATORY AND CLINICAL RESEARCH INTO PATIENT CARE

Clinical prediction of fetal asphyxia remains a major problem. Fetal asphyxia may occur in low-risk obstetric patients, and the predictive value of clinical risk factors is low.

A diagnosis of fetal asphyxia during labour can be made if a predictive fetal heart rate pattern is followed by fetal scalp sampling for a blood gas and acid-base assessment documenting the presence of a significant metabolic acidosis. However, the use of this invasive procedure is currently limited.

Fetal asphyxia at delivery can be ruled out or confirmed by routine cord blood gas and acid base assessment at delivery, as practised in many obstetric units. This information is of value to the neonatologist in the management of the newborn and to the obstetrician in quality assurance and medical legal reviews.

COMMENT

How long the translation of research into clinical practice takes has been explored in editorials and publications. An example is a publication from the American Journal of Medicine published in 2003.[28] This was a study of 101 selected articles in six journals (Science, Nature, Cell, the Journal of Experimental Medicine, the Journal of Clinical Investigation, and the Journal of Biological Chemistry) describing research findings with clear clinical promise. When followed up over 20 years, only 27 of the promising findings had been the subject of a clinical trial, and only five basic science findings were licensed for clinical use. The authors concluded that promising basic research rarely translates into clinical research or clinical practice.

Fetal asphyxia is an example of the long time frame required for the new knowledge arising from laboratory research to be translated into patient care. Astute clinicians in the 19th century observed that antepartum and intrapartum events may account for cerebral palsy in the surviving child. Much clinical speculation occurred during the first half of the 20th century. However, the significance of fetal asphyxia was not determined until laboratory studies were initiated.

Laboratory and clinical research conducted over the last 50 years has led to important progress in our understanding of the relationship between fetal asphyxia and brain damage responsible for cerebral palsy. However, as Lewis Thomas said, "We have come a long way indeed but just enough to be conscious of our ignorance."[29]

Many questions remain to be answered.

The advances in understanding of the significance of fetal asphyxia have been translated into patient care that may benefit some patients. However, the prevalence of cerebral palsy has remained essentially unchanged. The prediction and management of antepartum fetal asphyxia have not been achieved, nor have uniform prediction, diagnosis, and prevention of moderate and severe intrapartum fetal asphyxia been achieved.

The emphasis on translational research relates to the political, public, and professional desire to improve patient care. Although a desirable goal, it is often difficult to achieve. In the case of the prevention of brain damage and cerebral palsy in surviving children, there is a need for a continuum of both laboratory and clinical research. Further improvement in patient care will occur only when laboratory research resolves some of the outstanding questions and new clinical methods of fetal assessment are developed.

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