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Topical Review

Timing in Neural Maturation: Arrest, Delay, Precociousness, and Temporal Determination of Malformations

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ABSTRACT

Timing is primordial in initiating and synchronizing each developmental process in tissue morphogenesis. Maturational arrest, delay, and precociousness all are conducive to neurological dysfunction and may determine different malformations depending on when in development the faulty timing occurred, regardless of the identification of a specific genetic mutation or an epigenetic teratogenic event. Delay and arrest are distinguished by whether further progressive development over time can be expected or the condition is static. In general, retardation of *early* developmental processes, such as neurulation, cellular proliferation, and migration, leads to *maturational arrest*. Retardation of *late* processes, such as synaptogenesis and myelination, are more likely to result in *maturational delay*. Faulty timing of neuronal maturation in relation to other developmental processes causes neurological dysfunction and abnormal electroencephalograph maturation in preterm neonates. Precocious synaptogenesis, including pruning to provide plasticity, may facilitate prenatal formation of epileptic circuitry leading to severe postnatal infantile epilepsies. The anterior commissure forms 3 weeks earlier than the corpus callosum; its presence or absence in callosal agenesis is a marker for the onset of the initial insult. An excessively thick corpus callosum may be due to delayed retraction of transitory collateral axons. Malformations that arise at different times can share a common pathogenesis with variations on the extent: timing of mitotic cycles in mosaic somatic mutations may distinguish hemimegalencephaly from focal cortical dysplasia type 2. Timing should always be considered in interpreting cerebral dysgeneses in both imaging and neuropathological diagnoses.

Keywords: timing, delay, arrest, precociousness, synaptogenesis, myelination

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Timing is the essence in music as in neuroembryology.

The oboist who begins a musical phrase one measure too early—or too late—in the orchestral score, creates dissonance. Synapses that form too early—or too late—in relation to neuronal maturation, create neurological dysfunction.

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Introduction

The purpose of this review is to define developmental arrest, delay, and precociousness from an embryological perspective. Examples of each and correlations with postnatal clinical neurological expression of defective timing are offered by comparison with age-matched controls.

Maturational arrest denotes stoppage of development at a particular stage of ontogenesis with no expectation of further development.

Maturational delay denotes a slower than expected rate of development of a structure or process, but with the potential for further development.

Maturational precociousness denotes accelerated onset of development of a structure or of a physiological process of programmed development.

Neuroembryology is a term that can be applied either in the narrow sense of the embryological period proper of the first 6 weeks of gestation or more broadly applied to refer to development throughout the entire fetal period as well. The latter is more widely used at present.

In nervous system ontogeny, timing and synchrony may be even more fundamental than anatomical organization of neural tissue because defective timing of development often influences structural architecture to create malformations, whereas the reverse is not generally true: defective morphogenesis does not alter timing. Overlapping developmental processes in the embryonic and fetal development of the nervous system have precise, genetically programmed sequences, not only for morphogenesis but also the onset and window of opportunity of each process. Genetic mutations alter gene expression for both timing and anatomical organization. Such alterations are not in isolation, but in relation to all other overlapping and simultaneous processes that together require temporal integration. Epigenetic factors such as teratogenic environmental neurotoxins, inborn metabolic errors, hormonal alterations, and chronic ischemia also may affect the timing of progressive ontogenesis in brains without genetic mutations. Despite its primordial importance, developmental timing has received much less attention in the analysis of malformations than has developmental neuroanatomy.

Timing is a process initiated at fertilization and ending with senescence at the end of life. We meticulously watch time. Diseases have a natural "course" defined in large part by time. Calendars and clocks or their equivalents and variations have regulated activities in all human civilizations in recorded time. Timing is not even uniquely human. Animals and plants live seasonally. Even microbes have reproductive time spans. Each species of animal and plant life, both simple and complex, has its programmed life expectancy with allowances for individual biological variations within the aging span for its species.[1] Some simple species, such as the tentacled polyp (hydra) and medusa (jellyfish), can be immortal because of continuous renewal of all of its cells to stave off aging. Time is both physiological and conceptual, a fascination of philosophers over the millennia. Time travel is a favorite theme of science fiction. In medical care, early versus late timing is of primary importance for patient outcome, whether surgery for appendicitis, craniosynostosis or brain resection for intractable epilepsy, or antibiotics for meningitis. Timing can cause stress from embryonic to late adult life.

Historical perspective of terminology for aberrant timing

Esquirol first used the expression *défaut de dévelopement* (absence, lack, or arrest of development) in 1818,[2] a term also adopted by his student Georget in his thesis of 1820 and by Cruveilhier in 1828, who acknowledged and cited Esquirol.[3] The term *arrest*, in relation to development, was first applied in the English language by Charles Darwin in his treatise *Descent of Man*, published in 1871.[4] The concept of "arrest" was not discussed in any identified publication but was tacitly accepted throughout the nineteenth century. Sachs used the term in his autopsy report of the original case of Tay-Sachs disease in 1887,[5] but paid less attention to it when he had gathered more cases in which this feature was not as striking. He casually mentioned arrest in a section on developmental diseases without any elaboration of its meaning, presumably assuming it was self-explanatory, in later articles,[6] in his popular 1895 book, *Treatise on the Nervous Diseases in Children*, or in the last revised edition of 1926, coauthored with his associate L. Housmann. The concept of developmental diseases was briefly addressed, however, in neurology textbooks, for example by I. Wechsler in 1935. Many contemporary studies focus on the timing of genetic expression in the developing embryo and fetus, including cellular lineage and delayed differentiation,[7] an aspect that will one day be regarded as another historical milestone in the chronology of the concept.

Certain genetic disorders, such as Rett and Angelman syndromes, have been redefined as functional developmental arrests, rather than their traditional classification solely as degenerative diseases or static encephalopathies, also complementing their now known genetic mutation.[8,9] Developmental arrests are associated features in many inborn metabolic errors, such as aminoacidurias, organic acidurias, cerebral lipidoses, and leukodystrophies.

Maturational arrest and delay

The terms *maturational arrest and delay* both denote slower than physiological development, but they are not synonymous and interchangeable. Precise definition of the sometimes subtle distinction is primordial to understanding how aberrations of timing might contribute to malformations of the nervous system. It should be borne in mind that some genetic and epigenetic factors that produce aberrations in timing may not be precise events at a single moment in time, but may extend over a prolonged period during prenatal and postnatal life; hence, various stages of development can be recognized in the same brain in some cases.

As a generalization, developmental processes that occur primarily in the first half of gestation, such as neurulation, neuronagenesis, axonal pathfinding, and neuroblast migration, may become arrested but rarely are simply delayed. Examples are meningomyelocele, cerebellar hypoplasias, agenesis of the corpus callosum, and