Genetics, Neurostimulation, and Robotics: Implications for the Developing Child

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Abstract Progresses in molecular genetics have improved the diagnostic yield of severe neurodevelopmental disorders in childhood as neuromuscular diseases, epilepsy, and movement disorders. Consequently, for some disorders, a personalized therapy is now available ameliorating the genetic defect even in previously devastating diseases. For example, intrathecal anti-sense nucleotide therapy is now available for patients with spinal muscle atrophy. Early intervention is even proposed in asymptomatic carriers of proven detrimental mutations of the responsible gene, SMN-1. The latter case is now further addressed by the intervention of a neonatal pilot screening program for SMA in Bavaria. Furthermore, gene therapy approaches for this disease have currently been approved by the U.S. Food and Drug Administration (FDA). Other interventions as deep brain stimulation and robotic assisted rehabilitation are increasingly used to improve motor functions in children with movement disorders. However, all mentioned approaches bear high costs and address new challenges for public and private health services. Fortunately, there is increasing awareness of rare diseases in childhood prompting more research in order to find personalized therapy approaches in these diseases.

Keywords Antisense oligonucleotides · Gene therapy · Next generation sequencing · Deep brain stimulation · Robotics · Rare diseases

1 Genetics

Progresses in molecular genetics have improved the diagnostic yield of severe neurodevelopmental disorders in childhood as neuromuscular diseases, epilepsy, and movement disorders [6, 8, 14]. Consequently, for some disorders, a personalized therapy is now available ameliorating the genetic defect even in previously devastating diseases. For example, intrathecal anti-sense nucleotide therapy is now available for patients with spinal muscle atrophy [5]. Early intervention is even proposed

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in asymptomatic carriers of proven detrimental mutations of the responsible gene, SMN-1. The latter case is now further addressed by the intervention of a neonatal pilot screening program for SMA in Bavaria. Furthermore, gene therapy approaches for this disease have currently been approved by the U.S. Food and Drug Administration (FDA). These new and innovative therapies prompted a public discussion due to the high costs for both types of therapies [12]. The costs for gene therapy for SMA are about 2 Mio. US$, and thus comprises the most expensive drug ever approved. Nevertheless, an independent research institute defined the costs of the drug recently at "the upper limit of what seems to be justified and cost effective" [7]. Nevertheless, it is difficult to determine the real monetary value of a medication. Companies take high costs for development, admission, and merchandizing in account for pricing. Critics may claim that the price of a certain medication is also influenced by the impact of the medication itself (i.e., a medication, which "heals" a devastating disease as gene therapy in SMA, might trigger higher prices than other medications for symptom relief). Thus, the high demand for these medications will most likely enforce high pricing as it follows the economic concept of demand and offer. Taken together, these examples show that the cure of rare diseases is a matter of money and that release of new and very expensive drugs is likely to gain public attention in future and will be questioned beside the matter of effectiveness by issues of cost-effectiveness. Pharmaceutical companies should acknowledge that the price of a medication should more likely be related to real and reproducible costs related to development, admission, and merchandizing of the medication rather than to economic concepts of demand and offer in order to make a feasible pricing, which can be covered by national health programs.

For other neurological disorders with common manifestations in childhood as epilepsy, a wide range of genetic defects can be detected. Genes putatively causing epilepsy comprise a plethora of different functions within the CNS. Impairment of ion currents, distortion of cortical development, and enzyme deficiencies are some examples of genetic causes of epilepsy (Fig. 1). However, development of new treatment approaches is more difficult to achieve as compared to neuromuscular disorders as the brain comprises a sophisticated network of interactions and plasticity which evolves within the developing brain not only in utero but also during infancy and childhood. Thus, interfering with genetic causes of epilepsy will probably mean inventing any causal treatment approaches as early as possible in order to avoid false network programming in these cases. In addition, the target cells for therapy are more sophisticated to reach compared to other diseases: in some genetic epilepsies, a distinct neuronal cell type is mainly responsible for the resulting phenotype. Regarding the wide range of different neuron populations within the human brain, it will be a challenge to address different kinds of cell types for targeted therapeutical interventions such as gene therapy or application of anti-sense oligonucleotides.

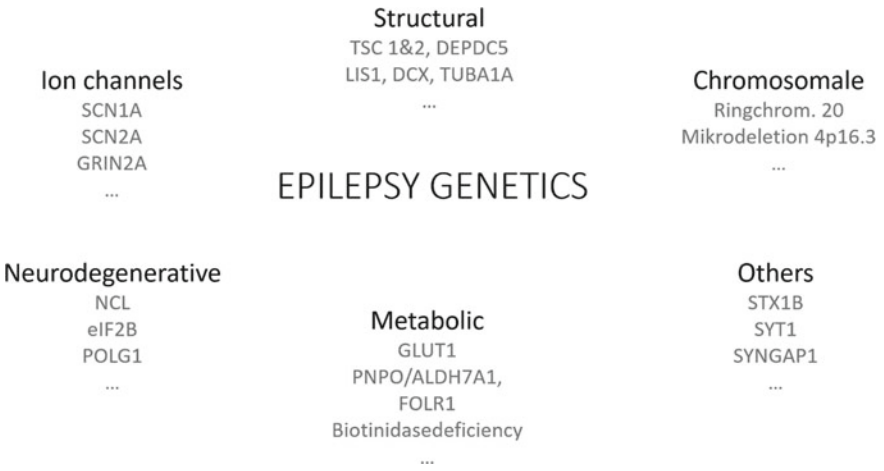

Fig. 1 The figure depicts only some selected causes of genetic epilepsies, which in total comprise a group of hundreds of different disorders

2 Neurostimulation

Neurostimulation is an effective therapeutic approach in some neurological disorders starting in childhood as movement disorders and epilepsy.

Deep brain stimulation is effective in patients with severe generalized dystonia [2, 9]. As a consequence of improved genetic testing, it could be unraveled that some genetic disorders (i.e., DYT-1 and KMT2B) are more likely to be responsive to deep brain stimulation than others closing the circle to what has been mentioned within the previous paragraph [3, 15]. DBS of the internal *globus pallidus* in severe dystonic movement disorders leads to significant reduction of motor impairment and increase in daily participation. However, besides even positive results of motor improvement over years, some patients report behavioral and mood disturbances during long-term stimulation.

Stimulation of the left vagal nerve may lead to seizure reduction in severe epilepsy syndromes [13]. Although the mechanism of action is not clearly understood, manipulation of thalamic networks is thought to contribute to this effect. The effect size is reasonable in some patients though seizure freedom can only be rarely reached. Thus, physicians have to cautiously discuss with the patients the expectations of such a way of stimulation, as expectation to the effect of the procedure might be too high.

3 Robotics

Task-specific body weight-supported treadmill therapy enabled by a robotic gait orthosis improves walking performance in children with central gait impairment [3,

10, 11]. Modulation of spinal networks and improvement of muscle energy consumption are thought to contribute to this effect. Robotic assisted treadmill therapy enabled by a driven gait orthosis (DGO) in adults has been established and shown significant improvements in spinal cord injured patients and stroke individuals. A pediatric DGO has recently been developed and reveals significant improvements in gait speed and endurance in both short- and long-term surveys. Thus, the introduction of robotic medicine in pediatric movement disorders contributes to regain of motor function in children with central gait impairment [1, 4]. These positive results are contrasted by the high costs for a robotic driven gait orthosis making it only available in certain specialized centers.

4 Conclusions

The scope of this report is to reflect the recent advances in medical interventions for children with neurological disorders on the one side. On the other side, the costs of some of these new interventions seem to have reached a tolerable upper limit, which is a matter of a public debate and critics. We believe that this discussion is very fruitful and helpful for patients with these rare diseases to find and approve new therapeutic targets, as both the public and pharmaceutical companies have neglected them for decades. These new approaches give hope to significantly decrease the burden of previously devastating diseases in future.

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