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Developmental Neurobiology of Cerebellar and Basal Ganglia Connections

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**Background:** The high prevalence of mixed phenotypes of Early Onset Ataxia (EOA) with comorbid dystonia has shifted the pathogenetic concept from the cerebellum towards the interconnected cerebellar motor network. This paper on EOA with comorbid dystonia (EOA-dystonia) explores the conceptual relationship between the motor phenotype and the cortico-basal-ganglia-ponto-cerebellar network.

**Methods:** In EOA-dystonia, we reviewed anatomic-, genetic- and biochemical- studies on the comorbidity between ataxia and dystonia.

**Results:** In a clinical EOA cohort, the prevalence of dystonia was over 60%. Both human and animal studies converge on the underlying role for the cortico-basal-ganglia-ponto-cerebellar network. Genetic -clinical and -in silico network studies reveal underlying biological pathways for energy production and neural signal transduction.

**Conclusions:** EOA-dystonia phenotypes are attributable to the cortico-basal-ganglia-ponto-cerebellar network, instead of to the cerebellum, alone. The underlying anatomic and pathogenetic pathways have clinical implications for our understanding of the heterogeneous phenotype, neuro-metabolic and genetic testing and potentially also for new treatment strategies, including neuro-modulation.

**Key words:** development, neurobiology, genetic, metabolic, cerebellum, basal ganglia, network, ataxia, dystonia, plasticity, Early Onset Ataxia.

**Abbreviations:**
EOA= Early Onset Ataxia, LOA=Late Onset Ataxia, SCA=Spino Cerebellar Ataxia, EOA-dystonia = EOA with comorbid dystonia, LOA-dystonia = LOA with comorbid dystonia, PPTG = pedunculo-pontine tegmental nucleus
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5. Assessment of EOA-dystonia phenotypes and genotypes

6. Treatment strategies including neuro-modulation
1. Introduction

The pathophysiology of movement disorders is classically attributed to dysfunctional activity of the motor center that contributes to the main feature of the phenotype. More recently, the awareness of “mixed” movement disorder phenotypes has shifted the attention from single motor centers to interconnected motor networks, instead. In children with Early Onset Ataxia (EOA; i.e. ataxia starting before the 25th year of life), dystonia is one of the most frequently occurring comorbid movement disorder features. These mixed EOA-dystonia phenotypes can reveal heterogeneous presentations, including (a) predominant ataxic features in combination with comorbid dystonia; (b) mild ataxic features in combination with primarily dystonic features; (c) hardly discernible or even absent ataxic features in combination with predominant dystonia; and (d) transient ataxic features which can wane over time and can be replaced by other movement disorder features, such as dystonia, or reversely, dystonic features that can diminish over time with cerebellar degeneration (due to modulating alterations within the underlying network activity). This phenotypic heterogeneity may not only limit the clinical consensus on phenotype-genotype relationships, but may also complicate diagnostic assessment and therapeutic treatment strategies.

Previous studies on cerebellar pathology have shown heterogeneity in mixed phenotypic presentations. This is illustrated by a CACNA1A mouse model showing paradoxical dystonia improvement with progressive loss of Purkinje cells. This model showed that cerebellar lesions can induce functional impairments at interconnected, distant motor centers (including the sensori-motor cortex, involved in the cortico-basal ganglia circuitry). In both patients with EOA (often consistent with autosomal recessive forms of ataxia) and in patients with Late Onset Ataxia (LOA) which are often consistent with autosomal dominant, neuro-degenerative forms of ataxia), the co-occurrence of mixed movement disorder features has been linked to altered cortico-basal ganglia-cerebellar network activity. From a timely perspective, these mixed movement disorder features are also postulated to originate by a complex interaction between abnormal development and maladaptive plasticity, and also between ageing and neuro-degeneration, potentially influencing the motor output by the cortico-basal-ganglia-ponto-cerebellar network. Especially during sensitive and critical time-windows of neurodevelopment, insights into the functioning of the interconnected motor centers appear relevant for the recognition, understanding of the pathophysiology and treatment of EOA-dystonia phenotypes.

In the present overview, we will focus on the prevalence and underlying pathogenesis of EOA-dystonia. Subsequently, we will discuss the prevalence of EOA-dystonia in a clinical EOA cohort, the anatomic
associations, the underlying biological pathways, neuro-metabolic associations and finally, the clinical implications for genetic assessment and treatment strategies, including neuro-modulation.

2. Cerebellar and Basal-Ganglia Connections

2.1 Cerebellum

Motor coordination is controlled by a complex network of motor centers including the basal ganglia, cerebral sensori-motor cortex, cerebellum and the efferent motor- and afferent sensory- pathways\textsuperscript{2,10}. In this network, the cerebellum plays a pivotal role, enabling information processing and modulation of timing, direction, and fluency of coordinated motor performances. The cerebellar cortex consists of a monolayer of inhibitory Purkinje cells sandwiched between a dense outer molecular layer of inhibitory interneurons (stellate and basket cells) and an inner layer of excitatory granule cells. Climbing fibers enter the Purkinje cell layer from the Inferior Olives, making excitatory synapses with the Purkinje Cells, leading to inhibition of the deep cerebellar output nuclei. Mossy fibers enter the granular layer from the pontine nuclei. These fibers form excitatory synapses with the granule cells which send their T-shaped parallel fibers into the outer molecular layer, where they make hundreds of thousands of synapses with Purkinje cell dendrites\textsuperscript{14}. By connections with basket cells, stellate cells (outer layer) and Golgi cells (granular layer) neural signaling can be sharpened. Purkinje dendrites are organized in a topographic manner, making topographic inhibitory GABA-ergic synapses with the deep cerebellar nuclei enabling positional coding\textsuperscript{15}. Cerebellar development and maturation (including synaptic pruning and myelination) starts early in fetal life, at \( \approx \) the 10\textsuperscript{th} postmenstrual week, and continues throughout childhood, resulting in a prolonged vulnerable period for external influences until puberty\textsuperscript{16-21}. In healthy, typically developing children, ongoing brain development, including the cerebellum and basal ganglia, is therefore reflected by the appearance of immature physiologic “ataxia-like” and “dystonia-like” features continuing until puberty, which are attributable to physiologic development and maturation instead of pathology\textsuperscript{22,23}. For an age-related overview of physiological movement disorder-like features and rating scale scores in relation with brain development\textsuperscript{23}, see figure 1. As these physiologic “movement disorder - like” features fulfill the criteria for pathologic rating scales, it is important to realize that longitudinal changes in ataxia rating scale scores could be confounded by physiological development. Clinical trials including young children may consider this point before interpreting relatively small margins in longitudinally changed scores as “therapeutic”\textsuperscript{5,24}.

2.2 Cerebello- Basal Ganglia- Thalamo-Cortical circuitry

Over recent years, the conceptual thinking about the underlying pathophysiology of mixed movement...
disorder features in non-degenerative dystonia has shifted the attention from the undisputable involvement of the basal ganglia to the over-all functioning of the entire cerebello-basal-ganglia-thalamo-cortical network. This conceptual development is a consequence of obtained insights that the cerebellum is involved in the conditioning and modelling of the cortico-basal ganglia signalling. In accordance with a simplified scheme (figure 2, set-up modified from Mori et al.), the cerebellum and basal ganglia interact through two different loops of motor networks. One loop consists of the cortico-cerebellar circuitry connecting the cerebellum (dentate nucleus) with the thalamus, cerebral cortex, and through cortico-pontine projections with the cerebellum. The other loop consists of the cortico-basal ganglia circuitry involving the stimulatory “direct”, the inhibitory “indirect” and the suppressed inhibitory “hyper direct” pathways connecting the basal ganglia output nuclei (globus pallidus and substantia nigra pars reticulata) with the thalamus, cerebral cortex and the basal ganglia input nuclei (striatum and subthalamic nucleus (STN)). Cerebellar-basal-ganglia interactions can occur at the pons (through the pedunculopontine tegmental nucleus (PPtG), with di-synaptic projections to the basal ganglia and projections to the cerebellar nuclei), at the thalamus and at the cortex (see figure 2).

Alterations in this cerebello-basal-ganglia-thalamo-cortical network may provide an explanation for many clinical observations in patients with dystonia and cerebellar abnormalities. In dystonic patients, imaging studies have shown co-existing hypo-activity and/or atrophy at the location of cerebellar cholinergic terminals at lobules VI and VII, which are involved in cerebellar sensorimotor projections to the cortex and working memory, respectively. The cerebellar lobules VI and VII are activated when motor tasks are complex and require motor planning and/or usage of a tool, particularly in young individuals during the early stages of motor learning. These findings may support the idea that the cholinergic projections to the cerebellum (arriving from the PPTG) are involved in the planning and execution of complex motor tasks involving sensorimotor integration and cognitive functioning. In patients with dystonic writer’s cramp, electrophysiological evaluations of the sensorimotor and premotor cortices showed that reduced cerebellar inhibition and modulation of the cortex could lead to abnormal sensorimotor integration and the building up of incorrect motor programs. During impaired neurodevelopment, maladaptive plasticity - the impaired ability of the nervous system to adequately modify or strengthen its synaptic connections – may thus have an underlying patho-physiological role in the initiation of dystonia. In the DYT1 dystonia mouse model, it was shown that there is a sensitive time-window for maladaptive plasticity during brain development, which can be attributed to neurotrophic factors and synaptic morphology. By silencing glutamate transporter 2 in an in vivo mouse model, White and Sillitoe showed that disruption of glutaminergic excitatory olivo-cerebellar synapses may induce abnormal firing and an immature structure of the Purkinje cells causing severe dystonia. Altogether, during the sensitive developmental “motor
learning period” of the cerebellum, these studies may indicate that maladaptive mechanisms can result in the consolidation of abnormal dystonic motor engrams.

3. EOA-dystonia prevalence and underlying anatomic- and biological- pathways

3.1 Prevalence of EOA-dystonia in a clinical cohort

In a cohort of 80 children with EOA, we have reported a prevalence of mild dystonic comorbidity (EOA-dystonia) in 65% of the patients. In this EOA cohort, specifically diseases associated with cerebellar atrophy and Purkinje cell pathology (such as Ataxia with Vitamin E Deficiency (AVED) and ataxia telangiectasia (AT)) appeared associated with more pronounced dystonic comorbidity, for an example see figure 3. Interestingly, cerebellar atrophy is not only observed in EOA with comorbid dystonia, but due to heterogeneity, also in EOA patients with primarily dystonia and a paucity of cerebellar signs, see for example figure 4. In our paediatric EOA cohort, there was no association between the severity of dystonia and EOA-disease duration and/or the patient’s age, implicating that other factors than neuro-degeneration can induce dystonic comorbidity. In this perspective, one could speculate that reduced cerebellar inhibition of the thalamo-cortical network connections is involved.

3.2 Underlying anatomic and biologic pathways

In the EOA cohort, radiologic investigation of MRI abnormalities in dystonic genotypes-phenotypes revealed a relation between cerebellar and pontine and/or basal-ganglia and/or thalamus involvement (p=.001), implicating cortico-basal-ganglia-ponto-cerebellar involvement. Subsequent genetic network and functional enrichment analysis in these EOA-dystonia genotypes showed enrichment for organelle- and cellular-component organization associated with energy production and signal transduction. Checking representativeness of our results by in silico analysis of shared genes in EOA and LOA and dystonia (from up-to-date clinical panels), confirmed that energy production and signal transduction (Krebs-cycle and fatty acid/lipid-metabolic processes) play a significant role in the pathogenesis of ataxia and comorbid dystonia.

3.3 Underlying metabolic disorders

The underlying biological pathways linked to EOA-dystonia including cellular energy production and signal transduction are thus associated with metabolic processes including Krebs (TCA) cycle and fatty acid-lipid-metabolic processes. Clinically, inherited metabolic disorders are frequently linked with cerebellar pathology and/or ataxia. The TCA cycle is crucial for mitochondrial ATP production, fulfilling the high-energy demands of the cerebellum, cortical areas and basal ganglia. Furthermore, the TCA cycle is crucial for the synthesis of gamma aminobutyric acid (GABA), the main neurotransmitter of Purkinje cells. As indicated, dysfunctional Purkinje cells are associated with
reduced inhibition and altered modulation of the sensori-motor cortex, leading to dystonia\textsuperscript{40,48}. In patients with mitochondrial deficits, energy failure of Purkinje cells can therefore be linked with ataxia and other hyperkinetic movement disorders, including dystonia\textsuperscript{30,49}. Furthermore, fatty acids and their metabolites are important for normal brain development and many neuro-metabolic diseases are associated with disrupted lipid- and cholesterol homeostasis\textsuperscript{50}. In the central nervous system, oligodendrocytes generate multiple layers of myelin around axons to enable saltatory nerve conduction. Additional roles of oligodendrocytes consist of the provision of metabolic support to neurons, and the regulation of ion and water homeostasis by adapting to activity-dependent neuronal signals\textsuperscript{51}. If we consider EOA from a metabolic perspective, there are about 150 inherited metabolic disorders that are listed with mixed EOA phenotypes\textsuperscript{52}, including dystonia, chorea and/or athetosis, hypokinetic-rigid syndrome, tremor, and myoclonus\textsuperscript{8,53}. Despite the heterogeneity in underlying metabolic gene defects\textsuperscript{47}, the vast majority (>95%) of these genotypes are described as a mixed EOA phenotypes including comorbid dystonia. Although we have identified Krebs-cycle and fatty acid/lipid-metabolic processes as the most statistically significant common metabolic pathways underling EOA-dystonia, other metabolic processes may thus cause a variety of mixed EOA phenotypes including comorbid dystonia, as well.

4. Clinical implications

4.1 Assessment of EOA-dystonia phenotypes and genotypes

In our previous study on EOA with comorbid dystonia, we have shown that overlapping gene networks and concurrent gene expression can lead to ataxia with dystonic comorbidity\textsuperscript{7}. Considering the fact that the overlap in gene networks is about 50% larger in EOA-dystonia than in LOA-dystonia\textsuperscript{7}, the estimated a priori chance for dystonic comorbidity in EOA seems also twice as much as in LOA. Comparing the reported clinical prevalence in EOA-dystonia versus LOA-dystonia (65% vs 0-50%, respectively\textsuperscript{11}) may support this assumption. Especially during the sensitive and critical time-windows of neurodevelopment, the effects by Purkinje cell pathology on cortical surround inhibition may be strengthened leading to a persistent, inappropriate execution of intended goal directed motor tasks. Interestingly, in our EOA cohort, we also observed severe and even predominating dystonic phenotypes in disorders with pronounced Purkinje cell pathology, such as in phenotypes of ataxia telangiectasia, and more rare phenotypes of ataxia with oculomotor apraxia type 4 (AOA4) and also AVED’s disease, in which predominant dystonia has been described before\textsuperscript{54,55} (see also figure 3).

Until now, it is still insufficiently known why Purkinje cells in neurodegenerative ataxia’s are specifically
vulnerable for the underlying gene mutation, whereas other cell populations could be affected, as well. In addition to the effects of high cerebellar metabolic demands, one could also patho-genetically link a broad group of EOA and LOA disorders (for instance AT, AVED, AOA-1,-2 and -4, Friedreich’s ataxia and other polyglutamine expansions) with cerebellar vulnerability by an underlying defect in DNA repair genes. In these EOA and LOA disorders, defective responses to DNA damage may lead to accumulated DNA damage and neuro-degeneration hallmark by mitochondrial dysfunction. Especially disorders with defective DNA single-strand break repair may almost exclusively impact the cerebellum. This could implicate a shared role between DNA repair defects and mitochondrial dysfunction as explanatory mechanisms for the vulnerability of Purkinje cells. In Purkinje cells, unmet high metabolic demands and dependence on oxidative metabolism, could lead to the generation of free radicals, causing single-strand DNA breaks and neuro-degeneration. However, other explanations, such as apoptosis due to more sensitivity for accumulated DNA damage, have been proposed, as well.

Altogether, these data converge on the conceptual approach that mixed EOA motor phenotypes are linked with underlying brain networks instead of with single motor centres. This conceptual approach is also substantiated by functional magnetic resonance imaging (fc-MRI) measuring resting state of networks. Previous fcMRI studies of the cerebellum have reported multiple results consistent with the underlying cerebrocerebellar circuitry. As a matter of fact, the majority of the human cerebellum is functionally coupled to cerebral association areas.

Due to their relationship with neuro-metabolic processes, mixed “EOA-dystonia” phenotypes may have implications for the clinical approach. Especially when there is an identifiable trigger leading to the disease onset, when the phenotype is of (sub)acute in onset, and when the phenotype is consistent with mixed movement disorder features (and other features identifiable by INAS), one could check for underlying treatable disorders (by MRI and laboratory investigations) before testing by next generation sequencing (NGS). Furthermore, we have discussed the heterogeneity in phenotypes and genotypes leading to EOA with dystonia, for instance by the effect of cerebellar pathology on cortical surround inhibition. As a consequence of the heterogeneous phenotype-genotype relationships, genetic diagnostic strategies may preferentially involve NGS testing with complete movement disorder gene lists, instead of testing with a single EOA gene panel.

4.2 Treatment strategies including neuro-modulation

For the heterogeneous EOA-dystonia disorders, there is a large variety in treatment strategies, including biochemical supplementation of the underlying enzymatic defect, pharmacological
treatment of the movement disorder features, functional neurosurgery and/or neuro-modulation techniques\textsuperscript{64,65}. The human cerebellum is easily accessible for non-invasive stimulation techniques including Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS)\textsuperscript{65}, aiming to modulate the cerebro-cerebellar circuitry by influencing tonic Purkinje cell activity\textsuperscript{66}. Due to the cerebellar network connections, these techniques can treat a variety of motor symptoms including ataxia and dystonia by addressing the dento-cerebello-thalamic pathway, including the cortex, striatum and subthalamic nucleus\textsuperscript{25,65,67,68}. These non-invasive stimulation techniques are relatively easily applicable and well-tolerated by patients\textsuperscript{69}. However, these techniques may also induce undesirable side effects, and there are still many caveats including: the optimal intensity, the timing of the stimulation, inter-individual variation between patient-responses, longevity of the effect, unknown effects of combined treatment and incomplete insight in optimal stimulation sites\textsuperscript{65,66,70-72}.

In animal models and humans, studies of invasive cerebellar deep brain stimulation (DBS) targeting the cerebellar dentate nucleus have shown that DBS could have a favorable effect on dystonic and dyskinetic phenotypes\textsuperscript{73,74}. In a recent mutant mouse model (Car8 waddles) for hereditary ataxia Miterko et al. investigated the potential benefits of DBS at the cerebellar nuclei in combination with physical activity\textsuperscript{75}. While cerebellar DBS alone improved mobility and muscle function, additional exercising in combination with the treatment regimen improved limb coordination and stepping. In this model, DBS exerted the most beneficial effect in mice with early-stage ataxia, suggesting that efficacy depends on the pre-existing integrity of the cerebellar circuitry\textsuperscript{75}. Beside the cerebellar nuclei, one could also consider different DBS targets from the perspective of the interconnected motor network, including the interconnected striatum, involving the internal Globus Pallidus or the Nucleus Subthalamicus\textsuperscript{25,65,76}. Furthermore, DBS at PPTg has shown to relieve pre-prepared movement blocks and improve postural sensory integration\textsuperscript{77,78}. Future animal and human studies will hopefully elaborate on these, and other promising techniques (including optogenetic stimulation), to further extent\textsuperscript{65}.

Conclusion

In EOA, we conclude that there is an interaction between the cerebellum and the cortico-basal-ganglia-ponto-cerebellar pathways, leading to comorbidity with dystonia and other movement disorder features. Changing the conceptual approach towards the underlying motor network has clinical implications for neuro-metabolic assessment, genetic NGS testing by complete movement disorder
gene lists and the consideration of treatment strategies, including potential targets for neuro-modulation.

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Legends

Figure 1: Movement disorder rating scale age-relatedness in perspective of the physiologic brain maturation in typically developing children\textsuperscript{23}

Legend: Diverse movement disorder rating scale scores for ataxia (ICARS, BARS, SARA) and dystonia (DIS-D, BFMMMS, BFMDS) are provided as the % of the maximum score per rating scale. Figure 1 indicates the age-relatedness of ataxia and dystonia movement disorder rating scale-scores in typically developing children between 4 and 16 years (A) and between 9 and 16 years of age (B) in perspective of maturation of the motor centers (determined by grey matter volume on MRI). Dystonia- and ataxia-motor rating scales reach the “adult” optimum value around 12 and ≥ 16 years of age, respectively.


Figure 2: Simplified scheme illustrating the interconnectivity between the basal ganglia and cerebellum \#

Legend: The interactions between the cerebellar circuit (right) and basal ganglia circuit (left) occur at the level of:

1. the pons through the pedunculopontine tegmental nucleus (PPTG, with di-synaptic projections to the basal ganglia and projections to the cerebellar nuclei);
2. thalamus (by projections from the PPTG, STN and cerebellar nuclei);
3. the cortex (receiving input from the thalamus, sending output connections to both the cortico-cerebellar and cortico-basal ganglia pathways).

Arrows indicate projection direction, arrows to both sides indicate bidirectional projections. Red arrows indicate mostly excitatory connections, blue arrows indicate mostly inhibitory connections, purple arrows indicate mixed excitatory / inhibitory connections.

The PPTG contains glutamate-, acetylcholine-, and GABA-releasing neurons. The PPTG receives GABA-ergic projections from the substantia nigra pars reticulata (basal ganglia output) that inhibit the cholinergic PPTG projections to the cerebellum and thalamus.

Abbreviations: GPe: globus pallidus externus, GPi: globus pallidus internus, PPTg: pedunculopontine...
Figure 3

Patient with TTP gene mutation (AVED) and dystonia as the main feature of the movement disorder.

Legend: This figure shows dystonic posturing of both hands and mouth.

Figure 4

Cerebellar atrophy in a paediatric patient with profound dystonia due to PNKP gene mutation (AOA4).

Legend: Sagittal and transverse sections showing diffuse, symmetrical cerebellar atrophy, with normal signal intensities of the grey and white matter. There are no abnormalities at the basal ganglia, thalamus, brain stem or cortex.
References


Movement disorder rating scale age-relatedness in perspective of the physiologic brain maturation in typically developing children

Figure 1
Figure 2

Cerebral Cortex

Basal Ganglia

Striatum

GPe

STN

SNr /GPi

Thalamus

Cerebellum

Cerebellar Cortex

Cerebellar Nuclei

Pons

Journal Pre-proof

+ (mostly) excitatory

- (mostly) inhibitory

mixed excitatory /inhibitory
Highlights

- In children with EOA, the prevalence of comorbid dystonia (EOA-dystonia) is more than 60%.
- EOA-dystonia is associated with altered signalling in the cortico-basal-ganglia-ponto-cerebellar (CBC) network.
- Altered metabolic processes and DNA repair mechanisms may share a role in the pathogenesis of EOA-dystonia.
- In EOA-dystonia, the conceptual CBC motor-network approach may provide new targets for neuro-modulation.
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: