EDITORIAL

The Era of Cerebellar Therapy

Hiroshi Mitoma[1,*] and Mario Manto[2,3]

[1]*Medical Education Promotion Center, Tokyo Medical University, Tokyo, Japan;* [2]*Service de Neurologie, CHU-Charleroi, Charleroi, Belgium;* [3]*Service des Neurosciences, Université de Mons, 7000 Mons, Belgium*

Abstract: Major advances in our understanding of the neurology/pathology, anatomy/physiology, and molecular biology of the cerebellum have opened a new door for cerebellar ataxias (CAs). We have now entered in the 'era of therapies'. Cures are knocking at the door. We discuss the hot topics in the therapeutic protocols available for CAs, including aminopyridines, noninvasive cerebellar stimulation, anti-oxidant drugs and therapies for immune-mediated cerbellar ataxias (IMCAs), topics emphasized in this issue. The history of the cerebellum is a typical example of the importance of apparently divergent and multi-disciplinary approaches.

Keywords: Cerebellar ataxias, cerebellum, therapy, aminopyridines, anti-oxidant drugs, noninvasive cerebellar stimulation, immunotherapies.

1. THE HISTORICAL ERAS OF NEUROLOGY/ PATHOLOGY, ANATOMY/PHYSIOLOGY, AND MOLECULAR BIOLOGY

The terminology of Cerebellar ataxias (CAs) encompasses a group of heterogenesous disorders characterized by motor incoordination and impaired cognitive/affective functions. CAs have significant impact on daily living activities of the afflicted patients. With the discovery of the importance of cerebellum in cognitive/affective operations from childhood and the ageing of the population, CAs are being recognized worldwide, both clinically and socially. It is anticipated that each public and private hospital will include a separate ataxia unit for patients with CAs in the next decade [1, 2].

Historically, after the reports of Jean Pierre Flourens, Franz Joseph Gall and Luigi Luciani, Joseph Jules François Félix Babinski attributed motor incoordination to cerebellar dysfunction at the beginning of the 20th century [3], and the clinical entity of multiple systemic atrophy, one of the most variant of degenerative CAs, was simultaneously established. Before Babinski, motor incoordination was often thought to be caused exclusively by lesions in the dorsal column of the spinal cord. The concept of CAs was subsequently brushed up by Gordon Holmes [4]. Holmes also reported on adiadochokinesia (first described by Babinski) and dysmetria, and defined asthenia and adventitious movement which could be more complex symptoms. From these pioneer studies, the field of classical cerebellar neurology (ataxiology) has been progressively established and matured. It provides detailed comparisons of clinical symptoms and associated pathological changes, and includes various clinical entities such as neurodevelopmental disorders, cerebellar tumors, cerebellitis, metabolic CAs, and degenerative CAs.

Since the 1960s, the blue prints of the cerebellum have been clarified. The classic book "The Cerebellum as a Neuronal Machine" authored by Eccles, Ito, and Szentágothai described the highly geometrical structure of the cerebellum (Fig. **1**) [5]. They identified the mossy fibers, which terminate on the granule cells, convey afferent information from the periphery and the cerebral cortex for coordinative controls. They also described another afferent system composed of the climbing fibers, which originate from the inferior olive nucleus and terminate on Purkinje cells (PCs). The parallel fibers (long axons of the granule cells running on the surface in the cerebellar cortex) induce PC activation, which subsequently dampens the neuronal activity of the deep cerebellar nuclei. However, the principles of actions in this highly geometrical structure are still controversial. Currently, there are two major theories on the cerebellar coordinative motor control systems: the time control machine and the learning machine. Llinãs proposed that rhythmic activity of the inferior nucleus neurons synchronizes a group of PCs [6]. On the other hand, Ito proposed that error signals from the climbing fibers reduce parallel fiber inputs onto the PCs and, thus eliminate inadequate PC activations through long-term depression [7]. Elaborated and improved theories have been proposed subsequently [1]. In the 1980-1990s, under the input of Schmahmann, clinical and scientific evidence was provided for the involvement of the cerebellum in the control of cognitive, affective and emotional functions [8-12]. The works of Strick have also led to novel views on cerebello-cerebral loops and connectivity with basal ganglia [13]. The uniformity of the compositional structure suggests a similar role in coordination, such as timing and/or prediction control, in the cognitive, affective and emotional domains.

*Address correspondence to this author at the Medical Education Promotion Center, Tokyo Medical University, Tokyo, Japan;
E-mail: mitoma@tokyo-med.ac.jp

1570-159X/19 $58.00+.00

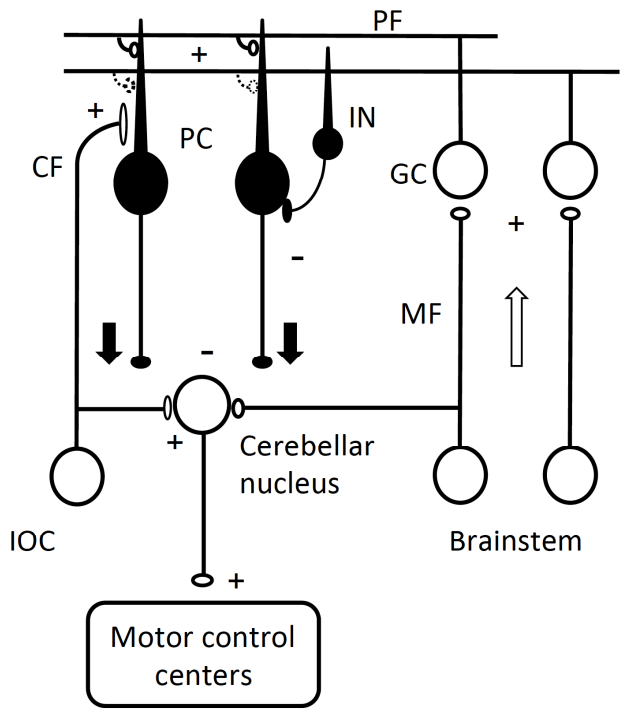

Fig. (1). Schematic diagram of the neural circuitry of the cerebellar cortex. Abbreviations: PF: parallel fibers, CF: climbing fibers, MF: mossy fibers, PC: Purkinje cells, GC: granule cells, IN: interneurons (Golgi cells, Basket cells, stellate cells, Lugaro cells), IOC: inferior olivary complex.

Since the 1980s, advances in molecular biology have identified various genetic abnormalities (more than 140 cerebellar disorders are associated with gene mutations) and re-classified the etiologies of cerebellar diseases based on molecular pathologies [14]. These advances have also clarified the molecular changes underlying cell death. In addition, cerebellar transplantation, using grafts of embryonic or fetal cerebellar tissue, has been attempted in laboratory animals, though the results clearly need further analysis to enter in the clinic [15].

In conclusion, the field of cerebellar medicine has matured after three historical eras in the last 200 years that have defined the neurology/pathology, physiology/anatomy, and molecular biology (Fig. **2**).

2. HOLMES PROVIDES EVIDENCE FOR POSSIBLE RESTORATION OF CEREBELLAR FUNCTION

Is improvement in CAs an absurd story? It is generally considered that the cerebellum has the capacity of self-repair after abrupt injury or stroke damage in any part of the cerebellum. This consideration originates from a classical study by Holmes on patients with gunshot injuries [4]. Holmes described the recovery process of two patients (pages 514-515). One had a limited lesion to the lateral lobe and the other had a larger and medial lesion in the lateral lobe. Despite the considerable damage, both patients walked with stability after 58 days and 71 days, respectively. Interestingly, there was no difference in the gait of the two patients, despite the marked difference in the extent of the two lesions. Such historical cases suggest that restoration of cerebellar function can occur in CAs. Nowadays, the evidence of possible recovery after a cerebellar stroke is not challenged anymore.

3. THE START OF THE ERA OF CEREBELLAR THERAPY

The integrated advances in the above three fields (neurology/pathology, anatomy/physiology, and molecular biology) have opened the door for efficacious treatments of cerebellar diseases. We review here the currently hot topics on the therapeutic management of CAs.

3.1. Physiologically-based Therapeutic Strategies

3.1.1. Aminopyridines as a Key-therapy in Selected CAs

Although most of the currently available medications described to improve CAs are not effective, aminopyridines (K^+ channel blockers), have therapeutic benefits in a subgroup of CA patients. Recent double-blind randomized studies have demonstrated that aminopyridines reduce the attacks of CAs in episodic ataxia type 2 (EA2) [16] and improve downbeat nystagmus of ataxic symptoms [17]. It is thought that these actions of aminopyridines are mediated through restoration of pacemaking precision in PC activities and thus diminish the frequency of CA attacks and cerebellar specific nystagmus [18]. It could be argued that the above improvements are due to restoration of clock-wise actions. Kalla R and Strupp M will review updated therapeutic benefits for aminopyridines in this issue.

3.1.2. Noninvasive Cerebellar Stimulation as a Complement Tool to Pharmacotherapy

A double-blind, randomized, sham controlled study showed the therapeutic benefits of noninvasive cerebellar stimulation (transcranial direct current stimulation or transcranial magnetic stimulation) in patients with CAs [19]. Although more than a single mechanism probably explains the improvement after such therapy, one possible explanation is the modulation of cerebellar output thanks to the cerebellar anatomy [20]. Neurons of the cerebellar nuclei, which convey cerebellar output signals to the motor cortex, are under profound inhibition by PCs (Fig. **1**). Coordinative motor commands for selection of a particular muscle movement are formulated by attenuation of this PC-mediated inhibition [21]. Thus, noninvasive cerebellar stimulation alters the degree of inhibition of the cerebellar nuclei by fine tuning neuronal excitability in the cerebellar cortex [20]. Further studies are needed to standardize the physiologically-based therapies, *e.g.*, the conditions of simulation, so as to maximize the efficiency of cerebello-cerebral controls. These problems are discussed in a review article by Ferruci R *et al*. (this issue).

3.2. Targeting Common Molecular Pathways Associated with Cell Death: Anti-oxidant Drugs

Friedreich ataxia, the most common hereditary ataxia, is characterized in the majority of cases by expansion of a

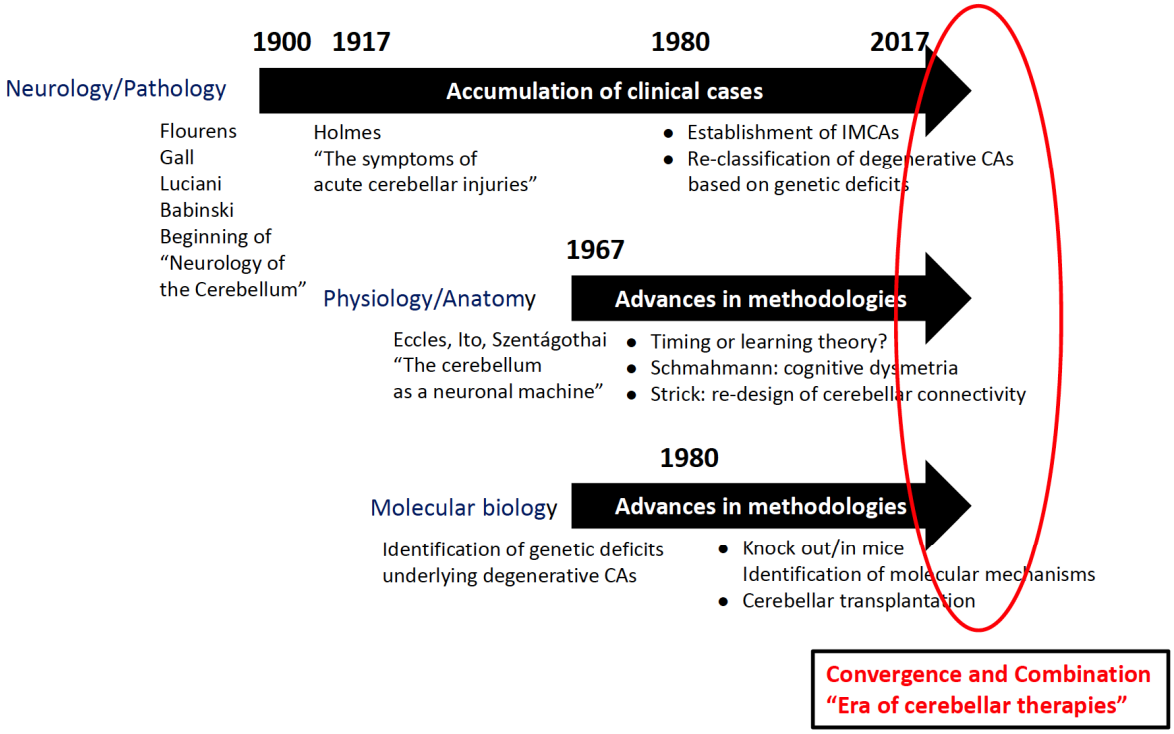

Fig. (2). A re-visit of the history of fundamental basic and clinical studies in cerebellar field. (*The color version of the figure is available in the electronic copy of the article*).

GAA triplets in the intron of the frataxin gene. The expansion hinders transcription, which reduces the mRNA levels of frataxin involved in iron-sulfur cluster synthesis [22]. These abnormalities lead to accumulation of iron in the mitochondria, and ultimately result in oxidative stress.

Mitochondrial dysfunction is also involved in the excitotoxicity, which is common in various diseases, including ischemia and certain immune-mediated and metabolic CAs (such as anti-GAD65 antibody-associated CA and ethanol withdrawal-associated CA). Taken together, the recent studies potentially implicate oxidative stress as a common cellular pathology responsible for neuronal cell death in the cerebellum. The results also highlight new therapies that can be designed to target oxidative stress, for the management of various types of CAs. Finally, these studies suggest that, although the etiology of CAs can be different, there might be multiple common pathways in disordered cellular activities, providing opportunities for the development of new therapies. The potential benefits of anti-oxidant drugs are discussed in an article by Barca E *et al.*(this issue).

3.3. Immune-mediated Cerebellar Ataxias: A New Clinical Entity and Therapeutic Potentials

Patients who show mild cerebellar atrophy but present with severe CA symptoms have been well described clinically. These patients are sometimes misdiagnosed as degenerative CAs. In the 1980s, the clinical entity of immune-mediated CAs (IMCAs) was established. IMCAs are not limited to the classical type (multiple sclerosis and paraneoplastic syndrome), but also includes gluten ataxia and anti-GAD65 antibody-associated CA [23]. Importantly, a proportion of these patients can respond to immunotherapies especially if these are used in the early stages of CA when the capacity for self-recovery is still preserved (*i.e.*, adequate cerebellar reserve) [23]. Avoidance of antigen exposure and the use of a combination of oral prednisolone, intravenous methylprednisolone, intravenous immunoglobulins, immunosuppressants, and/or plasma exchange are now recommended [23]. Detailed clinical features and therapeutic strategies for IMCAs are reviewed in an article by Mitoma H, Manto M, and Hampe CS (this issue).

CONCLUSION

Advancements in therapeutic strategies emphasize the need for divergent and multi-disciplinary approaches for the treatment of CAs. Once century after the publication of Holmes' classic paper (1917), major progress has been made in the understanding of the roles of the cerebellum. The translational efforts are growing [24], the clinical deficits are refined [25] and the neuroanatomical reports are still improving [26]. All the pieces are on place to reach success in therapeutics.

REFERENCES

[1] Manto, M. The cerebellum, cerebellar disorders, and cerebellar research-two centuries of discoveries. *Cerebellum,* **2008**, *7*(4), 505-516. [http://dx.doi.org/10.1007/s12311-008-0063-7] [PMID: 18855093]

[2] Bodranghien, F.; Bastian, A.; Casali, C.; Hallett, M.; Louis, E.D.; Manto, M.; Mariën, P.; Nowak, D.A.; Schmahmann, J.D.; Serrao, M.; Steiner, K.M.; Strupp, M.; Tilikete, C.; Timmann, D.; van Dun,

K. Consensus paper: Revisiting the symptoms and signs of cerebellar syndrome. *Cerebellum,* **2016**, *15*(3), 369-391. [http://dx.doi.org/10.1007/s12311-015-0687-3] [PMID: 26105056]

[3] Babinski, J. Sur le rôle du cervelet dans les actes volitionnels nécessitant une succession rapide de mouvements (diadococinésie). *Rev. Neurol. (Paris),* **1902**, *10*, 1013-1015.

[4] Holmes, G. The symptoms of acute cerebellar injuries due to gunshot injuries. *Brain,* **1917**, *40*, 461-535. [http://dx.doi.org/10.1093/brain/40.4.461]

[5] Eccles, J.C.; Ito, M.; Szentágothai, J. The cerebellum as a neuronal machine; Springer-Verlag: New York, **1967**. [http://dx.doi.org/10.1007/978-3-662-13147-3]

[6] Llinás, R.R. Inferior olive oscillation as the temporal basis for motricity and oscillatory reset as the basis for motor error correction. *Neuroscience,* **2009**, *162*(3), 797-804. [http://dx.doi.org/10.1016/j.neuroscience.2009.04.045] [PMID: 19393291]

[7] Ito, M. Cerebellar circuitry as a neuronal machine. *Prog. Neurobiol.,* **2006**, *78*(3-5), 272-303. [http://dx.doi.org/10.1016/j.pneurobio.2006.02.006] [PMID: 16759785]

[8] Timmann, D.; Daum, I. Cerebellar contributions to cognitive functions: a progress report after two decades of research. *Cerebellum,* **2007**, *6*(3), 159-162. [http://dx.doi.org/10.1080/14734220701496448] [PMID: 17786810]

[9] Koziol, L.F.; Budding, D.; Andreasen, N.; D'Arrigo, S.; Bulgheroni, S.; Imamizu, H.; Ito, M.; Manto, M.; Marvel, C.; Parker, K.; Pezzulo, G.; Ramnani, N.; Riva, D.; Schmahmann, J.; Vandervert, L.; Yamazaki, T. Consensus paper: the cerebellum's role in movement and cognition. *Cerebellum,* **2014**, *13*(1), 151-177. [http://dx.doi.org/10.1007/s12311-013-0511-x] [PMID: 23996631]

[10] Mariën, P.; Ackermann, H.; Adamaszek, M.; Barwood, C.H.; Beaton, A.; Desmond, J.; De Witte, E.; Fawcett, A.J.; Hertrich, I.; Küper, M.; Leggio, M.; Marvel, C.; Molinari, M.; Murdoch, B.E.; Nicolson, R.I.; Schmahmann, J.D.; Stoodley, C.J.; Thürling, M.; Timmann, D.; Wouters, E.; Ziegler, W. Consensus paper: Language and the cerebellum: an ongoing enigma. *Cerebellum,* **2014**, *13*(3), 386-410. [PMID: 24318484]

[11] Manto, M.; Mariën, P. Schmahmann's syndrome - identification of the third cornerstone of clinical ataxiology. *Cerebellum Ataxias,* **2015**, *2*, 2. [http://dx.doi.org/10.1186/s40673-015-0023-1] [PMID: 26331045]

[12] Hoche, F.; Guell, X.; Vangel, M.G.; Sherman, J.C.; Schmahmann, J.D. The cerebellar cognitive affective/Schmahmann syndrome scale. *Brain,* **2018**, *141*(1), 248-270. [http://dx.doi.org/10.1093/brain/awx317] [PMID: 29206893]

[13] Bostan, A.C.; Strick, P.L. The basal ganglia and the cerebellum: nodes in an integrated network. *Nat. Rev. Neurosci.,* **2018**, *19*(6), 338-350. [http://dx.doi.org/10.1038/s41583-018-0002-7] [PMID: 29643480]

[14] Ilg, W.; Bastian, A.J.; Boesch, S.; Burciu, R.G.; Celnik, P.; Claaßen, J.; Feil, K.; Kalla, R.; Miyai, I.; Nachbauer, W.; Schöls, L.; Strupp, M.; Synofzik, M.; Teufel, J.; Timmann, D. Consensus paper: management of degenerative cerebellar disorders. *Cerebellum,* **2014**, *13*(2), 248-268. [http://dx.doi.org/10.1007/s12311-013-0531-6] [PMID: 24222635]

[15] Cendelin, J. Transplantation and stem cell therapy for cerebellar degenerations. *Cerebellum,* **2016**, *15*(1), 48-50. [http://dx.doi.org/10.1007/s12311-015-0697-1] [PMID: 26155762]

[16] Strupp, M.; Kalla, R.; Claassen, J.; Adrion, C.; Mansmann, U.; Klopstock, T.; Freilinger, T.; Neugebauer, H.; Spiegel, R.; Dichgans, M.; Lehmann-Horn, F.; Jurkat-Rott, K.; Brandt, T.; Jen, J.C.; Jahn, K. A randomized trial of 4-aminopyridine in EA2 and related familial episodic ataxias. *Neurology,* **2011**, *77*(3), 269-275. [http://dx.doi.org/10.1212/WNL.0b013e318225ab07] [PMID: 21734179]

[17] Kalla, R.; Glasauer, S.; Büttner, U.; Brandt, T.; Strupp, M. 4-aminopyridine restores vertical and horizontal neural integrator function in downbeat nystagmus. *Brain,* **2007**, *130*(Pt 9), 2441-2451. [http://dx.doi.org/10.1093/brain/awm172] [PMID: 17664175]

[18] Alviña, K.; Khodakhah, K. The therapeutic mode of action of 4-aminopyridine in cerebellar ataxia. *J. Neurosci.,* **2010**, *30*(21), 7258-7268. [http://dx.doi.org/10.1523/JNEUROSCI.3582-09.2010] [PMID: 20505092]

[19] Benussi, A.; Koch, G.; Cotelli, M.; Padovani, A.; Borroni, B. Cerebellar transcranial direct current stimulation in patients with ataxia: A double-blind, randomized, sham-controlled study. *Mov. Disord.,* **2015**, *30*(12), 1701-1705. [http://dx.doi.org/10.1002/mds.26356] [PMID: 26274840]

[20] Mitoma, H.; Manto, M. The physiological basis of therapies for cerebellar ataxias. *Ther. Adv. Neurol. Disorder.,* **2016**, *9*(5), 396-413. [http://dx.doi.org/10.1177/1756285616648940] [PMID: 27582895]

[21] Panyakaew, P.; Cho, H.J.; Srivanitchapoom, P.; Popa, T.; Wu, T.; Hallett, M. Cerebellar brain inhibition in the target and surround muscles during voluntary tonic activation. *Eur. J. Neurosci.,* **2016**, *43*(8), 1075-1081. [http://dx.doi.org/10.1111/ejn.13211] [PMID: 26900871]

[22] Wong, A.; Yang, J.; Cavadini, P.; Gellera, C.; Lonnerdal, B.; Taroni, F.; Cortopassi, G. The Friedreich's ataxia mutation confers cellular sensitivity to oxidant stress which is rescued by chelators of iron and calcium and inhibitors of apoptosis. *Hum. Mol. Genet.,* **1999**, *8*(3), 425-430. [http://dx.doi.org/10.1093/hmg/8.3.425] [PMID: 9949201]

[23] Mitoma, H.; Adhikari, K.; Aeschlimann, D.; Chattopadhyay, P.; Hadjivassiliou, M.; Hampe, C.S.; Honnorat, J.; Joubert, B.; Kakei, S.; Lee, J.; Manto, M.; Matsunaga, A.; Mizusawa, H.; Nanri, K.; Shanmugarajah, P.; Yoneda, M.; Yuki, N. Consensus paper: neuroimmune mechanisms of cerebellar ataxias. *Cerebellum,* **2016**, *15*(2), 213-232. [http://dx.doi.org/10.1007/s12311-015-0664-x] [PMID: 25823827]

[24] Neureither, F.; Ziegler, K.; Pitzer, C.; Frings, S.; Möhrlen, F. Impaired motor coordination and learning in mice lacking anoctamin 2 calcium-gated chloride channels. *Cerebellum,* **2017**, *16*(5-6), 929-937. [http://dx.doi.org/10.1007/s12311-017-0867-4] [PMID: 28536821]

[25] Grothe, M.; Lotze, M.; Langner, S.; Dressel, A. Impairments in walking ability, dexterity, and cognitive function in multiple sclerosis are associated with different regional cerebellar gray matter loss. *Cerebellum,* **2017**, *16*(5-6), 945-950. [http://dx.doi.org/10.1007/s12311-017-0871-8] [PMID: 28612183]

[26] He, N.; Langley, J.; Huddleston, D.E.; Ling, H.; Xu, H.; Liu, C.; Yan, F.; Hu, X.P. Improved neuroimaging atlas of the dentate nucleus. *Cerebellum,* **2017**, *16*(5-6), 951-956. [http://dx.doi.org/10.1007/s12311-017-0872-7] [PMID: 28669058]