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Case report

The patient with mild diencephalic–mesencephalic junction dysplasia – Case report and review of literature

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ABSTRACT

Diencephalic–mesencephalic junction dysplasia (DMJD) is very rare congenital brain malformation. We present a 66-years-old man with mild cognitive impairment, dysarthria, deafness, gait abnormality, and involuntary movements of the trunk. The first symptoms, psychomotor excitation and anxiety begun when he was over thirty years old however the symptoms gradually intensified and slowly progressed. The magnetic resonance imaging scans showed partial DMJD. According to recent date it represented type-B of the malformation with relatively mild phenotype in relation to the previously described in literature type-A. To the best of our knowledge this is the first description of an adult patient diagnosed with DMJD anomaly.

1. Introduction

Midbrain–hindbrain malformations (MHMs) are a rare heterogeneous group of structural posterior fossa abnormalities. They can be caused either by embryogenic disruptions or genetic mutations. The structural heterogeneity appears on some classifications based on wide spectrum of clinical manifestations, morphological pathologies, embryological and genetic defects [1–3]. They include Joubert syndrome and related disorders [4,5], horizontal gaze palsy and progressive scoliosis [6], pontine tegmental cap dysplasia [7], pontocerebellar hypoplasia [8], rhombencephalosynapsis [9]. The radiologically described patterns of structural differences in different MHMs can be used in correlation with clinical symptoms to estimate the possible impact of morphological changes on a patients' prognosis and mortality.

Diencephalic–mesencephalic junction dysplasia (DMJD) is a very rare MHM caused by early anteroposterior patterning defect of neural tube. During embryogenesis, mesencephalon is one of three primary vesicles (along with prosencephalon and rhombencephalon) whereas diencephalon is the secondary vesicle formed from prosencephalon (along with telencephalon). The diencephalic–mesencephalic junction (DMJ) is one of two important signaling centers of encephalon embryonic development (along with mesencephalic–rombencephalic junction). DMJ defects can probably appear due to impaired secretion of fibroblast growth factor 8 (FGF8) as well as impaired regulation the anterior–posterior expression of the engrailed (En) and

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Paired box (Pax) transcription factors [10,11]. However nothing is known of the mechanisms of DMJ defects in humans.

For the time being there have been published only few cases of DMJD patients [1,2,12,13] describing the possible correlations between the exact radiological imaging and clinical manifestations of the disorder. In a majority of cases, the neurological and general symptoms were rapidly accumulating in the first months after birth, but at the same time there was also a group of patients described by Severino et al. [13] as type B DMJ pattern. The group was neurologically less impaired in comparison to patients classified as type A DMJ pattern (Fig. 1).

2. Case report

1wThe 66-years-old man was hospitalized in Department of Neurology 3 times between 2014 and 2016. At this time he was suffering from deep disorders of speech articulation, deafness, gait disorders and involuntary movements of trunk. It is possible that the patient presented some retardation of psychomotor growth in childhood, but his parents were not aware of it. During his adolescence gradual deafness started leading finally to a complete lack of hearing at the age of sixty. When the patient was in his fifties slight involuntary movements of trunk begun. Also mild cognitive impairment appeared at this time followed by minor right hemiparesis and gait disorder. The symptoms gradually progressed. The patient's family became aware of the illness when the patient was almost sixty years old. One year later, after death of his son, symptoms of psychomotor excitation and anxiety appeared and progressed over two years. The patient was usually uneasy, irritable, depressed and anxious. He had tendency to speak and walk very quickly and rapidly. The patient was not examined nor diagnosed until the age of 65. At this age all of the symptoms of the illness were advanced and affected the daily life. The family history was negative.

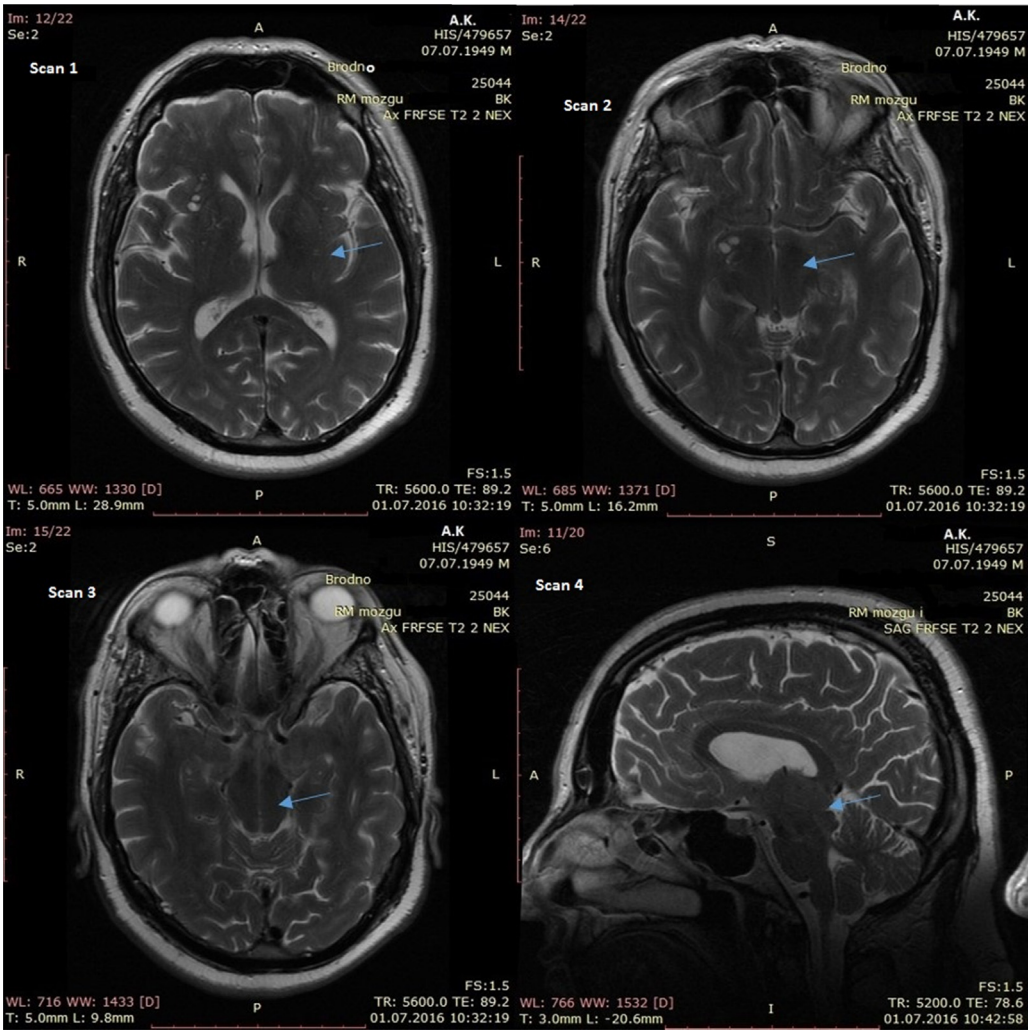

Fig. 1 – Structural brain images T_2-weighted MR images of the patient with *type B* DMJD. Scan 1: Abnormal contour of the thalamus and basal ganglia (arrow). Scan 2: Abnormal contour of the midbrain with fusion of the hypothalamus (arrow). Scan 3: Enlargement of the midbrain (arrow). Scan 4: Incomplete thalamic–mesencephalic cleavage sagittal plane with parenchymal bands connecting the interthalamic adhesion with the midbrain (arrow). These all scans show abnormal picture of the brain.

Table 1 – Dieencephalic–mesencephalic junction dysplasia: type-A, type-B; onset, clinical symptomps and magnetic resonance imaging [12,13,14] – compared to our subject AK type B.

	Onset	Clinical symptoms	MRI findings
Type-A DMJD Pattern	Early onset. The neurological symptoms appear in the first months of the patient life.	Clinically, patients are affected by facial dysmorphisms, cognitive deep imparment, progressive microcephaly, spastic tetraparesis and dystonic/ dyskinetic movements and seizures. The course of the illness is severe.	MRI scans show completely suthalamic-mesencephalic fusion on sagittal plane. Abnormal midbrain contour on axial images, Midbrain ventral cleft (butterfly sign) and hypoplasia or agenesis of corpus callosum. The thalamic is larger than normal. Basal ganglia abnormalities are present ranging from bilateral agenesis of the putamen and corpus pallidum.
Type-B DMJD Pattern	The neurological symptoms appear later in the first years often in the adolescence or in the adulthood of the patient life.	Clinically patients suffer from mild cognitive disorders, speech disorders, pyramidal tract signs, gait disorders, and a minor movement failure. Sometimes patients present unilateral moderate hemiparesis and walk with support or have seizures. The course of the illness is usually mild and progress of symptoms is rather slow.	MRI scans show incompletely subthalamic-mesencephalic fusion of brain. Incompletely Interthalamic adhesion. Slightly small midbrain. The corpus callosum and the anterior commissure are hypoplastic in only few patients. The thalamic is relatively large.
The subject, our patient. Type-B DMJD Pattern	The first, serious symptoms, psychomotor excitation and anxiety begun when the subject was over thirty years old. Probably our patient was very little retardation of psychomotor growth which appeared in his childhood and little lack of hearing which appeared in his adolescence.	Clinically all symptoms of illness appeared when our patient was in his fifties. He was suffering from mild cognitive disorders, speech articulation – dysarthria, gait disorders and deafness, involuntary movements of trunk and he had minor right hemiparesis.	MRI scans show incompletely subthalamic-mesencephalic fusion of brain. Incompletely interthalamic adhesion. Slightly small midbrain. The thalamic is relatively large.

Table 2 – Midbrain–hindbrain morphometry in children diagnosed with type A and type B DMJ anomaly compared to controls from the article: Mariasavina Severino et al. compared to our subject [13].

	Cases: type A (*N* = 11) Median [1st–3rd quartiles]	Controls (*N* = 110) Median [1st–3rd quartiles]	Cases: type B (*N* = 17) Median [1st–3rd quartiles]	Controls (*N* = 170) Median [1st–3rd quartiles]	The subject 66 years old man A.K.type-B
AP midbrain (mm)	14.8 [12.2–17.3]	15.1 [13.7–17]	14 [13.5–15.2]	15.7 [14.7–17.2]	21.3
AP pons (mm)	14.6 [11.1–17.3]	18.3 [15.5–21]	16.6 [16.1–17.8]	19 [17.7–21.3]	21.7
AP medulla (mm)	9.8 [5.9–10.1]	11.2 [9.6–12.5]	10.2 [9.8–11.2]	11.6 [10.6–12.7]	13.0
M/Pap ratio	1 [0.9–1.2]	0.8 [0.8–0.9]	0.8 [0.8–0.9]	0.8 [0.8–0.9]	
CC midbrain (mm)	12.5 [11–15.3]	12 [10.9–13.1]	12.6 [11.2–14.3]	12.8 [11.7–14]	14.7
CC pons (mm)	15.4 [12.7–18.2]	20.6 [16.2–23]	19.6 [18–21.1]	21.6 [19.1–24]	24.4
M/Pcc ratio	0.9 [0.6–0.9]	0.6 [0.6–0.6]	0.6 [0.6–0.7]	6 [0.6–0.6]	
CC medulla (mm)	13.2 [12.3–14.2]	14.5 [12–16.1]	16.3 [14.8–18]	15 [13–16.5]	14.0
CC vermis (mm)	30 [19.2–31.6]	39.9 [26–43.4]	38.1 [33.6–39.7]	40.8 [36.8–44.8]	41.4
AP vermis (mm)	17.5 [12.9–26]	24.7 [18.1–27.6]	21.3 [20.5–26.2]	26 [23–28]	29.0
TR cerebellum (mm)	74.1 [48.2–81]	90.8 [57.3–98.5]	92.8 [76–101]	94 [81.7–101]	105

AP anteroposterior diameter, *CC* craniocaudal diameter, *M/Pap ratio* midbrain to pons ratio of AP diameters, *M/Pcc ratio* midbrain to pons ratio of CC diameters, *TR* transverse diameter.

The neurological examination showed deep bilateral deafness, severe disorders of articulation of the speech, mild cognitive impairment, moderate gait disorders and mild involuntary movements of the trunk. The patient's presented bend neck and trunk. The movements were chaotic, rapid and restless. Psychological investigation revealed pronounced impulsiveness and loss of control. He was overexcited and had a very short attention span. Mild cognitive impairment, mostly disorders of memory and learning was diagnosed. The speech therapist ascertained that the patient had deep disorders of fluency and was inarticulate. The time of phonation was shorter than normal. His speech was unstable and nasal (Tables 1 and 2).

The MRI scans showed abnormal picture of the brain. Both of the thalamus were relatively large. The mesencephalon was small in craniocaudal dimension. These structures were almost completely linked fitting well to the description of DMJD type-B. DNA of the patient was examined by a molecular cytogenetic method of array comparative genomic hybridization. The aCGH did not show unbalanced chromosomal abnormalities.

The patient was treated with quetiapine and risperidone with some improvement in his mood. Also dysarthria and gait slightly improved.

3. Discussion

There are two mainly types of diencephalic–mesencephalic junction dysplasia. The type-A exhibits neurological symptoms during the first months of a patient's life. The course of type-A DMJD is usually severe [12]. The MRI scans show complete hypothalamic-mesencephalic fusion on axial plane, with possible midbrain ventral cleft [13]. In type-B the neurological symptoms appear later, often in the patient's adulthood. The course of the illness is usually mild and progress of symptoms is rather slow. This type is characterized by incomplete hypothalamic-mesencephalic fusion on sagittal plane. This complete or not complete junction between diencephalon and the midbrain is ill defined [14]. Zaki et al. [12] described 6 patients with a novel characteristic brain malformation at the level of the diencephalic–mesencephalic junction. The neurological and general symptoms begun at the first months of their life. Neurological examination showed severe cognitive impairment, spastic quadriparesis and truncal, axial hypotonia. These children suffered from epileptic seizures. Brain magnetic resonance imaging demonstrated a dysplasia of diencephalic–mesencephalic junction with a characteristic ''butterfly'' like contour of the midbrain an axial sections [12]. Additional imaging features exhibited variable degrees of supratentorial ventricular dilatation and hypoplasia or agenesis, or extreme thinning of the corpus callosum. In the others children who suffer from DMJD type-A MRI demonstrated basal ganglia abnormalities ranging from bilateral agenesis of the putamen and globus pallidus. The other finding of the MRI scans were partial agenesis of the hemispheres and schizoencephaly [12,13]. They had postnatal progressive microcephaly. These children often died in the age of few months or years [12,13]. The portrayed 66-year-old man suffered from very mild neurological symptoms in comparison to the Egyptian children. The progression of symptoms was very slow. Really serious symptoms of the disease appeared when he was almost in his sixties. MRI scans were typical for type-B of DMJD. The mild type-B of DMJD is more difficult to recognition than type-A. The symptoms of this type of DMJD are mild or moderate and the progress of symptoms is really slow [13]. Patients presented with pyramidal tract signs, speech and gait disturbances [14]. They often had no consciousness of their condition in a younger age. Some of these patients with type-B presented moderate uniteral hemiparesis, walked with support or had tonic–clonic seizures [13]. The MRI scans show in the some of these patients hypoplastic corpus callosum. Sometimes the MRI examination shows hemisphere hypoplasia with white matter signal abnormalities, small hippocampus [13]. These patients who suffer from this kind of the illness are often diagnosed in later, when they are already adults. Furthermore the first symptoms of the illness as psychomotor excitation and gait disturbance or speech disorders were very little and were not perceptible. The patients were not diagnosed in the younger age because the symptoms of the illness were not affected their daily life. The same was in our subject. The patient's family became aware of the illness late, when the symptoms and progress of this illness were really serious.

Children with DMJD described by Zaki et al. were from three consanguineous Egyptian families with possible autosomal recessive inheritance. Despite exome sequencing in these affected individuals, no obvious candidate gene has emerged. Our case was sporadic. There is correlation of MRI with clinical findings [14]. MRI is essential for the diagnosis DMDJ type A and type-B.

One should remember that different neurological symptoms as deafness, disorders of articulation of the speech, mild cognitive impairment, mild disorders of gate and involuntary movements with slow progress in the adult life could be the symptoms of the type-B diencephalic–mesencephalic junction dysplasia and MRI is crucial for the correct diagnosis.

Conflict of interest

None declared.

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