Research Article

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Symmetrical Central Tegmental Tract Hyperintensity on T2-weighted Images in Pediatrics: A Systematic Review

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Abstract

Purpose: The aim of the present study is to provide a systematic literature review of the current evidence about the Central Tegmental Tract Hyperintensity (CTTH).

Methods: The literature search was performed on December 2017 using Medline PubMed, Google Scholar and Cochrane Central databases. Statistical analysis was performed using Kolmogorov-Smirnov, chi-square and the Mann-Whitney U tests.

Results: Twenty publications were included. Of these, 11 were retrospective studies and 9 were case reports. In total, CTTH was reported in 226 cases. The age parameter showed a significantly non-Gaussian distribution (KS test; p-value < 0.001). The median age was 1,83 years (range: 7 days – 21 years; P25 = 1.00 year, P75 = 3.00 years; IQR = 2 years). The two most common clinical conditions associated to CTTH were cerebral palsy (51 cases; 22.6%) and glutaric aciduria type 1 (50 cases; 22.10%). CTTH was often found in the absence of other concomitant brain MRI abnormalities (32 cases; 21.8%).

Conclusions: CTTH is an uncommon neuroimaging finding that is mainly related to the acquisition\improvement of a physiologicalmotor developmental process. The finding is influenced by hypoxic-ischemic and toxic-metabolic factors. Data regarding DWI and follow-up are largely unreported and deserve to be further explored.

Keywords: Central tegmental tract, MRI, Cerebral palsy, Glutaric aciduria type 1, Brainstem

Introduction

The Central Tegmental Tract (CTT) is an extrapyramidal pathway connecting the red nucleus of the mesencephalon and the inferior olivary nucleus of the medulla oblongata [1],[2]. The CTT is part of the dentato-rubro-olivary tract, also called the Guillain-Mollaret triangle. It also includes an ascending tract connecting the reticular nuclei of the brainstem with the thalamus [1],[2].

The CTT is one of the earliest regions where myelination occurs. In humans its myelination begins at 9 months after conception and is still incomplete at 23 months after birth [1],[3],[4].

The CTT is usually not visible on MRI after birth. CTT hyperintensity (CTTH) on T2-weighted and/or Diffusion Weighted Images (DWI) is an uncommon neuroimaging finding (Figure 1).
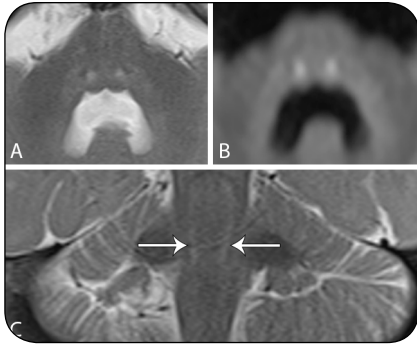
Figure 1: Brain MRI with axial T2 (A), axial DWI (B) and coronal T2 (C) images, in a 1-year-old boy presenting with epilepsy. Hyperintensity on T2-weighted images and slight diffusion restriction of the CTT are shown (A, B and arrows in C).

CTTH has been defined as an area of bilateral symmetrical hyperintensity at the location of the CTT on T2-weighted images and DWI on more than two consecutive axial slices [1].

It has been suggested that CTTH might be an age-related physiological process that can be influenced and modified by endogenous–exogenous noxious agents [5]. In fact, CTTH has been reported in association with a broad spectrum of clinical conditions including cerebral palsy, hypoxic-ischemic encephalopathy, neurodevelopmental and neurometabolic disorders [1],[2],[5]. Moreover, it was also shown that medical treatment with vigabatrin (VGB), in young infants with West Syndrome (WS), can be responsible for CTTH [6],[7].

CTT lesions were also reported in 25 autopsy cases in association with congenital brain anomalies, neurodegenerative disorders, metabolic disorders, neuromuscular disorders, and postnatal brain disorders [8]. The cases were classified into three groups on the basis of the severity of the lesions.

Group I included 1 lissencephaly, 1 hypoxic-ischemic encephalopathy, 2 congenital metabolic errors, 1 acute necrotizing encephalopathy and 1 putaminal bleeding.

Group II was composed by 2 Cockayne syndrome, 7 congenital metabolic errors, 2 hypoxic-ischemic encephalopathy, 1 subacute sclerosing panencephalitis and 1 dysentery encephalopathy.

Group III included 4 congenital brain anomalies, 1 lactic acidemia and 2 hypoxic-ischemic encephalopathy [8].

White matter degeneration, intra-myelinic edema,

vacuolation, gliosis and myelin loss were discussed as potential neuropathologic underlying processes causing the observed MRI signal changes [1],[6],[7]. However, CTTH remains an unclear phenomenon and no definitive etiology has been reported to date.

The aim of the present study is to provide a comprehensive literature review of the current evidence on CTTH. To this extent, we evaluated and systematically collected clinical and MRI findings in patients reported with CTTH in the available peer-reviewed literature.

Methods

The literature search was performed in December 2017 using Medline PubMed, Google Scholar and Cochrane Central databases.

Combinations of keywords were: "tegmental tract AND hyperintensity" and "tegmental tract AND MRI". Articles found in more than one search scheme were counted only once.

All types of studies published in peer reviewed journals were searched with no limit about year of publication, but only studies written in English were included in this review.

The title and abstract of each study were discussed by all authors, to define whether each study was matching or not with the topic of our review.

The reference list of each selected article was reviewed to identify additional studies of potential interest.

The first electronic search provided 86 articles, of which the title and the abstract were screened. Among these, 63 were excluded because they didn't match the topic of our study and 6 were excluded because they were written in a different language from English. Two papers were excluded after retrieving and analyzing the full text because they didn't match with the topic of our study.

Five additional papers, considered to be relevant to our study, were included after analyzing the reference lists of the previously selected articles. The study inclusion process is shown in figure 2.

For each of the papers included we evaluated the following features: number of reported patients with CTTH, age at detection, gender, clinical condition,

associated imaging findings including DWI and imaging follow-up.
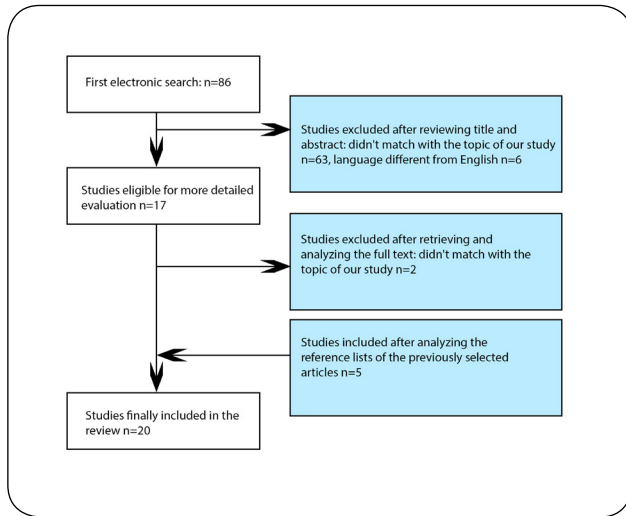
Figure 2: Flow chart showing the systematic review selection process.

Statistical Analysis

First, to test whether the age of patients showed a Gaussian or non-Gaussian distribution, the Kolmogorov-Smirnov (KS) test was used. Then we calculated median and percentiles (P25, P75) and interquartile range (IQR) for the age distribution.

To test if the distributions of male and female patients were different, the chi-square test was applied. The Mann-Whitney U test was used to check age differences between genders.

Results

Number and type of studies

According to the inclusion criteria, 20 publications relevant to the topic were included. Of these, 11 were retrospective studies and 9 were case reports (Table 1) [1-3],[5],[6],[9-23].

Total number of CTTH, age and gender

On the basis of our search strategy and selection criteria, we found a total of 226 patients with CTTH reported in literature.

The age parameter showed a significantly non-Gaussian distribution (KS test; p-value < 0.001) (Figure 3).

The median age was 1, 83 years (range: 7 days–21 years; P25=1.00 year, P75=3.00 years; IQR=2 years). The

age of individual patients was not available in 111 cases.

Regarding the patients gender, 54 (41%) were females and 78 (59%) males. The difference in gender distribution was statistically not significant (χ^2 test; p = 0,288).

Details about the gender of individual patients with CTTH were not available in 94 cases.

Both gender and age were available in 85 cases (53 males and 32 females); the age was not statistically different between this two groups according to gender (Mann-Whitney U test; p = 0,982).

Table 1: Studies included in the review

Authors	Year	Study Type	N° of CTTH
van der Knaap et al.	1998	Retrospective	3
Sugama and Eto	2003	Case Report	4
Khong et al.	2003	Case Report	2
Rossi et al.	2003	Case Report	2
Tada et al.	2004	Case Report	1
Sakai et al.	2006	Case Report	3
Takanashi et al.	2006	Case Report	1
Yoshida et al.	2008	Retrospective	20
Yoshikawa et al.	2008	Case Report	1
Pearl et al.	2009	Retrospective	4
Harting et al.	2009	Retrospective	14
Mkaouar-Rebai et al.	2010	Case Report	1
Aguilera-Albesa et al.	2012	Retrospective	34
Bindu et al.	2014	Retrospective	23
Mohammad et al.	2015	Retrospective	21
Singh et al.	2015	Case Report	1
Staufner et al.	2016	Retrospective	6
Derinkuyu et al.	2017	Retrospective	47
Işık et al.	2017	Retrospective	34
Govender et al.	2017	Retrospective	4

Clinical Status

The most common clinical condition associated with CTTH was cerebral palsy (51 cases; 22.6%), followed by glutaric aciduria type 1 (50 cases; 22.10%) and epilepsy (26 cases; 11.5%).

Less frequent clinical conditions were: developmental delay (24 cases; 11.5%), West Syndrome (or Infantile

Spasm) (14 cases; 6.2%), hypotonia (12 cases; 5.3%), Wilson's disease (10 cases; 4.4%), seizure (10 cases; 4.4%), treatment with vigabatrin (9 cases; 4%), encephalopathy (8 cases; 3.5%), macrocephaly (8 cases; 3.5%), ataxia (8 cases; 3.5%), Leigh syndrome (6 cases; 2.6%) and mental retardation (6 cases; 2.6%). A list of the most frequent clinical conditions reported in association to CTTH, can be found in table 2. Less frequent clinical conditions present in 2 cases (0.9%) orin 1 case (0.4%) are listed in table 3.

Figure 3: Histogram of the age distribution in patients with CTTH showing a clear predominance of patients below 6 years of age.

Table 2: Most frequent clinical conditions

Clinical Condition	N° of cases	Percentage
Cerebral Palsy	51	22.60%
Glutaric aciduria type 1	50	22.10%
Epilepsy	26	11.50%
Developmental Delay	24	10.60%
West syndrome	14	6.20%
Hypotonia	12	5.30%
Wilson's disease	10	4.40%
Seizure	10	4.40%
Vigabatrin	9	4%
Encephalopathy	8	3.50%
Macrocephaly	8	3.50%
Ataxia	8	3.50%
Leigh syndrome	6	2.60%
Mental Retardation	6	2.60%

Associated Imaging Findings

CTTH was most commonly reported without other associated brain MRI abnormalities (32 cases; 21.8%).

The most common concomitant brain abnormality was widening of the sylvian fissures (27 cases; 18.3%). Findings present in 21 cases (14.3%) were WM signal changes, underdeveloped frontotemporal lobes, dilatation of quadrigeminal cistern and incomplete hippocampal inversion.

Less common findings were: basal ganglia signal changes (18 cases; 12.2%), dentate nucleus signal changes (16 cases; 10.1%), thinning\hypoplasia of the corpus callosum (10 cases; 6.8%), mild ventriculomegaly (8 cases; 5.4%), general atrophy (7 cases; 4.8%), periventricular leukomalacia (7 cases; 4.8%), signal changes of the cerebellum (5 cases; 3.4%) and of the medulla oblongata (5 cases; 3.4%).

A complete list of the most frequent brain MRI abnormalities reported in association to CTTH, can be found in the table 4. Less frequent findings present in 4 cases (2.7%), 3 cases (2%), 2 cases (1.4%) and 1 case (0.7%) are listed in table 5.

Details about the presence of associated brain MRI abnormalities were not available in 79 cases.

DWI and Follow-up

CTTH was associated with diffusion restriction in 28/81 cases (34.6%); conversely, the DWI images were reported to be negative in 53/81 cases (65.4%).

DWI\ADC data were not available in 125 cases and not useful for our purpose because it was reported as a mean group effect in 20 cases.

When reported (n = 34), CTTH disappeared at follow-up in 14 cases (41.2%) and persisted in 20 cases (58.8%). Follow-up data were not reported in 192 cases.

Discussion

In this study, we have performed a systematic review of the current knowledge on CTTH. CTTH is a poorly understood and poorly investigated phenomenon. This finding has been described in a limited number of studies, both retrospective studies and case reports. In total, CTTH was reported in 226 cases without statistically significant difference between genders.

The two most common clinical conditions associated to CTTH were cerebral palsy and glutaric aciduria type 1. Moreover, CTTH was often found in the absence of other concomitant brain MRI abnormalities. Data regarding DWI and follow-up were largely unreported.

Table 3: Less frequent clinical conditions

Clinical Conditions present in 2 cases (0.9%)	Mitochondrial Disorder, Dystonia, Trauma, Speech delay, Absence of relevant medical history or symptoms, Nasal mass, Brain malformation, Birth asphyxia.
Clinical Conditions present in 1 case (0.4%)	Myelomeningocele, Retinal changes associated to papilledema, History of surgery for posterior fossa tumor, History of surgery for craniosynostosis, Possible metabolic disease, Pearson Syndrome, Noonan Syndrome, Cardiac hypertrophy, Non-ketotic hyperglycinemia, Neuroblastoma, Neck hemangioma, Nasal malformation, Facial Dysmorfism, Unspecified Dysmorfism, Migraine, Microcephaly, Methionine Adenosyltransferase I/III Deficiency, Leigh-like syndrome, Tremor, Spastic paraplegia, Kearns-Sayre syndrome, Hearing loss, Hyperphenylalaninemia, Headache, Gorlin syndrome, Fetal distress and apnea, Legs spasticity, Schizencephaly, Elevated creatine kinase, Diencephalic syndrome, Mutation in the adenosine triphosphatase (ATPase) 8 gene, Cytomegalovirus infection, Aicardi-Goutières syndrome, Congenital toxoplasmosis, Cleft palate, Brain tumor, Muscle rigidity, Battered child, Angelman Syndrome, Adenosine kinase deficiency in 6 cases, Acute lymphocytic leukemia (post-chemotherapy), Achondroplasia, Abducens palsy, 6-Pyruvoyltetrahydropterin Synthetase Deficiency.

Table 4: Most frequently associated imaging findings

Associated Imaging Findings	N° of cases	Percentage
Absence of other Brain MRI Abnormalities	32	21.80%
Widening of the Sylvian Fissures	27	18.30%
White Matter Signal Changes	21	14.30%
Underdeveloped Fronto-Temporal Lobes	21	14.30%
Dilatation of Quadrigeminal Cistern	21	14.30%
Incomplete Hippocampal Inversion	21	14.30%
Basal Ganglia Signal Changes	18	12.20%
Dentate Nucleus Signal Changes	16	10.10%
Thinning\Hypoplasia of the Corpus Callosum	10	6.80%
Mild Ventriculomegaly	8	5.40%
General Atrophy	7	4.80%
Periventricular Leukomalacia	7	4.80%
Cerebellum Signal Changes	5	3.40%
Medulla Oblongata Signal Changes	5	3.40%

The overall age distribution we found in this review showed that the majority of patient reported with CTTH was below the age of 6 years. In particular, CTTH was most frequent between the ages of 1 and 2 years, with a median age of 1,83 years. According to these results CTTH seem to be mostly an age-related phenomenon.

The largest portion of the CTT in humans is composed by rubro-olivary fibres, deriving from the parvocellular part of the red nucleus and projecting to the ipsilateral inferior olivary nucleus; the rubro-olivary fibers are dominant in humans and small in lower mammals [24],[25]. On the other hand, the rubro-spinal tract, connecting the magnocellular part of the red nucleus to the ipsilateral brainstem and the contro-lateral spinal cord, is dominant in lower mammals and small in humans [24],[25]. This anatomical difference is associated with a reduction in size of the medial longitudinal fascicle and an increase in size of the corticospinal tracts, CTT, and olivary nuclei in humans [24], considered to be related to the functional evolution from quadripedal to bipedal locomotion [26],[27]. The age peak of CTTH observed in children might reflect neural correlates of the acquisition/improvement of motor tasks such as the ability to walk since the rubro-olivary fibers, representing the majority

of the CTT, are linked to bipedal locomotion [5]. However, the age range observed in our study was broad (7 days – 21 years), suggesting that this phenomenon is not always and exclusively related to a specific developmental process or milestone.

CTTH was reported in association with a wide spectrum of diseases as well as in healthy subjects [5]. In our study, the most frequently associated clinical condition was Cerebral Palsy (CP). CP is also the most common movement disorder in children, occurring in about 2,1/1000 newborns [2],[28]. This condition is caused by abnormal development or damage of the brain occurring during pregnancy, childbirth or shortly after birth, with consequent impairment of body movement control, muscle control, muscle coordination, muscle tone, reflex, posture and balance [2],[28]. Recently, a greater frequency of CTTH in patients with CP (19%) compared to a control group (3.5%) was reported [2]. The most frequent etiology of CP is neonatal hypoxic-ischemic encephalopathy [2]. Thus, hypoxic-ischemic insult might be one of the factors responsible for the occurrence of CTTH, especially taking into account the vulnerability of the CTT at the time of brain insults due to intensive maturation [29].

The second most common clinical condition associated to CTTH was glutaric aciduria type 1.

Glutaric aciduria type 1 is a rare neurometabolic disease with an autosomal recessive inheritance and with a high morbidity and mortality if not diagnosed promptly [19]. Glutaric aciduria type 1 is caused by deficiency of glutaryl-CoA dehydrogenase enzyme. The prevalence of the disease is as much as 1/100,000 newborns [30]. In a study in children with glutaric aciduria type 1, CTTH was found to be particularly frequent, reported in 21 children (72%) with this disease. The neurotoxic effect of glutaric aciduria type 1 can be chronical and starts early in utero, leading to abnormal brain development as well as abnormal white matter maintenance [16]. Therefore, toxic-metabolic insult might be another noxious factor potentially leading to CTTH. This concept is also strengthened by evidence showing that medical treatment with VGB can be neurotoxic and can be associated to CTTH and to other MRI abnormalities especially of the basal ganglia [6],[7],[31],[32]. The VGB-related MRI abnormalities can be reversible after drug discontinuation [6],[7],[31]. Although the pharmacological explanation of the VGB-neurotoxicity is not known, it was suggested that an increase of GABA concentrations might lead to neuronal excitotoxicity due to the depolarizing effects in the immature brain [33].

In our review, CTTH was mainly found without concomitant MRI findings. The most common findings associated with CTTH were widening of the sylvian fissures, WM signal changes, underdeveloped frontotemporal lobes, dilatation of the quadrigeminal cistern and incomplete hippocampal inversion. Most of these findings represent the typical MRI picture of glutaric aciduria type 1 [16]. Thus, when CTTH is encountered in clinical practice, neuroradiologists should look for MRI stigmata of glutaric aciduria type 1.

Data regarding DWI were poorly reported. When

Table 5: Less frequently associated imaging findings.

Associated Imaging Findings present in 4 cases (2.7%)	Substantia Nigra Signal, Signal Changes, Cerebellar atrophy, Hydrocephalus, Corticospinal Tracts Signal Changes, Periventricular Gliosis, Bilateral Hypertrofic Olivary Degeneration.
Associated Imaging Findings present in 3 cases (2%)	Cerebral Peduncles Signal Changes, Slight changes of the Corpus Callosum, Intracranial Tumor, Myelination Delay, Subthalamic Nuclei Signal Changes.
Associated Imaging Findings present in 2 cases (1.4%)	Arachnoid Cyst, Polymicrogyria, Migration Disorder, Periventricular unspecified Signal Changes, Cortical Dysplasia.
Associated Imaging Findings present in 1 case (0.7%)	History of Surgery for Posterior Fossa Tumor, Holoprosencephaly, Left Temporal Atrophy, Posterior Limbs of the Internal Capsule Signal Changes, Abnormal Gyration, Pontine Signal Changes, Basal Ganglia Atrophy, Transient Lesion of the Splenium of the Corpus Callosum, Left Frontal Signal Changes, Incomplete Band Heterotopia, Optic Nerves Signal Changes, Fornices Signal Changes, Cephalohematoma, Sturge-Weber syndrome, Subcortical Leukomalacia, Interpeduncular Nucleus Signal Changes, Pallido-Cortical–Nigro-Cortical Tracts Signal Changes, Putamen Signal Changes, Periaqueductal Grey Matter Signal Changes, Thalamus Signal Changes.

available, CTTH was most frequently observed without diffusion restriction (65.4%). A restricted diffusion pattern was reported in 34.6% of cases. This finding might reflect abnormal axial diffusivity across the CTT not necessarily related to myelinic changes such as intramyelinic edema [3],[5],[34]. However, the role of DWI needs to be further explored to understand if there might be a different pathogenesis between cases with isolated T2 hyperintense signal and cases with T2 hyperintensity associated to restricted diffusion.

Data regarding CTTH follow-up were unreported in the large majority of studies. The fact the CTTH can be a transient phenomenon, such as in 14 cases (41.2%) in our review, might encourage further longitudinal studies on this topic.

On a neuropathological standpoint, Shioda et al. [8] reported symmetrical CTT lesions in 25 of 120 cases (20.8%). As mentioned above, they classified the lesions into three groups according to the severity. In group I, CTT lesions were associated to diffuse tegmental damage, suggesting a different phenomenon as compared to CTTH observed with MRI. In the groups II and III they found a total of 20 cases with lesions of the CTT and sparing of the medial longitudinal fasciculus, the medial and lateral lemniscus. In these groups, the authors found mild to moderate fiber loss with gliosis or increased vacuoles within the CTT. The lesions of CTT were associated to various causes of brain disorders, with a predominance of lysosomal disorders and congenital brain anomalies and with a total of four cases of hypoxic–ischemic encephalopathy [8]. This finding might reflect the vulnerability of the CTT to metabolic and hypoxic–ischemic insults. Moreover, van der Knaap et al. [9] reported neuropathology data in a patient with leukoencephalopathy with vanishing white matter and with CTTH, showing symmetric area of localized demyelination involving the central tegmental tract and the superior central nucleus on both sides.

However, there is insufficient evidence to conclude that the CTT lesions reported by neuropathology analysis can always be considered the mirror of CTTH as observed with MRI. Additional studies bridging the MRI and neuropathology are needed to better understand the neuropathological correlate of CTTH.

Conclusion

CTTH is an uncommon neuroimaging finding that is mainly related to the acquisition\improvement of a physiologicalmotor developmental process.

The two most common clinical conditions associated to CTTH were cerebral palsy and glutaric aciduria type 1, supporting the concept that this finding is influenced by hypoxic-ischemic and toxic-metabolic factors.

Data regarding DWI and follow-up are largely unreported and deserve to be further explored.

Author Contributions

Guarantors of integrity of entire study, C.A.M., J.V.G.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, C.A.M., J.V.G.; statistical analysis, C.A.M., J.V.G, T.D.B.; and manuscript editing, all authors

References

1. Yoshida S, Hayakawa K, Yamamoto A, et al. Symmetrical central tegmental tract (CTT) hyperintense lesions on magnetic resonance imaging in children. Eur Radiol. 2009;19(2):462-469. doi: https://doi.org/10.1007/s00330-008-1167-7

2. Derinkuyu BE, Ozmen E, Akmaz-Unlu H, Altinbas NK, Gurkas E, Boyunaga O. A magnetic resonance imaging finding in children with cerebral palsy: Symmetrical central tegmental tract hyperintensity. Brain Dev. 2017;39(3):211-217. doi: https://doi.org/10.1016/j.braindev.2016.10.004

3. Takanashi J, Kanazawa M, Kohno Y. Central tegmental tract involvement in an infant with 6-pyruvoyltetrahydropterin synthetase deficiency. AJNR Am J Neuroradiol. 2006;27(3):584-585. https://www.ncbi.nlm.nih.gov/pubmed/16551996

4. Brody BA, Kinney HC, Kloman AS, Gilles FH. Sequence of central nervous system myelination in human infancy. I. An Autopsy Study of Myelination. J Neuropathol Exp Neurol. 1987;46(3):283-301. doi: https://doi.org/10.1097/00005072-198705000-00005

5. Aguilera-Albesa S, Poretti A, Honnef D, et al. T2 hyperintense signal of the central tegmental tracts in children: disease or normal maturational process? Neuroradiol. 2012;54(8):863-871. doi: https://doi.org/10.1007/s00234-012-1006-z

6. Pearl PL, Vezina LG, Saneto RP, et al. Cerebral MRI abnormalities associated with vigabatrin therapy:

MRI Abnormalities with Vigabatrin. Epilepsia. 2009;50(2):184-194. doi: https://doi.org/10.1111/j.1528-1167.2008.01728.x

7. Dracopoulos A, Widjaja E, Raybaud C, Westall CA, Snead OC. Vigabatrin-associated reversible MRI signal changes in patients with infantile spasms: Reversible MRI Signals with Vigabatrin. Epilepsia. 2010;51(7):1297-1304. doi: https://doi.org/10.1111/j.1528-1167.2010.02564.x

8. Shioda M, Hayashi M, Takanashi J, Osawa M. Lesions in the central tegmental tract in autopsy cases of developmental brain disorders. Brain Dev. 2011;33(7):541-547. doi: https://doi.org/10.1016/j.braindev.2010.09.010

9. van der Knaap MS, Kamphorst W, Barth PG, Kraaijeveld CL, Gut E, Valk J. Phenotypic variation in leukoencephalopathy with vanishing white matter. Neurol. 1998;51(2):540-547. doi: https://doi.org/10.1212/WNL.51.2.540

10. Sugama S, Eto Y. Brainstem lesions in children with perinatal brain injury. Pediatr Neurol. 2003;28(3):212-215. doi: https://doi.org/10.1016/S0887-8994(02)00623-9

11. Khong P-L, Lam BCC, Chung BHY, Wong K-Y, Ooi G-C. Diffusion-weighted MR imaging in neonatal nonketotic hyperglycinemia. AJNR Am J Neuroradiol. 2003;24(6):1181-1183. https://www.ncbi.nlm.nih.gov/pubmed/12812951

12. Rossi A, Biancheri R, Bruno C, et al. Leigh Syndrome with COX deficiency and SURF1 gene mutations: MR imaging findings. AJNR Am J Neuroradiol. 2003;24(6):1188-1191. https://www.ncbi.nlm.nih.gov/pubmed/12812953

13. Tada H, Takanashi J, Barkovich AJ, Yamamoto S, Kohno Y. Reversible white matter lesion in methionine adenosyltransferase I/III deficiency. AJNR Am J Neuroradiol. 2004;25(10):1843-1845. https://www.ncbi.nlm.nih.gov/pubmed/15569761

14. Sakai Y, Kira R, Torisu H, Ihara K, Yoshiura T, Hara T. Persistent diffusion abnormalities in the brain stem of three children with mitochondrial diseases. Am J Neuroradiol. 2006;27(9):1924-1926. http://www.ajnr.org/content/27/9/1924

15. Yoshikawa H, Nakano K, Watanabe S. Central tegmental tract lesion in a girl with holoprosencephaly presenting with West syndrome. Eur J Paediatr Neurol. 2009;13(4):376-379. doi: https://doi.org/10.1016/j.ejpn.2008.06.009

16. Harting I, Neumaier-Probst E, Seitz A, et al. Dynamic changes of striatal and extrastriatal abnormalities in glutaric aciduria type I. Brain. 2009;132(7):1764-1782. doi: https://doi.org/10.1093/brain/awp112

17. Mkaouar-Rebai E, Kammoun F, Chamkha I, et al. A de novo mutation in the Adenosine Triphosphatase (ATPase) 8 gene in a patient with mitochondrial disorder. J Child Neurol. 2010;25(6):770-775. doi: https://doi.org/10.1177/0883073809344351

18. Bindu PS, Taly AB, Sonam K, et al. Bilateral hypertrophic olivary nucleus degeneration on magnetic resonance imaging in children with Leigh and Leigh-like syndrome. Br J Radiol. 2014;87(1034):1-8. doi: https://doi.org/10.1259/bjr.20130478

19. Mohammad SA, Abdelkhalek HS, Ahmed KA, Zaki OK. Glutaric aciduria type 1: neuroimaging features with clinical correlation. Pediatr Radiol. 2015;45(11):1696-1705. doi: https://doi.org/10.1007/s00247-015-3395-8

20. Singh P, Kaur A, Kaur R, Aggarwal S, Singh R. Symmetrical central tegmental tract hyperintensities on magnetic resonance imaging. J Pediatr Neurosci. 2015;10(3):235. doi: https://doi.org/10.4103/1817-1745.165666

21. Staufner C, Blom HJ, Dionisi-Vici C, et al. MRI and 1H-MRS in adenosine kinase deficiency. Neuroradiol. 2016;58(7):697-703. doi: https://doi.org/10.1007/s00234-016-1676-z

22. Işık U, Dinçer A. Central tegmentum tract hyperintensities in pediatric neurological patients: Incidence or coincidence. Brain Dev. 2017;39(5):411-417. doi: https://doi.org/10.1016/j.braindev.2016.11.013

23. Govender R, Mitha A, Mubaiwa L. A review of patients with glutaric aciduria type 1 at Inkosi Albert Luthuli Central Hospital, Durban, South Africa. South African Med J. 2017;107(3):201-204. doi: https://doi.org/10.7196/SAMJ.2017.v107i3.11332

24. Nathan PW, Smith MC. The rubrospinal and central tegmental tracts in man. Brain. 1982;105(2):223-269. doi: https://doi.org/10.1093/brain/105.2.223

25. Massion J. Red nucleus: past and future. Behav Brain Res. 1988;28(1-2):1-8. doi: https://doi.org/10.1016/0166-4328(88)90071-X

26. Onodera S, Hicks TP. A comparative neuroanatomical study of the red nucleus of the cat, macaque and human. Matsunami H, ed. PLoS ONE. 2009;4(8):e6623. doi: https://doi.org/10.1371/journal.pone.0006623

27. Habas C, Cabanis EA. Cortical projection to the human

red nucleus: complementary results with probabilistic tractography at 3 T. Neuroradiol. 2007;49(9):777-784. doi: https://doi.org/10.1007/s00234-007-0260-y

28. Oskoui M, Coutinho F, Dykeman J, Jetté N, Pringsheim T. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol. 2013;55(6):509-519. doi: https://doi.org/10.1111/dmcn.12080

29. Dambska M, Laure-Kamionowska M, Liebhart M. Brainstem lesions in the course of chronic fetal asphyxia. Clin Neuropathol. 1987;6(3):110-115.

30. Lindner M, Kölker S, Schulze A, Christensen E, Greenberg CR, Hoffmann GF. Neonatal screening for glutaryl-CoA dehydrogenase deficiency. J Inherit Metab Dis. 2004;27(6):851-859. doi: https://doi.org/10.1023/B:BOLI.0000045769.96657.af

31. Wheless JW, Carmant L, Bebin M, et al. Magnetic resonance imaging abnormalities associated with vigabatrin in patients with epilepsy: MRI Abnormalities in Patients with Epilepsy. Epilepsia. 2009;50(2):195-205. doi: https://doi.org/10.1111/j.1528-1167.2008.01896.x

32. Quattrocchi CC. Magnetic resonance imaging differential diagnosis of brainstem lesions in children. World J Radiol . 2016;8(1):1. doi: https://doi.org/10.4329/wjr.v8.i1.1

33. Ben-Ari Y. Basic developmental rules and their implications for epilepsy in the immature brain. Epileptic Disord. 2006;8(2):91-102. https://www.ncbi.nlm.nih.gov/pubmed/16793570

34. Simao GN, Zarei Mahmoodabadi S, Snead OC, Go C, Widjaja E. Abnormal axial diffusivity in the deep gray nuclei and dorsal brain stem in infantile spasm treated with vigabatrin. Am J Neuroradiol. 2011;32(1):199-203. doi: https://doi.org/10.3174/ajnr.A2224