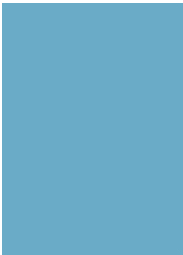


Section

1

Introduction

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Excerpt  
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# Introduction

## Chapter

## 1

# Principles of Progressive Brain Disorders in Childhood

Throughout this book, emphasis is made on principles. Several of them are described here.

*The Role of Genomics in Neurological Practice.* Imminent changes in the approach to disease genomics will simplify the identification of affected individuals and strengthen the observational and mechanistic perspectives adopted in this book. Rather than rendering observation and clinical understanding irrelevant or obsolete, detailed genomic information complements the approach to neurological disorders by circumscribing the origin of disease to specific abnormal protein function. Further, comprehending the impact of mutations on the organism will always rely on empirical description and experimentation. Diagnosing will be greatly simplified for both typical and atypical affected individuals when their complete genome is analyzed as a matter of routine, rendering many ancillary procedures irrelevant. Diseases will thus be identified with increasing accuracy, but most of them will continue to be confronted with insufficient treatments. Therefore, observational and mechanistic research can only be expected to flourish.

*Variable Expression of Later-onset Childhood Neurodegenerative Disorders.* That late-manifesting diseases deviate from stereotypic forms of presentation is puzzling, especially for canonical single-gene defects for which early (infantile or juvenile) disease forms are well characterized. In general, late-onset disease forms are much more variable in manifestations and also milder in clinical course. It seems reasonable to assume that one gene should impair one biological process and that this should lead to only one form of disease. Yet, the phenomenon of late-onset disease variability may relate to the uncovering, by the primary disease process, of otherwise sub- or pre-clinical forms of dysfunction that differ from the primary disease and which become manifest in conjunction with it. According to this contention, a late-onset

disease-causing mutation may have a permissive effect on latent pathology that manifests variably as it unfolds in later life. By extension, this may also account for the early-onset single-gene diseases that are associated with different phenotypes.

*Primary and Secondary Injury.* That all or much of a phenotype may be due to pathological processes far removed from the original causal defect seems to stand to reason. This may account for the existence of common final pathways of disease, in which two or more primary pathological processes converge into a shared set of biological events. These ultimate events may supplant the original disease mechanism and give rise to most of the observable clinical and biological abnormalities. For example, mutations in disparate, biologically unrelated genes may converge into the same type of abnormality by impairing a single cell structure. This, however, should not uncritically lead to the elevation of the secondary process to the status of centrality. The fact that vulnerable nodes occur in all biological systems does not necessarily imply that these nodes are targets for disease amelioration or reversal, for it is the primary process that may require remediation. In other words, some of the more eloquent nodes may be a source of epiphenomena rather than reporters of central pathogenesis.

*Patterns of Neural Regression.* Whereas the phenomenology of normal neural development and behavior is relatively well understood, much less is known about the behavioral neurology of neurodegenerative deterioration in children. This is compounded by the naturally evolving set of powers of the developing brain, which are impacted in both unknown global and selective ways by progressive diseases. It is not known whether the familiar diseases that primarily involve neural circuits in the adult operate similarly in the child because the nature and function of such circuits in development remains underinvestigated.

Chapter 1: Principles of Progressive Brain Disorders in Childhood

Table 1.1 Patterns and stages of neurobehavioral degradation in childhood

	Intellectual deterioration	Combined intellectual and motor deterioration
Early	Language decline	Extrapyramidal manifestations and language decline
Intermediate	Loss of individuation	Loss of ambulation and individuation
Advanced	Passivity	Inability to sit and indifference

In contrast with the adult, and regardless of disease mechanism, there are two main observable patterns of deterioration in children: a mostly intellectual pattern of decline and a combined motor and intellectual pattern of degeneration.

For unknown reasons, sensory system degeneration, while biologically observable, is largely silent in children, such that it is the motor and intellectual behaviors that define the phenotype. In the intellectual pattern of deterioration, language is generally compromised and constitutes the first sign of disease. Self-awareness of intellectual deterioration is very rare in children, as are memory and comprehension complaints. A second stage of intellectual deterioration is characterized by the loss of individual awareness. The child's aspirations, self-preservation tendencies, and self-consciousness are lost in this phase. Lastly, a third stage is characterized by impassivity to the external and internal environment. In the combined motor and intellectual pattern of deterioration, extrapyramidal manifestations (principally ataxia and dystonia) are usually more disabling than pyramidal tract dysfunction. Motor deterioration proceeds on par with intellectual decline, giving the appearance of global encephalopathy. Later, loss of ambulation tends to coincide with loss of self-individuation. In a third phase, the inability to sit is accompanied by indifference to the environment. In contrast with the adult, the ill child is less prone to reflect on his or her own mortality despite the capacity to do so when confronted with others' illnesses.

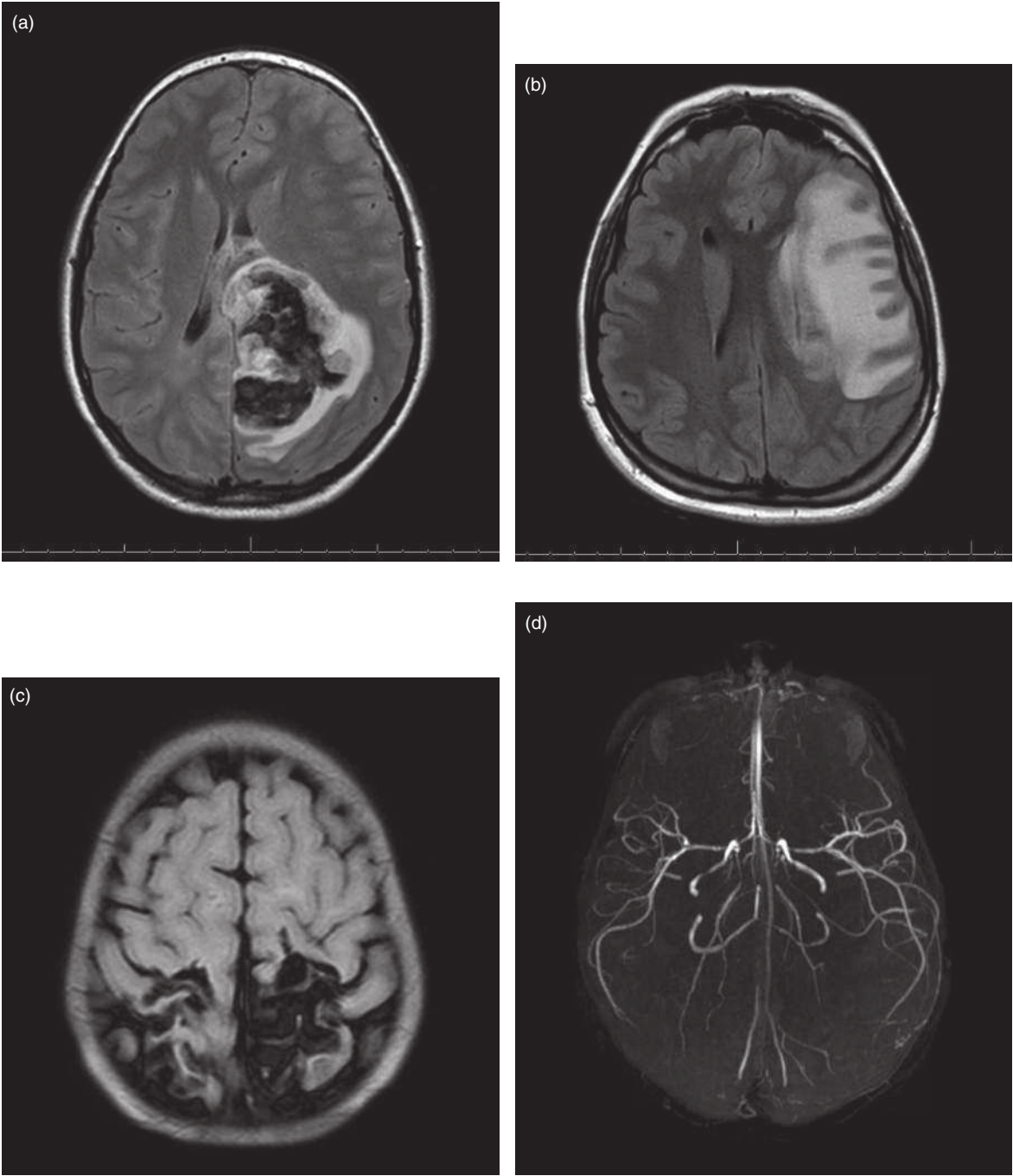
*Localization in Neurodegenerative Neurology.* The developing brain is much less specialized regionally and functionally than the adult nervous system. In children, the extent or size of an injury is more important than its location (Figure 1.1). Therefore, there are usually few practical gains from attempting to localize lesions or pathological processes. Even highly circumscribed lesions such as focal strokes tend to be silent or cause defects that would be unexpected in an adult. Many acquired focal

lesions recover rapidly and leave no sequelae. Similarly, the ability to predict later life residual deficits is very limited. The main predictor of future neural performance is the size of residual unaffected brain volume rather than site of injury or neural circuit affected. Similar observations were made by Soviet scientists on adult soldiers who suffered two sequential brain injuries: Whereas the clinical consequences of the first injury could be predicted on a functional anatomical basis, impairment due to the second injury depended not on its location but on its size.

*Infections, Injuries, Immunizations, and Other Potential Precipitant Factors.* Many childhood degenerative disorders follow or temporally associate with seemingly unrelated injuries or otherwise inconsequential pathological processes. For example, Leigh syndrome often manifests some time after a trivial respiratory or gastrointestinal infant illness. This has given rise to debate, as the causal role of several common interventions such as vaccinations has been called into question in relation to numerous severe neurological disorders. The source of this argument against causation is rooted in a particularly strict conception of the notion of causation in which a cause must always act via a known all-or-nothing mechanism. However, it seems likely that a single – and otherwise innocent – event could set in motion a dormant disease mechanism when acting at the appropriate time, and that the absence or prevention of such an event would allow the pathological mechanism to remain quiescent or unprovoked. If this counterfactual argument is accepted, there seems to be little reason to negate causation. In this paradigm, causation is a probabilistic – rather than a mechanistic – event acting through unclear mechanisms, and one that is not well reflected in the law or in common medical practice. The debate will thus likely continue.

*Early Diagnosis and Early Treatment.* A common argument is that early treatment of a severe disease

Section 1: Introduction



**Figure 1.1** Extensive but minimally symptomatic brain lesions in children. **A.** Pilocytic astrocytoma in a 6-year-old child causing mild headaches. **B.** Tumefactive multiple sclerosis in an 11-year-old girl associated with right finger numbness. **C.** Chronic ischemic injury to the hemispheres in a 4-year-old leading to mild leg spasticity. **D.** Magnetic resonance angiography of the case in **C.** Severe stenosis of the arteries that irrigate the cerebral hemispheres is noted in the context of widespread cerebral circulatory failure. There is reduced flow through the supraclinoid internal carotid and vertebrobasilar arteries. The superior portion of the basilar artery and the proximal posterior cerebral arteries exhibit particularly reduced flow.

## Chapter 1: Principles of Progressive Brain Disorders in Childhood

should lead to better outcomes or even to reversal of disease manifestations in contrast with treatments administered in more advanced disease stages. This notion, however, is clouded by the assumption that most treatments modify fundamental disease biological aspects. The reality is that therapy for neurological disorders is often far removed from primary pathological events. If a treatment addresses a secondary (in terms of importance) biological abnormality or a disease manifestation that results from the uncovering of an unrelated premorbid pathological state, then time to treatment may afford little impact on disease course. Given the current widespread uncertainties about what constitute primary and secondary events in the vast majority of neurological disorders, it seems unlikely that early treatments obligatorily afford superior benefit to delayed forms of therapy.

*Tolerability of Severe Mutations.* Man is prone to deleterious mutations. In a significant fraction of cases, individuals affected by a canonical, well-known disease harbor two or more mutations in unrelated genes, one or more of which may remain silent as a disease modifier. Analogously, some so-called obligatory disease-causing mutations occur in normal subjects. The simplest interpretation of these paradoxes resides in the concept of gene. A functioning gene extends beyond the self-replicating DNA structure that specifies the genetic code to include regulatory elements of genomic and non-genomic nature. This principle was advanced in the mid-twentieth century, when the structure of DNA and the mechanism of inheritance were unknown. Thus, a pathogenic mutation may be viewed as a necessary – but not always sufficient – prerequisite for the expression of a phenotype. The role of the environment, understood as the exposure to the cell's external and internal milieu also needs to be called into question, since most cells of all organisms are exposed to a strictly controlled environment that varies little with lifestyle and other extrinsic factors. It is thus possible that higher order properties that emerge from simpler biological processes such as mutations account for causation and pathogenesis as observed in medical practice.

*Evidence-based Medicine and Other Statistical Constructs.* The foundational documents of the evidence-based current state that one advantage of this new approach to medicine is that therapeutic

interventions can be effectively assessed with little regard for underlying pathophysiological mechanisms. Today, the practice of evidence medicine constitutes a form of reductionist phenomenology devoid of mechanistic insight. In its extreme form, it is a reincarnation of the trial-and-error approach to therapeutic development validated by statistical reasoning. The value of such conceptual construct in neurodegenerative disorders is very limited – if not outright misleading – for several reasons: First, the relative rarity of these diseases render them statistically intractable. Second, important individual variations can be negated by lumping together several disorders with a similar phenotype – such as autistic spectrum disorders – with the intent of achieving a sufficient sample size at the expense of disregarding crucial biological differences. Third, evidence-based medicine assigns a quantitative evidence value to qualitative outcomes that are not easily amenable to numeric ordering. Fourth, this approach is oblivious to individual innovation and therapeutic experimentation, which is how many treatments have been developed.

The chapters that follow have been structured to first provide an overview of normal neurological development as it relates to illness and deterioration. A discussion of the main forms of neurodegenerative mechanisms follows. Next, individual neurodegenerative diseases have been divided by age of onset, understanding that such boundaries are largely arbitrary. Lastly, the phenomenon of regression and behavioral deterioration is analyzed for several non-degenerative conditions, many of which are amenable to effective treatment. The book has been written for continuous reading. However, individual chapters are self-contained and can be read separately. Clinical case reports and text boxes summarizing the main disease features are provided in many cases to facilitate retention of the material. When possible, clinical histories have been given precedence over ancillary diagnostic methods. As reflected in the cases described in the text, today much of the medical literature containing the most thorough medical histories and clinical insights emerges from underdeveloped countries where ancillary investigations are often relegated to a confirmatory role or rendered superfluous by clinical acumen. I try to follow that paradigm in my own medical practice.