Anatomical and Biochemical Pathogenesis of Motor Pathway Disruption in Cerebral Palsy: A Narrative Review

Siti Fatimah Mukhtar[1], Asma Hayati Ahmad[2,3], Zul Izhar Mohd Ismail[1,*], Anna Alicia Simok[1] and Jafri Malin Abdullah[3,4]

[1]*Department of Anatomy, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia*

[2]*Department of Physiology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia*

[3]*Brain and Behaviour Cluster, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia*

[4]*Department of Neurosciences, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia*

Abstract: *Background*: Cerebral palsy (CP) is a neurodevelopmental disorder characterized by motor impairments caused by brain lesions that affect motor pathways.

Objective: This review describes the complex interaction between the thalamus and cerebral cortex in CP, the understanding of which would explain its pathophysiology and treatment strategies.

Discussion: Cerebral palsy classification is based on motor impairment presentation, each with specific neurological deficits related to the disruption of specific motor pathways. The thalamus serves as a crucial relay station in these pathways, transmitting ascending and descending signals to the cortex via thalamocortical and corticothalamic tracts. Brain injuries like periventricular leukomalacia, hypoxic-ischemic encephalopathy, or malformations disrupt these pathways, leading to motor deficits. Advanced imaging techniques such as diffusion and functional magnetic resonance imaging (MRI) reveal altered connectivity patterns in CP, offering insights into its pathophysiology and aiding diagnosis. Studies have highlighted the variability of clinical presentations in CP and the correlation with specific brain regions affected. Deep brain stimulation and repetitive transcranial magnetic stimulation targeting the thalamus emerge as promising therapeutic opportunities to restore motor function in CP by addressing pathway disruptions.

Conclusion: This review provides a comprehensive overview of motor pathways in CP, emphasizing the role of the thalamus and cortical connectivity in motor impairments. Understanding this complex connectivity provides an avenue for optimum and targeted therapeutic interventions to improve outcomes for individuals with CP.

Keywords: Cerebral palsy, connectivity, imaging, thalamocortical pathway, targeted therapy.

1. INTRODUCTION

Cerebral palsy (CP) primarily affects motor function due to damage to the developing brain, which can occur before, during, or shortly after birth. One crucial aspect of motor function involves the pathways connecting the cerebral cortex and thalamus. The integrity of motor tracts between the cerebral cortex and thalamus plays a significant role in the manifestation of motor impairments. The severity and type of motor impairment in CP often correlate with the extent of damage or abnormal development in these tracts. The reciprocal connection between the thalamus and the motor cortex is vital in complex motor movement [1]. This review aims to explore the anatomical and biochemical basis for motor pathway disruption in cerebral palsy. Understanding the intricate interactions that occur between the cerebral cortex, thalamus, and related motor pathways is imperative to effectively treat and intervene for people with cerebral palsy,

2. CEREBRAL PALSY

Cerebral palsy (CP) is defined as a group of permanent neurodevelopmental disorders that affect motor skills, movement, and posture due to non-progressive lesions in the developing brain of neonates [2]. This condition may also involve other functions, including communication, cognition, and behavior, depending on the area of brain injury [3]. Based on a systematic review by McIntyre *et al*. [4], the current prevalence of cerebral palsy is 1.6 per 1000 live births in high-income countries but a higher rate in low- and middle-income countries, which is 3.4 per 1000 live births.

Apart from motor symptoms, CP is also known to affect other functions, including cognition or intellectual

*Address correspondence to this author at the Department of Anatomy, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia; Tel: +609 7676075; Fax: +609 765 3370;
E-mail: zulizhar@usm.my

outcomes and behavioral symptoms, as well as social and public health. Intellectual disability is very common in CP and is correlated with the severity of motor impairment and early onset of epilepsy [5]. The pathogenesis of cognitive disability in CP is strongly related to the extent of brain lesions. It was found that the white matter tract integrity, in particular, superior longitudinal fasciculus, was shown to be the biomarker of cognitive visual impairment [5]. It was also found that the communication and social interactions of CP patients without an intellectual disability develop in a manner akin to that of healthy individuals. CP patients with intellectual disabilities were shown to have lower performance in establishing their communication and social relationships, but they vary between individuals [6]. In addition, children with moderate forms of physical disability often experience mild cognitive problems. However, some patients with severe motor impairment who are thought to have major intellectual disabilities may show normal-range reasoning abilities [5]

Some CP children may have perinatal events such as neonatal encephalopathy or neonatal stroke leading to the condition [7]. A study by Monokwane *et al*. [8] reported that the risk factor for CP includes serious neonatal infection, perinatal complications, and maternal human immunodeficiency virus (HIV) infection. In term infants, small for gestational age (SGA) is a known risk factor for cerebral palsy [9]. Moderate to late preterm infants with small gestational age also have a higher risk of developing CP, according to a meta-analysis by Zhao *et al*. [10]. CP is also predisposed to genetic factors. A recent study has shown that gene mutations were found in 1-2% of CP cases, most of which were familial. The genetic analyses of CP cases using the next-generation exome sequencing method reveal that up to 31% of sporadic CP cases have clinically relevant copy number changes of the gene, and 14% of cases have likely single-gene mutations. Because of the genetic variations' heterogeneity, more investigations need to be done to establish the genetic cause of CP [11].

3. MOTOR DEFICITS IN CEREBRAL PALSY

Cerebral palsy (CP) is the primary cause of motor disability in children, some of whom need physical assistance for their daily activities [12]. Classification of cerebral palsy can be based on the number of limbs affected and the type of motor presentations of the patients [2]. Monoplegic CP affects only one limb, usually the arm, while diplegic CP involves two limbs, either upper or lower limbs. Hemiplegic CP affects the upper and lower limbs on one side of the body, whereas quadriplegic CP affects all four limbs [3]. Based on the motor disorder, cerebral palsy can be classified into three predominant subtypes, namely: spastic, ataxic, and dyskinetic [13]. Spastic CP can be unilateral or bilateral and is characterized by abnormal posture/movement, hypertonia, and hyperreflexia due to corticospinal tract damage. Ataxic CP is described as having an abnormal pattern of posture/movement and loss of orderly muscular coordination, often due to cerebellar damage. Dyskinetic CP is characterized by an abnormal pattern of posture/movement with uncontrolled stereotyped movements due to basal ganglia injury [14].

4. ROLE OF THE THALAMUS IN MOTOR PATHWAYS

The thalamus acts as a relay station, an integration center that is involved in processing and transmitting motor and sensory signals between the cortex and other areas in the central nervous system, such as the basal ganglia, cerebellum, and spinal cord. The anatomical subdivision of the thalamus is based on the spatial locations of the group of nuclei. These are the anterior group of nuclei, the medial group of nuclei, the lateral group of nuclei, and the intralaminar nuclei. Functional subdivision of the thalamic nuclei is based on connections between the nuclei and the cerebral cortex. Functionally, the thalamic nuclei can be divided into motor relay nuclei, sensory relay nuclei, specific relay nuclei, and association nuclei.

The motor relay nuclei of the thalamus are mainly the ventral anterior (VA) and ventral lateral (VL) nuclei (Figure **1**). Regarding the motor pathway involving the thalamus, VA and VL thalamic nuclei relay the motor information from the deep cerebellar nuclei and basal ganglia to the cerebral cortex. Information from the somatic motor system, basal ganglia, and cerebellum is also relayed at the VA and VL nuclei before reaching the motor cortical areas [15]. The VA nucleus receives afferent fibers from the globus pallidus of basal ganglia and sends the efferent fibers to the premotor cortex, which is important for motor planning. The VL nucleus receives afferent fibers from the cerebellum and basal ganglia and sends the efferent fibers to the frontal cortex and primary motor cortex, which is important for movement and motor planning [16, 17].

The sensory relay nuclei consist of the ventral posterior medial (VPM) and ventral posterior lateral

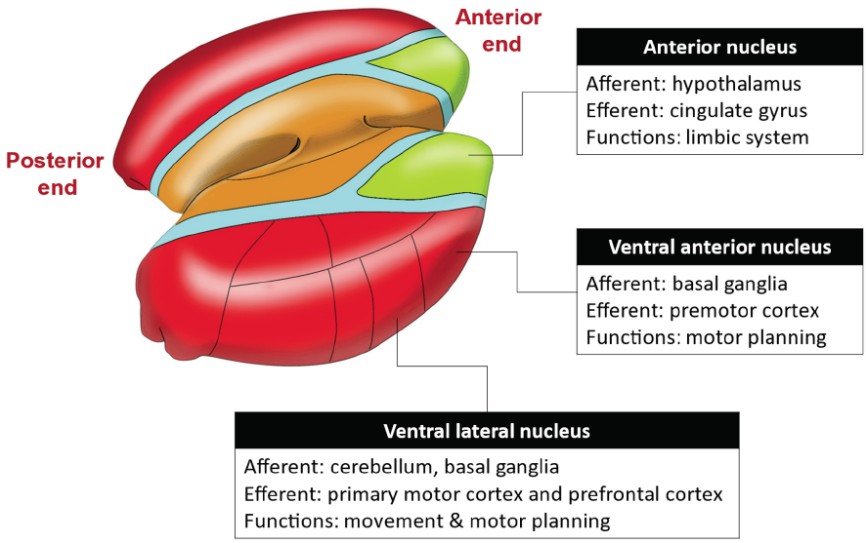

Figure 1: Motor relay nuclei of the thalamus.

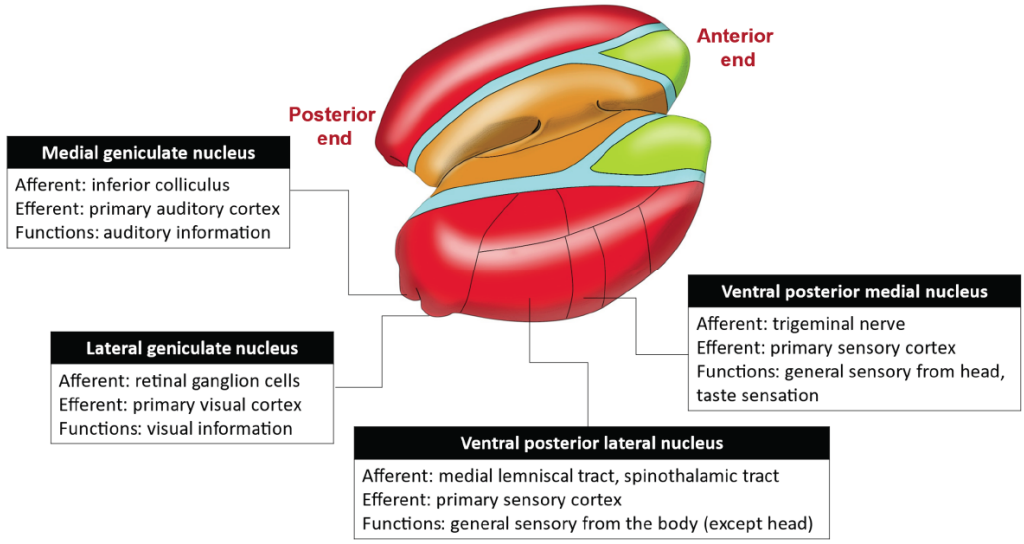

Figure 2: Sensory relay nuclei of the thalamus.

(VPL) nuclei, the medial geniculate nucleus (MGN), and the lateral geniculate nucleus (LGN) (Figure **2**). Somatosensory information from the orofacial region is relayed at the VPM, whereas information from the body is relayed at the VPL. The MGN is responsible for processing sensory information related to hearing, while the LGN is important for vision. Specific relay nuclei comprise the ventral tier of the lateral nuclear group. Specific relay nuclei have reciprocal connections with the sensory or motor cortex. Association nuclei indirectly receive sensory and motor information via a relay in other thalamic nuclei and various brain regions. Association nuclei consist of the dorsomedial nucleus (DMN), lateral dorsal nucleus (LDN), lateral posterior nucleus (LPN), and pulvinar nucleus [16, 17].

In order to understand the circuit between the thalamus and cortex, it is also convenient to divide the thalamus into dorsal and ventral regions according to its embryonic origin. The dorsal division consists of the nuclei within which are relay cells projecting to the cerebral cortex. The ventral division of the thalamus comprises the reticular nucleus and the ventral part of the LGN, both of which do not project to the cerebral cortex. The thalamic reticular nucleus gives out fibers to the thalamic relay cells in the dorsal division of the thalamus [18]. The dorsal part of LGN is included in the dorsal division of the thalamus and thus has connections with the cerebral cortex. So, only the relay nuclei in the dorsal division of the thalamus have direct connections with the cerebral cortex.

5. PATHWAYS BETWEEN THALAMUS AND CEREBRAL CORTEX

There are two main pathways between the thalamus and cerebral cortex, namely the thalamocortical pathways and corticothalamic pathways. Both pathways are further classified into two classes, which are driver (feedforward) and modulator (feedback) projections (Figure **2**). The driver pathways transport the input between the neurons, while the modulator pathways regulate the driver information accordingly (Figure **3**) [18]. The thalamocortical pathways involve projections from the thalamus to various areas of the cerebral cortex, including the motor cortex [19, 20]. The corticothalamic pathways involve projections from the cerebral cortex to the thalamus, helping modulate sensory information and motor responses.

The cerebral cortex is organized into six layers that contain specific types of neurons according to their pathways [21]. The corticothalamic pathways are associated with layers V and VI of the cerebral cortices. The corticothalamic pathways from layer V are considered as feedforward (driver), whereas the corticothalamic pathways from layer VI are described as feedback (modulator) routes. However, the other layers of the cerebral cortex may also contain some input from the thalamus depending on the cortical area and the thalamic nuclei involved in that circuit [22]. The thalamocortical pathways involve three classes of neurons in the thalamic relay nuclei, namely, core, intralaminar, and matrix neurons. The core thalamocortical pathway is known as a driver (feedforward), while the matrix thalamocortical pathway is considered a modulator (feedback) projection [22]. Core neurons project into the middle layers of the cortex and innervate a single or several cortical regions. Matrix neurons project diffusely to superficial cortical layers, including layer I (Figure **3**) [18].

One of the feedforward pathways includes the cortico-thalamo-cortical (transthalamic corticocortical) pathways. In the trans thalamic corticocortical circuit, there are two types of thalamic relay nuclei, which are first order nuclei and higher order nuclei. The first-order nuclei receive information from the subcortical course, whereas the higher-order nuclei receive input from a cortical area. Examples of the first-order nucleus and the higher-order nucleus are the lateral geniculate nucleus and pulvinar, respectively [18]. Thalamic motor nuclei, namely ventral anterior and ventral lateral nuclei, are organized in a mosaic pattern by input from basal ganglia and deep cerebellar nuclei. First-order nuclei zones receive the input from the cerebellum, while the higher-order nuclei zones receive the innervation from layer V of the motor cortex and also from the basal ganglia.

The feedback pathway from the cerebral cortex to the thalamus involves two types of corticothalamic neurons, distinctively the neurons from layer VI and layer V of the cerebral cortex. Corticothalamic neurons from layer VI are small, pyramidal cells with narrow vertical dendrites. Upon leaving the cortex, their axons give off a few branches that surround the dendritic area

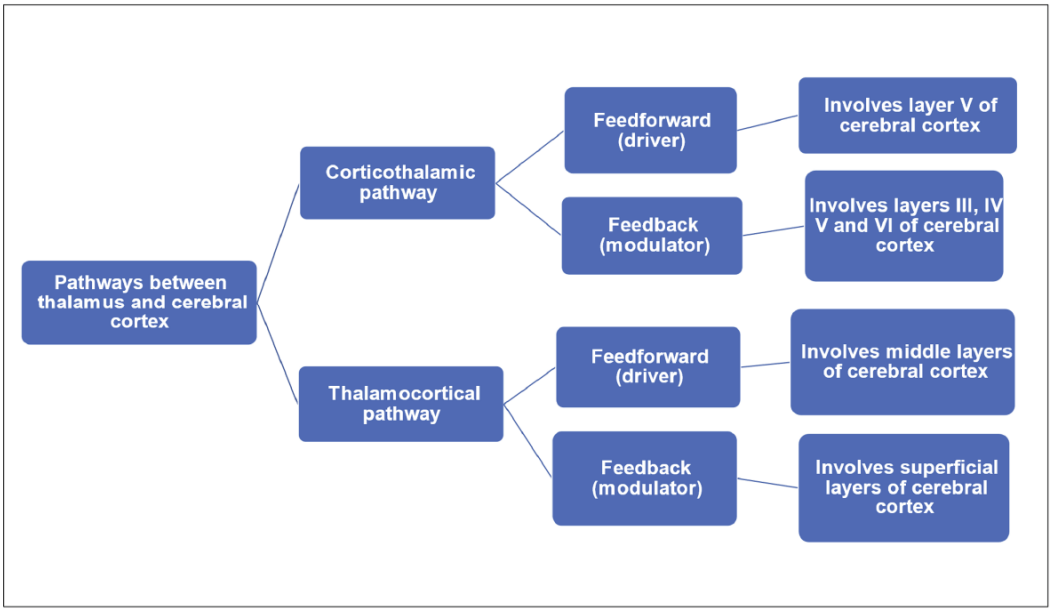

Figure 3: Summary of the pathways between the thalamus and cerebral cortex (adapted from Sherman & Guillery [23]).

of the cell in the same layer VI. Their main axons descend subcortically to reach the thalamus only. They enter a confined area of the dorsal thalamic nucleus in a topographic manner, according to the related cortical region. In contrast, the corticothalamic neurons from layer V are large, pyramidal cells with a thick dendrite. Their axons give off collaterals that can initially ascend up to the cortical levels III and IV, then descend subcortically. Their subcortical target structures include not only the thalamus but also the brain stem and spinal cord [24,25]. The morphological differences of these neurons could also explain the unique relation between the cells in the thalamic nuclei and the associated individual areas of the cortex.

6. BIOCHEMICAL SUBSTRATE OF THALAMO-CORTICAL PATHWAYS

On another note, there is a difference in the amount and types of calcium-binding proteins (calbindin/parvalbumin/calretinin) in the thalamic nuclei. Even though the biochemical implication of these proteins is unknown, they portray some significant associations. Parvalbumin is associated with the sensory and motor pathways and is highly targeted to a distinct cortical region. However, the calbindin is related to the subcortical pathways and less specific to the cerebral cortices. Pathways associated with parvalbumin sink deep into layers III and IV of the cerebral cortices, whereas the pathways containing the calbindin protein project onto the superficial cortical layers of I, II, and III.

Thalamic nuclei with an abundance of calbindin are found to be lacking parvalbumin and vice versa. Intralaminar neurons, however, contain a mixture of calbindin and parvalbumin. These findings are beneficial in the study of the synchronization between thalamo-cortical circuits [24, 26]. Pathways between the thalamus and cerebral cortex can also be classified according to the neurotransmitter involved.

The thalamo-cortical pathway is also known as the Glutamatergic pathway, which is the feed forward route [18]. Glutamate is the main excitatory neurotransmitter in the human central nervous system. The corticothalamic pathway is also known as the GABAergic pathway, which is the feedback track. Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the mammalian central nervous system. Thalamic relay cells are glutamatergic, whereas the reticular cells and interneurons are GABAergic [18]. Interneurons and reticular cells provide inhibitory information to the relay cells. The neurodegenerative disorder could be due to the impact of some disturbance in the receptor activities. Hence, modulating the pathways involving the glutamate receptor might be a therapeutic approach to these diseases [27]. The balance between excitatory and inhibitory activities is critical for normal neuronal function.

7. PATHOGENESIS OF MOTOR IMPAIRMENT IN CEREBRAL PALSY

In individuals with CP, motor pathways can be disrupted due to various forms of brain injury, such as periventricular leukomalacia, hypoxic-ischemic encephalopathy, or brain malformations. Periventricular leukomalacia is characterized by the death of small areas of brain tissue around the ventricles, leading to the loss of white matter, primarily affecting the motor pathways. Periventricular leukomalacia is a specific type of white matter abnormality in patients with "ventriculomegaly with irregular outlines of the trigone and body of the lateral ventricle, a small amount of periventricular white matter, deep prominent cerebral sulci, and periventricular signal defects of low intensity on T1-weighted images and high intensity on T2-weighted MRI images" [28, 29]. Hypoxic-ischemic encephalopathy occurs due to oxygen deprivation around the time of birth. It can cause widespread brain damage, affecting both the thalamus and motor cortex, leading to various forms of CP [28, 30]. Brain malformations are abnormal brain development that can directly impact the formation and function of motor pathways, leading to motor deficits.

The specific biochemical pathways contributing to motor dysfunctions in CP are diverse and involve various aspects of neurodevelopment, neurotransmission, inflammation, and metabolic processes. Some deep mechanistic insights into how specific biochemical pathways contribute to motor dysfunction in CP include neuroinflammation, oxidative stress, excitotoxicity, altered GABAergic signaling, abnormal extracellular matrix, and lack of maternal growth factor [31]. The pathway for neuroinflammation involves the activation of microglia and astrocytes, leading to the release of pro-inflammatory cytokines and reactive oxygen species (ROS) [32]. Compared to controls, CP patients had higher levels of five growth factors (GFs) (NGF-β, EGF, GDF-15, G-CSF, and BMP-9) and one anti-inflammatory cytokine (IL-10), as well as eight pro-inflammatory cytokines (IFN-γ, GM-CSF, TNF-α, IL-2, IL-4, IL-6, IL-17A, and IL-12) [33].

These inflammatory mediators can cause neuronal injury and disrupt the development of motor pathways, leading to motor dysfunction. Persistent inflammation is linked to altered synaptic plasticity and neuronal network formation, affecting motor control [34]. Excessive inflammatory cytokines cause cell apoptosis, leading to hypoxic ischaemic conditions [31]. It was previously established that hemodynamic pathways and oxidative stress were important factors in the pathophysiology of brain damage in preterm newborns prior to 32-week gestation [35]. Premature babies are particularly vulnerable to oxidative damage because of an imbalance caused by excess free radicals and low levels of antioxidant enzymes, including glutathione reductase, superoxide dismutase, catalase, and glutathione peroxidase [35]. Compared to healthy control, GABAergic receptor binding potential was increased in CP within the paracentral lobule, cingulate cortex, visual cortex, and cerebellum despite significant grey matter volume reduction, whereas the receptor binding potential was diffusely decreased in the prefrontal, temporal, parietal, and subcortical nuclei [36].

Lesions in the grey matter may also contribute to cerebral palsy, which includes motor cortex dysfunction, thalamic dysfunction, and subcortical damage [37]. For motor cortex dysfunction, lesions in the motor cortex can result in spasticity, where muscles are continuously contracted. This makes movement difficult and can cause stiffness. For thalamic dysfunction, damage to the thalamus can result in altered sensory processing, affecting motor planning and execution. The thalamus' role as a sensory relay is crucial for coordinated movement. For subcortical damage, injury to subcortical areas like the basal ganglia can lead to dyskinetic CP, characterized by involuntary movements, such as dystonia (twisting movements) and athetosis (slow, writhing movements).

8. FINDINGS OF MOTOR PATHWAY DISRUPTIONS BETWEEN THALAMUS AND CEREBRAL CORTEX IN CEREBRAL PALSY

As mentioned earlier, the motor pathways between the thalamus and cerebral cortex in individuals with CP could be disrupted or damaged due to various forms of brain injury, such as periventricular leukomalacia, hypoxic-ischemic encephalopathy, or brain malformations [38]. Thalamocortical pathway damage can affect the relay of sensory and motor information, contributing to the impaired motor function seen in CP. The thalamus might receive and send distorted signals to the motor cortex. Corticothalamic pathway alterations could impair the feedback mechanism essential for fine-tuning motor activities.

Based on a systematic review of neuroimaging in cerebral palsy by Korzeniewski *et al*. [28], the majority of cerebral palsy patients (83%) have some abnormal radiological findings, with the white matter disruption (including motor pathways) being the most common cause. However, about 17% of the patients have no abnormal findings on MRI or computed tomography (CT) scans. Other common radiological findings in cerebral palsy include ventriculomegaly, cerebrospinal fluid space abnormalities, and brain atrophy, whereas solely grey matter damage is the rarest. The diagnosis of CP is primarily based on the patient's clinical presentation. Neuroimaging is not mandatory to diagnose cerebral palsy; however, it provides significant value in the study of the etiology and pathogenesis of the disease. Neuroimaging, which includes magnetic resonance imaging (MRI) or computed tomography (CT) scan, was suggested by The American Academy of Neurology for all cases of cerebral palsy of unknown cause [28,39]. In diffusion MRI, the motor pathways disruption can be quantitatively analyzed using the tractography method and then reported in terms of connectivity or connection probability index. In functional MRI, the motor pathways can be reported as functional connectivity, as mentioned in the subsequent sections.

Mahanna *et al*. [40] showed the involvement of superior, anterior, and posterior thalamic radiation disruption in cerebral palsy based on a diffusion MRI study on the thalamocortical pathways in CP patients. Zhang *et al.* [41] performed a diffusion tensor imaging (DTI) study investigating the topological characteristics in bilateral spastic cerebral palsy. For the motor cortices, they discovered that only the reduction in connectivity to left premotor cortex 2 (left middle frontal gyrus) and right premotor cortex 3 (right inferior frontal gyrus pars triangularis) in spastic cerebral palsy revealed a significant difference with the healthy children. A possible factor for this result could be associated with the thalamic GABAergic pathways. In principle, the increased activity of the thalamic GABAergic pathway would result in fewer connections between the thalamus and motor cortices due to its inhibitory GABA effect. However, some damage to the GABAergic pathway resulted in reduced inhibition, thus increasing the connection probability indices between the thalamus and the motor cortices [42,43]. An increase in thalamic connectivity could also be

regarded as the compensatory mechanism in the lesioned brain.

Two hemiplegic spastic CP patients in the diffusion MRI study by Mukhtar *et al*. [44] showed the connectivity pattern of distribution that corresponded to their clinical presentation. It was evident from the substantially lower values of connection probability indices in one hemisphere that the patients had unilateral brain lesions causing the contralateral motor impairment, as evidenced by their neurological examination findings. Both unilateral spastic cerebral palsy patients in the current study were born preterm. This would impose a higher risk for these patients to develop perinatal stroke, leading to a decrease in the thalamo-cortical connectivity.

Several studies have agreed that brain connectivity in spastic cerebral palsy was variable, consistent with the findings of the current study [45-47]. Simon-Martinez *et al*. [48] reported that the abnormal functional connectivity was also dependent on the corticospinal tract wiring in individuals rather than specific across all unilateral CP populations. They performed a functional MRI study on the connectivity between the primary motor cortex, premotor cortex, supplementary motor area, and primary somatosensory areas in unilateral cerebral palsy. They found that the group with contralateral corticospinal tract lesions showed higher connectivity between the primary motor cortex and premotor cortices. Meanwhile, the bilateral corticospinal tract lesion group showed higher connectivity in the other region, between the primary motor cortex and somatosensory association areas in the dominant hemisphere.

In the study by Mukhtar *et al*. [44], it was found that decreased connection probability indices (CPI) between the thalamus and motor cortices showed that these pathways faded away in cerebral palsy patients. This finding was supported by Burton *et al*. [49] study that stated the thalamocortical pathways were "absent or diminished" in the spastic diplegic cerebral palsy and was superseded by higher intracortical connections. They performed a functional MRI study on the motor and somatosensory areas in the spastic diplegic cerebral palsy. Abnormal motor connectivity in cerebral palsy was attributed to the white matter insult causing injury to the subplate neurons during the third trimester period [49, 50]. The subplate is described as the temporary layer below the cortical plate and comprises subplate neurons and extracellular matrix. Subplate neurons play a key role in the establishment of the thalamocortical axons and the first neuronal pathway between the thalamus and layer IV of the cerebral cortex [51]. Hence, the damage of the subplate neurons may suppress the formation of the thalamocortical axons in cerebral palsy patients and could explain the least connection probability indices between the thalamus and some motor cortices in the current study. The decreased CPI value could also be related to some distortion in the MRI images of the respective patients.

The variability of clinical presentation of cerebral palsy reflects different regions of brain injury related to its function. Hence, a study on impaired brain structures is vital because the anatomical connectivity in the brain reflects the motor functions in CP [52,53]. Understanding the specific motor pathway disruption in cerebral palsy is important in deciding the appropriate treatment strategies for CP patients. The rehabilitation treatment must be tailored to the specific condition to improve motor functions in CP patients [54].

Diffusion MRI enables the motor pathways in terms of white matter tracts to be visualized and analyzed *in vivo*. It provides both qualitative and quantitative measures of the integrity of white matter. This MRI modality can be considered a diagnostic and prognostic tool for various neurological conditions. The current study provided evidence that the white matter tracts in these pathways were mostly disrupted in cerebral palsy implicated in motor impairment. The current work also revealed the uniqueness of the brain wiring in cerebral palsy in accordance with the patient's clinical presentation. These findings added up to the understanding of the pathophysiology of motor disability in spastic cerebral palsy patients. It can offer input towards targeted therapy and rehabilitation to improve the motor functions of cerebral palsy patients. The thalamus, particularly the lateral motor nuclei as well as the ventral anterior and ventral intermediate nuclei, is a target for deep brain stimulation in cerebral palsy [55]. The thalamus was also found to be a target for the treatment of repetitive transcranial magnetic stimulation (rTMS) to improve motor function in cerebral palsy [41]. Perhaps the patients could experience some improvement in daily activities, especially with the reduction in spasticity of upper and lower limbs, following treatment and therapy.

9. CONCLUSION

This review focuses on the motor pathways between the thalamus and cerebral cortex in CP, a

neurodevelopmental disorder that impairs motor functions due to brain lesions. It is essential to investigate the integrity of motor tracts between the thalamus and cerebral cortex in CP patients to correlate with their symptoms of motor impairment as it involves processing and transmitting motor signals to the cortex [56]. CP's impact on motor pathways, particularly the corticospinal, thalamocortical, and corticothalamic tracts, leads to various motor deficits classified into spastic, ataxic, and dyskinetic subtypes. The role of the thalamus as a motor relay station is very crucial in these pathways because conditions like periventricular leukomalacia or hypoxic-ischemic encephalopathy result in motor impairments. Advanced imaging techniques like diffusion MRI and functional MRI have shown altered connectivity in CP, highlighting the importance of these pathways in understanding and treating CP.

These pathways illustrate the complexity of the underlying mechanisms contributing to motor dysfunction in CP. A deeper understanding of the additional biochemical pathways can guide therapeutic strategies to modulate these processes to improve motor function in individuals with cerebral palsy. Significant efforts have been directed towards enhancing the accurate diagnosis of CP in early childhood, hence implementing early interventions to improve functional outcomes [5]. To effectively target early intervention in CP prevention, it is essential to comprehend all of the pathways involved in cerebral palsy. Currently, a few methods have been identified to reduce the risk of developing CP, including the administration of magnesium sulfate to mothers in preterm labor and hypothermia therapy in full-term newborns with moderate neonatal encephalopathy [31].

Findings of the advanced MRI modalities suggest that targeted therapies, such as deep brain stimulation and repetitive transcranial magnetic stimulation, could improve motor functions in CP patients by addressing specific pathway disruptions. Since there has been considerable intervention for motor outcomes in CP, other measures should also be performed to improve non-motor symptoms, such as speech, behavioral, cognitive, or intellectual outcomes. Hence, a holistic approach is crucial and needed to assist these special needs children for a better future.

ACKNOWLEDGEMENTS

Not applicable.

FUNDING

This work was not supported by any funding.

ETHICAL APPROVAL

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

LIST OF ABBREVIATIONS

CP = cerebral palsy

CPI = connection probability indices

CT = computed topography

DMN = dorsomedial nucleus

DTI = diffusion tensor imaging

LDN = lateral dorsal nucleus

LGN = lateral geniculate nucleus

LPN = lateral posterior nucleus

MGN = medial geniculate nucleus

MRI = magnetic resonance imaging

rTMS = repetitive transcranial magnetic stimulation

VA = ventral anterior

VL = ventral lateral

VPL = ventral posterior lateral

VPM = ventral posterior medial

REFERENCES

[1] Antón-Bolaños N, Espinosa A, López-Bendito G. Developmental interactions between thalamus and cortex: a true love reciprocal story. Curr Opin Neurobiol 2018; 52: 33-41. https://doi.org/10.1016/j.conb.2018.04.018

[2] Patel DR, Neelakantan M, Pandher K, Merrick J. Cerebral palsy in children: A clinical overview. Transl Pediatr 2020; 9: S125-35. https://doi.org/10.21037/tp.2020.01.01

[3] Hallman-Cooper JL, Rocha Cabrero F. Cerebral Palsy. StatPearls Publishing 2021.

[4] McIntyre S, Goldsmith S, Webb A, Ehlinger V, Hollung SJ, McConnell K, *et al*. Global prevalence of cerebral palsy: A systematic analysis. Dev Med Child Neurol 2022; 64: 1494-506. https://doi.org/10.1111/DMCN.15346

[5] Fluss J, Lidzba K. Cognitive and academic profiles in children with cerebral palsy: A narrative review. Ann Phys Rehabil Med 2020; 63: 447-56. https://doi.org/10.1016/j.rehab.2020.01.005

[6] Tan SS, van Gorp M, Voorman JM, Geytenbeek JJM, Reinders-Messelink HA, Ketelaar M, *et al*. Development curves of communication and social interaction in individuals with cerebral palsy. Dev Med Child Neurol 2020; 62: 132-9. https://doi.org/10.1111/dmcn.14351

[7] Morgan C, Fahey M, Roy B, Novak I. Diagnosing cerebral palsy in full-term infants. J Paediatr Child Health 2018; 54: 1159-64. https://doi.org/10.1111/jpc.14177

[8] Monokwane B, Johnson A, Gambrah-Sampaney C, Khurana E, Baier J, Baranov E, *et al*. Risk Factors for Cerebral Palsy in Children in Botswana. Pediatr Neurol 2017; 77: 73-7. https://doi.org/10.1016/j.pediatrneurol.2017.07.014

[9] Freire G, Shevell M, Oskoui M. Cerebral palsy: Phenotypes and risk factors in term singletons born small for gestational age. European Journal of Paediatric Neurology 2015; 19: 218-25. https://doi.org/10.1016/j.ejpn.2014.12.005

[10] Zhao M, Dai H, Deng Y, Zhao L. SGA as a Risk Factor for Cerebral Palsy in Moderate to Late Preterm Infants: a System Review and Meta-analysis. Sci Rep 2016; 6: 38853. https://doi.org/10.1038/srep38853

[11] MacLennan AH, Thompson SC, Gecz J. Cerebral palsy: Causes, pathways, and the role of genetic variants. Am J Obstet Gynecol 2015; 213: 779-88. https://doi.org/10.1016/j.ajog.2015.05.034

[12] Araneda R, Ebner-Karestinos D, Paradis J, Klöcker A, Saussez G, Demas J, *et al*. Changes Induced by Early Hand-Arm Bimanual Intensive Therapy Including Lower Extremities in Young Children with Unilateral Cerebral Palsy: A Randomized Clinical Trial. JAMA Pediatr 2024; 178: 19-28. https://doi.org/10.1001/jamapediatrics.2023.4809

[13] Al-Sowi AM, AlMasri N, Hammo B, Al-Qwaqzeh FAZ a. Cerebral Palsy classification based on multi-feature analysis using machine learning. Inform Med Unlocked 2023; 37: 101197. https://doi.org/10.1016/j.imu.2023.101197

[14] Te Velde A, Morgan C, Novak I, Tantsis E, Badawi N. Early diagnosis and classification of cerebral palsy: An historical perspective and barriers to an early diagnosis. J Clin Med 2019; 8. https://doi.org/10.3390/jcm8101599

[15] Sheridan N, Tadi P. Neuroanatomy, Thalamic Nuclei. StatPearls Publishing 2020.

[16] Patestas MA, Gartner LP. A Textbook of Neuroanatomy. 1st ed. Blackwell Publishing 2006.

[17] Bhuiyan PS, Rajgopal L, Shyamkishore K. Inderbir Singh's Textbook of Human Neuroanatomy. 10th ed. Jaypee Brothers Medical Publishers 2018. https://doi.org/10.5005/jp/books/18462

[18] Sherman SM. Functioning of circuits connecting thalamus and cortex. Compr Physiol 2017; 7: 713-39. https://doi.org/10.1002/cphy.c160032

[19] George K DJM. Neuroanatomy, Thalamocortical Radiations. NCBI Bookshelf A Service of the National Library of Medicine, National Institutes of Health 2024.

[20] Pannek K, Fripp J, George JM, Fiori S, Colditz PB, Boyd RN, *et al*. Fixel-based analysis reveals alterations in brain microstructure and macrostructure of preterm-born infants at term equivalent age. Neuroimage Clin 2018; 18: 51-9. https://doi.org/10.1016/j.nicl.2018.01.003

[21] Agirman G, Broix L, Nguyen L. Cerebral cortex development: an outside-in perspective. FEBS Lett 2017; 591: 3978-92. https://doi.org/10.1002/1873-3468.12924

[22] Harris JA, Mihalas S, Hirokawa KE, Whitesell JD, Choi H, Bernard A, *et al*. Hierarchical organization of cortical and thalamic connectivity. Nature | 2019; 575. https://doi.org/10.1038/s41586-019-1716-z

[23] Sherman SM, Guillery RW. Exploring the Thalamus and Its Role in Cortical Function, 2nd ed. MIT Press 2009.

[24] Jones EG. Synchrony in the Interconnected Circuitry of the Thalamus and Cerebral Cortex. Ann N Y Acad Sci 2009; 1157: 10-23. https://doi.org/10.1111/j.1749-6632.2009.04534.x

[25] Guo KH, Yamawaki N, Barrett JM, Tapies M, Shepherd GMG. Cortico-thalamo-cortical circuits of mouse forelimb S1 are organized primarily as recurrent loops. Journal of Neuroscience 2020; 40: 2849-58. https://doi.org/10.1523/JNEUROSCI.2277-19.2020

[26] Żakowski W. Neurochemistry of the Anterior Thalamic Nuclei. Mol Neurobiol 2017; 54: 5248-63. https://doi.org/10.1007/s12035-016-0077-y

[27] Tomita S. Glutamatergic pathways and receptors. Essentials of Cerebellum and Cerebellar Disorders: A Primer for Graduate Students, Springer International Publishing 2016; pp. 231-6. https://doi.org/10.1007/978-3-319-24551-5_29

[28] Korzeniewski SJ, Birbeck G, DeLano MC, Potchen MJ, Paneth N. A systematic review of neuroimaging for cerebral palsy. J Child Neurol 2008; 23: 216-27. https://doi.org/10.1177/0883073807307983

[29] Gotardo JW, de Freitas Valle Volkmer N, Stangler GP, Dornelles AD, de Athayde Bohrer BB, Carvalho CG. Impact of peri-intraventricular haemorrhage and periventricular leukomalacia in the neurodevelopment of preterms: A systematic review and meta-analysis. PLoS One 2019; 14: e0223427. https://doi.org/10.1371/journal.pone.0223427

[30] Schneider J, Miller SP. Preterm brain Injury: White matter injury. Handb Clin Neurol, Elsevier B.V. 2019; vol. 162: pp. 155-72. https://doi.org/10.1016/B978-0-444-64029-1.00007-2

[31] Marret S, Vanhulle C, Laquerriere A. Pathophysiology of cerebral palsy. Handb Clin Neurol, Elsevier B.V. 2013; vol. 111: pp. 169-76. https://doi.org/10.1016/B978-0-444-52891-9.00016-6

[32] Singh D. Astrocytic and microglial cells as the modulators of neuroinflammation in Alzheimer's disease. J Neuroinflammation 2022; 19. https://doi.org/10.1186/s12974-022-02565-0

[33] Than UTT, Nguyen LT, Nguyen PH, Nguyen XH, Trinh DP, Hoang DH, *et al*. Inflammatory mediators drive neuroinflammation in autism spectrum disorder and cerebral palsy. Sci Rep 2023; 13. https://doi.org/10.1038/s41598-023-49902-8

[34] Bellingacci L, Canonichesi J, Mancini A, Parnetti L, Di Filippo M. Cytokines, synaptic plasticity and network dynamics: a matter of balance. Neural Regen Res 2023; 18: 2569-72. https://doi.org/10.4103/1673-5374.371344

[35] Cannavò L, Rulli I, Falsaperla R, Corsello G, Gitto E. Ventilation, oxidative stress and risk of brain injury in preterm newborn. Ital J Pediatr 2020; 46. https://doi.org/10.1186/s13052-020-00852-1

[36] Lee JD, Park HJ, Park ES, Oh MK, Park B, Rha DW, *et al*. Motor pathway injury in patients with periventricular leucomalacia and spastic diplegia. Brain 2011; 134: 1199-210. https://doi.org/10.1093/brain/awr021

[37] Reid SM, Dagia CD, Ditchfield MR, Reddihough DS. Grey matter injury patterns in cerebral palsy: Associations between structural involvement on MRI and clinical outcomes. Dev Med Child Neurol 2015; 57: 1159-67. https://doi.org/10.1111/DMCN.12800

[38] Reddihough DS, Collins KJ. The epidemiology and causes of cerebral palsy. Australian Journal of Physiotherapy 2003; 49: 7-12. https://doi.org/10.1016/S0004-9514(14)60183-5

[39] Novak I, Morgan C, Adde L, Blackman J, Boyd RN, Brunstrom-Hernandez J, *et al*. Early, accurate diagnosis and early intervention in cerebral palsy: Advances in diagnosis and treatment. JAMA Pediatr 2017; 171: 897-907. https://doi.org/10.1001/jamapediatrics.2017.1689

[40] Mahanna AM, El-Toukhy NAEG, Mousa AE, Megahed KF, Ashamallah GA. Does motor deficit in children with cerebral palsy correlate with diffusion tensor metrics abnormalities in thalamocortical pathways? Egyptian Journal of Radiology and Nuclear Medicine 2021; 52. https://doi.org/10.1186/s43055-021-00463-8

[41] Zhang W, Zhang S, Zhu M, Tang J, Zhao X, Wang Y, *et al*. Changes of Structural Brain Network Following Repetitive Transcranial Magnetic Stimulation in Children With Bilateral Spastic Cerebral Palsy: A Diffusion Tensor Imaging Study. Front Pediatr 2021; 8. https://doi.org/10.3389/fped.2020.617548

[42] Tang L, Ge Y, Sodickson DK, Miles L, Zhou Y, Reaume J, *et al*. Thalamic resting-state functional networks: Disruption in patients with mild traumatic brain injury. Radiology 2011; 260: 831-40. https://doi.org/10.1148/radiol.11110014

[43] Munivenkatappa A, Agrawal A. Role of Thalamus in Recovery of Traumatic Brain Injury. J Neurosci Rural Pract 2016; 07: S076-9. https://doi.org/10.4103/0976-3147.196468

[44] Mukhtar SF, Ahmad AH, Simok AA, Abdullah JM, Abdullah AN, Zabri SH, *et al*. Disruption of Thalamocortical Connectivity in Spastic Cerebral Palsy: A Probabilistic Tractography Study. Journal of Intellectual Disability - Diagnosis and Treatment 2022; 10: 322-33. https://doi.org/10.6000/2292-2598.2022.10.06.6

[45] Ballester-Plané J, Schmidt R, Laporta-Hoyos O, Junqué C, Vázquez É, Delgado I, *et al*. Whole-brain structural connectivity in dyskinetic cerebral palsy and its association with motor and cognitive function. Hum Brain Mapp 2017; 38: 4594-612. https://doi.org/10.1002/hbm.23686

[46] Samsir S, Zakaria R, Abdul Razak S, Ismail MS, Abdul Rahim MZ, Lin C-S, *et al*. Characterisation of the Corticospinal Tract Using Diffusion Magnetic Resonance Imaging in Unilateral and Bilateral Cerebral Palsy Patients. Malaysian Journal of Medical Sciences 2018; 25: 68-78. https://doi.org/10.21315/mjms2018.25.5.7

[47] Woodward KE, Carlson HL, Kuczynski A, Saunders J, Hodge J, Kirton A. Sensory-motor network functional connectivity in children with unilateral cerebral palsy secondary to perinatal stroke. Neuroimage Clin 2019; 21: 101670. https://doi.org/10.1016/j.nicl.2019.101670

[48] Simon-Martinez C, Jaspers E, Alaerts K, Ortibus E, Balsters J, Mailleux L, *et al*. Influence of the corticospinal tract wiring pattern on sensorimotor functional connectivity and clinical correlates of upper limb function in unilateral cerebral palsy. Sci Rep 2019; 9: 8230. https://doi.org/10.1038/s41598-019-44728-9

[49] Burton H, Dixit S, Litkowski P, Wingert JR. Functional connectivity for somatosensory and motor cortex in spastic diplegia. Somatosens Mot Res 2009; 26: 90-104. https://doi.org/10.3109/08990220903335742

[50] Rocha-Ferreira E, Hristova M. Plasticity in the Neonatal Brain following Hypoxic-Ischaemic Injury. Neural Plast 2016; 2016: 1-16. https://doi.org/10.1155/2016/4901014

[51] Ohtaka-Maruyama C. Subplate Neurons as an Organizer of Mammalian Neocortical Development. Front Neuroanat 2020; 14: 8. https://doi.org/10.3389/fnana.2020.00008

[52] Passingham RE, Stephan KE, Kötter R. The anatomical basis of functional localization in the cortex. Nat Rev Neurosci 2002; 3: 606-16. https://doi.org/10.1038/nrn893

[53] Ferre-Fernández M, Murcia-González MA, Barnuevo Espinosa MD, Ríos-Díaz J. Measures of motor and functional skills for children with cerebral palsy: A systematic review. Pediatric Physical Therapy 2020; 32: 12-25. https://doi.org/10.1097/PEP.0000000000000661

[54] Tornberg ÅB, Lauruschkus K. Non-ambulatory children with cerebral palsy: effects of four months of static and dynamic standing exercise on passive range of motion and spasticity in the hip. Peer J 2020; 8: e8561. https://doi.org/10.7717/peerj.8561

[55] Sanger TD. Deep brain stimulation for cerebral palsy: where are we now? Dev Med Child Neurol 2020; 62: 28-33. https://doi.org/10.1111/dmcn.14295

[56] Torrico TJ, Munakomi S. Neuroanatomy, Thalamus. StatPearls 2023.

Received on 31-07-2024 Accepted on 10-09-2024 Published on 11-12-2024

https://doi.org/10.6000/2292-2598.2024.12.04.9