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Promise and possibility in the hypotonia infant

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Abstract

Floppy infant syndrome comprises a broad spectrum of etiological abnormalities that pose considerable diagnostic challenge. Current genetic and molecular methodologies have streamlined diagnostic algorithms and significantly advanced their resolution. Prospects for genetic therapy, however, are mixed, and likely to be restricted by the anatomical complexity of stable, central motor functions.

Introduction

Infant hypotonia, colloquially termed floppy infant syndrome, comprises a broad spectrum of etiological abnormalities historically notorious for posing diagnostic challenge. Characterized by a generalized reduction in muscle tone, problems of clinical polymorphism are considerably exacerbated by the nonspecificity of its clinical markers and nosological dependence [1]. Presenting symptoms such as frog like posture, inability to resist gravitational inclines, and an excessive range of joint mobility trace their origin to a spectrum of medical impairments seen in many somatic and infant neurological diseases. M Iraschi's diagnostic algorithm [2], notably, is illustrative for the exploratory range that may be tasked prior to reaching a confirmatory diagnosis.

In commenting on current diagnostic and therapeutic prospects, on the other hand, Paul Fisher of Stanford's Department of Neurology and Pediatrics, proposed a singularly optimistic view of genetic and molecular insights not only for diagnosis but also for the therapeutic resolution of overt disease symptoms [3]. Citing a fifty year dated, J Pediatric article on the hypotonic infant [4], Fisher noted the review's coverage of advances in pathological understanding within the preceding 50 year period, and then the succession of new understandings that have transpired since the review's publication. In his reading much of the newly inspired therapeutic promise appears to emerge directly from the rapidly expanding molecular diagnostic methods, now routinely used in clinical evaluation.

Recent articles, like that by Prasad and Prasad, which appeared in the journal Seminars in Fetal and Neonatal medicine [5], share Fisher's optimistic assessment of diagnostic capability. While clinically based evaluative protocols for hypotonia remain indispensable despite their limitations, an expanding array of molecular assays promises reliability, rapidity, and specificity for many hypotonia etiologies. A number of these are now being diagnosed alone, or with minimal preliminary evaluation, like spinal muscular atrophy in combination with electromyography. Comparative genomic hybridization with various restriction endonuclease cocktails, moreover, has proven especially powerful in detecting very low levels of sequence variation, and is currently replacing more traditional cytogenetic assays.

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Diagnostic successes raise, by extension, the prospect of successfully appropriating similar methodologies for correcting or, minimally, ameliorating defective coding sequences that are the etiological basis for infant hypotonia. Indeed, similar sentiments propelled the convening of the national convocation in Washington DC in December of 2015, headed by David Baltimore, on the universally applicable benefits and dangers of implementing CRISPR technology [6]. Extrapolating therefrom, gene therapy has the theoretical potential to 'permanently' correct coding defects by inserting or otherwise introducing correct sequences that yield normal gene products. With the generation of the correctly restored protein or peptide product, or the prevention of undesirable ones through techniques like missense or reverse RNA that block translation, positive outcomes are thereby directly related to the functional adequacy of the corrected product.

This premise has been the stimulus for investigations into the efficacy of gene therapy to treat human disease for over two decades now, and its considered use for similarly treating central nervous system diseases in the past decade [7]. Based on this conception of therapy through molecular adequacy, chief obstacles to implementation of genetic therapy in nerve tissue are identified chiefly with access to the genetic machinery that repairs the protein product, or to the molecular machinery of production, and includes such varied issues as crossing the blood brain barrier, availing type specific tissue, and stimulating transcription with DNA promoters.

Access to the cellular tissue of the nervous system, in fact, has advanced significantly with recent progress in the engineering of viral delivery vehicles and synthetic nano particles. Foust et al [8], for example, reported that AAV serotype 9 (AAV9) was able to traverse the blood brain barrier, and yield widespread, but variable transgene expression in both astrocytic and neuronal cells. Depending on dosage, transduction efficiency ranged from sparse to high, however, and effected varying neuron to astrocyte ratios, based on the use of green fluorescent protein immunoassays. Nonetheless, the list of viral vectors used for therapy is extensive, with their potential further amplified by a variety of genetic engineering procedures that can modify discrete bases or large modular sequences [9]. In contrast to viral vectors, non-viral, nanoparticles lack biomolecular modalities that have been evolutionarily refined. However, they are potentially amenable to a much broader range of synthetic alterations, making them, in many instances, a preferred mode of transport. Nanoparticles not only can be made from a variety of molecular compounds but also be constructed from numerous nanometer sized configurations, including liposomes, nanotubes, and magnetic nanoparticles [10].

Given the number of etiologies that may express the symptoms of hypotonia, on the other hand, the specific premise of molecular adequacy alone seems, if not open to question, at least subject to variable outcome, and, more than likely, to encounter circumstances where this premise may be invalid. Loci contributing to hypotonic symptoms (Table 1), for instance, situate in muscle (e.g., congenital myotonic dystrophy), neuromuscular junction (e.g., congenital myesthenia gravis), motor nerve (e.g., hypomyelinating neuropathy), motor soma of the spinal cord (e.g., spinal muscular atrophy), and in brain tissue (e.g., cerebral dysgenesis and metabolic diseases). Hence, gene therapy approaches seem more suited to applications where tissue homogeneity is moderately high and where the expression of the gene product has a direct bearing on physiological function. These considerations appear to favor applications that are more distally localized with respect to a brain based origin, that is, in muscle masses, myelinating nerve segments, and at motor synaptic junctions.

Table 1

Central Nervous System	
Chromosome disorders (Prader-Willi)	
Metabolic diseases	
Cerebral dysgenesis	
Spinal cord injuries	
Hypoxic-ischemic injuries	
Motor Neuron	
Spinal muscular atrophies	
Motor Nerve	
Congenital hypomyelinating neuropathy	
Familial dysautonomia	
Infantile neuraxonal degeneration	
Neuromuscular Junction	
Congenital and transient myasthenia gravis	
Infantile botulism	
Muscle Tissue	
Muscular dystrophies	
Metabolis myopathies	
Central core disease	
Fiber myopathies	

Less likely are the multiple genetic impairments that affect brain tissue, and that are estimated to comprise nearly 70 percent of all diagnosed cases of hypotonia [5]. In this regard one of the signal discoveries of early neuroscientific research revealed the critical dependence of the structuring of network architectures on sensorial activity [11]. In a telling observation, Wiesel and Hubel showed that cats could be made blind by depriving them of light stimulation during a critical window when the cortical visual networks were formed. Restoring activity after this period was incapable of reversing the effect. That is, once the synaptic contacts and network processes had been established molding influences were no longer effective in modifying the anatomical structure; the animals, therefore, were permanently blind due to the presence of a central brain rather than a retinal lesion. Such a result runs counter to a thesis premised on molecular adequacy alone and reveals that functionally restoring a gene product is not in itself a tool sufficient for network restoration.

Intuitively, this can be understood in the highly complex, three dimensional network that is structured under the influence of sensorial activity and that works in concert with developmental processes to yield a functional architecture. Such architectures, moreover, are intrinsically oriented toward recurrent connectivities where reciprocal inhibitory and excitatory innervation underpins the expression of non-linear, dynamical physiologies known to characterize brain neural activity. In the absence of developmental or translational machineries the ability to restore function appears compromised. Hence, situating gene products whose corrected sequences have been replaced in these loci is likely to be incapable of restoring the neural features needed for normal physiological functioning.

Further, this is not an obstacle limited to early developmental periods only, but a feature spanning a lifespan of brain activity, which remains intrinsically plastic and responsive to ongoing

environmental change. Navigational exploration, for example, has been shown to depend on multimodal sensorial activity and topographical mappings, which are internally bound together in hippocampal loci through oscillatory activity [12]. In cases of CNS impairments linked to hypotonia, therefore, overcoming these hurdles by genetic therapy will likely require a broader range of therapeutic options.

Significantly, the appearance of CNS hypotonia in early infancy relates the timing of symptomatic expression to synaptogenic errors generated during major formative epochs; that is, when the critical windows for synaptogenesis of principal brain networks are formed [13]. These heightened periods of plasticity involve many different factors, which include features such as genetic regulation, responsivity to developmental cues, and sensitivity to activity dependent stimuli. Major periods are now known to encompass synaptogenesis in the brain stem (early), thalamus (intermediate), and cortical zones including the cerebellum (late). Accordingly, they are also likely to constitute periods when genetically introduced products might be combined with adjunct therapies to mitigate hypotonia symptoms. Sensoria dependent strategies, for example, such as biofeedback and physical therapy [14] are conceptually appealing for their potential to evoke activity dependent circuit construction. The generation of the motor image, for example, a covert action undertaken only mentally and as a simulation of a non-executed action, can be expected to evoke activity dependent representations for motor movement in the posterior parietal and premotor cortices [15] that may be pertinent to hypotonia. Determining therapeutic effectiveness, nonetheless, will remain a study in prospects.

Conclusion

Historical timelines are a provocative and revealing indicator of medical trends. Yet the relations they index, like much of the complex medical art, are correlative rather than causative. For infant hypotonia, gene therapy's therapeutic promise is a hopeful but not a uniform warrant on possibility.

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