Cognitive Impairment In Cerebellar Malformations: A Logit Model Based On Cognitive Testing

Hasnaa Mohamed Elbendary[1], Ehab Mohamed Eid[2], Yasser Nassef[3], Ahmed Fathay,[3]
Rasha Khattab[4], Walaa Hany Ali,[3] and wafaa Osaman[5]
[1]Clinical Genetic Department , National Research Centre, Egypt, [2]Professor of Preventive Medicine and Epidemiology, Medical Studies Department for Children, Faculty of Postgraduate Childhood Studies, Ain Shams University, Egypt, [3]Child Health department, National Research Centre, Egypt, [4]Lecturer of Radiology, Faculty of Medicine, Ain Shams University, Egypt, [5]Lecturer of Pediatric, Faculty of Medicine, Ain Shams University, Egypt.

Abstract

Background: Though the cerebellum has long been recognized long time ago for its major role in motor functions and coordination, recently confirmed that the cerebellum has great rule in higher order functions, it shapes and dominates the functions of many brain areas, especially cognition and behavior, through different connections and tracts between the cerebellum and cerebral cortex.T he complex development of the cerebellum together with the high number of involved genes and the long embryonic development of the cerebellum make the cerebellum vulnerable to a broad spectrum of malformations and disruption. Neuroimaging plays a key role in the diagnosis of posterior fossa malformations.

Objective: Our scope was to determine to what extent cerebellar malformations affect behaviour, cognition, motor functions and quality of life.

Methodology: A total of 60 patients proven with cerebellar malformations were enrolled and classified into five groups according to MRI finding. Patients were underwent brain MRI, behavioural, cognitive, motor and quality of life assessment by, (CBCL) child behavior check list, Wechsler intelligent quotient test, (SARA) scale for the assessment and rating ataxia and quality of life scoring respectively.

Results: Our finding highlighted that children with cerebellar malformations experience high prevalence of Cogntive, as well as poor quality of life due to functional disabilities, except patients with Dandly walker malformations, although they have favourable neuro-developmental outcome but this does not prevent them from experiencing poor quality of life.

Conclusion: Cerebellar malformation is heavily connected to cognition, behavior and affect in addition to impairment in the motor function, especially patients with joubert syndrome they experienced high level of behavior and affect abnormalities so, It can be stated that different types of congenital cerebellar malformations lead to a complex picture that can be incorporated under the picture of cognitive syndrome.

Recommendations: Further studies need to be done in order to confirm role of cerebellum in higher orders functions like behavior, emotion processing and cognition.

Keywords: CBCL, SARA, QOL, Wechsler, Cerebellar malformations.

اعتلال الإدراك لدى الاطفال المصابين بتشوهات خلقيه فى تكوين المخيخ تقديم نموذج استنادا على التقييم المعرفى

المقدمة: المخيخ من اكثر اجزاء المخ تعرضا لتشوهات فى التكوين وذلك نتيجه التطور المعقد للمخيخ ونتيجه الكم الهائل من الجينات المتحكمة فى تكوينه ولقد اتسع فى الاونه الاخيره دور التصوير المغناطيسى على المخ فى تشخيص تشوهات الحفره الخلفية من المخ. على الرغم من معرفه المخيخ منذ زمن بعيد بدوره الكبير فى التحكم فى الوظائف الحركيه ووظائف الاتزان ولكن فى العصر الحديث ومنذ زمن ليس بعيد تم اكتشاف او اعلان دور اخر للمخيخ لا يقل أهميه عن دوره فى الوظائف الحركيه والاتزان وهو دوره فى التحكم فى وظائف الإدراك والمعرفة والسلوك وتم إثبات علاقته الوثيقه بهذه الوظائف وذلك من خلال مناطق من الخرائط والارتباطات العصبيه بين القشره الدماغية والمخيخ.

الهدف: الهدف من هذا البحث هو تحديد الى مدى تؤثر تشوهات تكوين المخيخ على تطور السلوك والمعرفة والإدراك لدى الاطفال المصابين وتقييم جوده الحياه لديهم.

المنهجية: تم استنتاج من خلال هذا البحث ان الاطفال المصابين بتشوهات فى تكوين المخ لديهم شيوع وتأثير على السلوك والقدرات المعرفيه وأيضا الحرمين وبالتالى تؤثر سلبيا على جوده الحياه لديهم. النتائج: : إثبات وجود علاقه وثيقه بين تشوهات تكوين المخيخ واضطرابات فى التطور السلوكى والمعرفى بالإضافة الى تأثيرها على القدرات الحركيه. وأيضا معرفه كافه الأنواع من العيوب الخلفية بالمخيخ وتقسيمها من خلال أشعه الرنين المغناطيسى على المخ.

الخلاصة: وتبين من خلال هذه الدارسه اعلان او تصريح بان العيوب الخلقيه بالمخيخ تؤدى الى صوره معقده من الاعتلال الذهنى بالإضافة الى الاعتلال الحركى.

التوصيات: نحن بحاجه ملحه الى المزيد من الأبحاث فى المستقبل للتأكيد على دور المخيخ فى السلوك والوظائف المعرفيه.

الكلمات الاستفتاحيه: تشوهات تكوين المخيخ– اختبار واكسلر– تقييم الحركه– تقييم السلوك.

Introduction:

The pediatric cerebellum is well known for its motor skills processing, controlling, and modulating movement, lately well known and documented relation- ship between the cerebellum and higher cognitive functions, based on neurological findings,

Anatomical analysis revealed that cognitive symptoms result from lesions of the posterior lobe of the cerebellum, while the vermis was constanly implicated with behavioral- affective problems (Schmahmann JD, Sherman 1998).

Cerebellar malformations may be classified as predominantly involving the cerebellum or involving both the cerebellum and brainstem. Thus, not surprisingly, most cerebellar malformations are associated with neurodevelopmental issues affecting multiple domains: motor, communication, cognition, emotional regulation, and executive function. (Tavano& Borgatti, 2010).

Neuropsychological assessment of patients with cerebellar malformations is challenging due to language and cognitive impairment and sometimes oculo motor apraxia, speech, and that may interfere with administration and interpretation of neuropsychological evaluations of patients specially w ith joubert syndrome (Summers et.al., 2017).

Aims:

The aims of the present study are to study the effect of cerebellar malformations on the proper development of behavior through assessment of the neurobehavioral outcomes and cognitive functions, to assign the neuroimaging findings among children with cerebellar malformations and categorize them, and to correlate the neurological and neuroimaging findings in children with cerebellar malformations.

Methodology:

- Type of the study: Cross section explorative study.
- Patients: Patients were recruited from Neuropeadtric clinic of National Research Centre, (NRC) and Ain Shams university Neuropeadtric clinic, during the period from October 2017 to October 2018.

  Their age at presentation ranged between 4 and 10 years of both sexes. Patients were recruited from the Patients were chosen sequentially according to the following Inclusion criteria:

  1. Age range from (4- 10) years
  2. Patients with cerebellar malformations as cerebellar hypoplasia either vermin and/ or hemispheric hypoplasia
  3. Molar tooth image (MTI) as in Joubert syndrome related disorders, ponto cerebellar hypoplasia, posterior fossae anomalies like Dandy Walker malformations).
  4. Patients with non- progressive cerebellar atrophy assigned from the history and neurological evaluation.
- The study included 60 patients with cerebellar malformation; 31 males and 29 females chosen according to presentation, Full personal and family history, Full medical history including the history of the present illness, course and progression. Development milestones, both motor and cognitive.
- Basic anthropometric measurement (Weight, Height and Head Circumference).

Thorough clinical evaluation including general and neurological examinations. MRI brain was done for all patients as a clue for diagnosis and recruiting them, Scale for the Assessment and Rating of Ataxia (SARA) SARA is a clinical scale developed by Schmitz- Hübsch et.al., (2006) which assesses a range of different impairments in cerebellar ataxia. Psychological Assessment by Child Behavior Checklist (CBCL): The Child Behavior Checklist (CBCL) was a parent- report questionnaire on which the child was rated on various behavioral and emotional problems. (Achenbach and Rescorla, 2001). followed by assessment of cognitive The Wechsler Intelligence Scale for Children (WISC): developed by David Wechsler, is an individually administered test for children between the ages of 6 and 16. The Fifth Edition Arabic Version (WISC- V; Wechsler, 2014), Finally quality of life was evaluated by World Health Organization Quality of Life (WHOQOL- BREF): a shorter version of the widely used QOL assessment instrument that comprises 26 items in the domains of physical health, psychological health, social relationships, The 4 domains are physi- cal health, psychological health, social relationships, and environment (WHOQOL Group 1998).

Statistical Analysis:

Quantitative data were statistically represented in terms mean and standard division (SD). And using One Sample T- Test to compare each group with the certain value.

Qualitative data were statistically represented in terms number and percent. Comparison between difference groups in the presents study was done using Crosstabs with Chi- Square Test with Risk Estimate and Symmetric Measures.

A probability value p- value less than or equal to 0.05 was considered significant.

All statistical calculations were done using computer program Statistical Package for Social Science (SPSS) version (16.0).

Research Ethical Considerations:

The study proposal was approved by the scientific ethical committee of the Faculty of Postgraduate Childhood Studies and the local ethical committee of the Faculty of the National Research center, and it was conducted according to the guidelines of Helsinki, the guidelines for the Ethical Conduct of Medical Research involving children, revised by the Royal College of Pediatrics and Child Health: Ethics Advisory Committee.

Results:

We assigned 60 patients who met our selection criteria of having cerebellar malformations between 2017 and 2018, type of our study Cross section explorative study.

The studied patients were classified according to MRI (conventional MRI technique) finding into five heterogenous groups their percentage; Molar tooth image (MTI) (48.3%), Cerebellar hypoplasia (25%), Pontocerebellar hypoplasia (PCH) (11.7%), Complete vermin hypoplasia

(CVH) (10%) and Dandy walker malformation (DWM) (5%).

IQ assessment was done for our studied group using wecshler scoring and found a score of WAIS- IV FSIQ of 57 in all patients- except those with DWM- would typically reflect extremely Impaired Intellectual Functioning. Most of our studied group exhibit an extremely low full scale IQ category (40%), followed by 12% showing very low category.

Quality of life (QOL) Our patients had assessment of QOL using WHOQOL score (WHOQOL Group 1998), and demonstrated that the greater percentage rated very poor 40%, neither poor nor good 28.3%, poor 20%, good 11.7%.

Table (1) Percentage of each catogrey of the studied patients according MRI finding.

		No.= 60
Mri Finding	MTI	29 (48.3%)
	CBH	15 (25%)
	CVH	6 (10%)
	PCH	7 (11.7%)
	DWM	3 (5%)
Mri Severity Score	Mean±SD	3.17 ± 1.24
	Range	0- 5

Table (2)

Wecshler I Q		No.= 60
FSIQ	Mean ± SD	57.56 ± 17.91
	Range	25- 99
Fsiq Category	Average	4 (7.0%)
	Low Average	1 (1.8%)
	Very Low	12 (21.1%)
	Extremely Low	40 (70.2%)
Verbal IQ	Mean ± SD	62.81 ± 19.01
	Range	30- 105
Verbal Iq Category	Average	5 (8.8%)
	Low Average	7 (12.3%)
	Very Low	3 (5.3%)
	Extremely Low	42 (73.7%)
Performance IQ	Mean ± SD	56.25 ± 18.26
	Range	20- 95
Performance Iq Category	Average	1 (1.8%)
	Low Average	6 (10.5%)
	Very Low	9 (15.8%)
	Extremely Low	41 (71.9%)

Table (2): IQ varied between between average, low average, very low and extremely low, majority of our patients were in the range of extremely low. IQ ranges from 25- 99, Mean was 57.7, Cases with intellectual disability represented 90%.

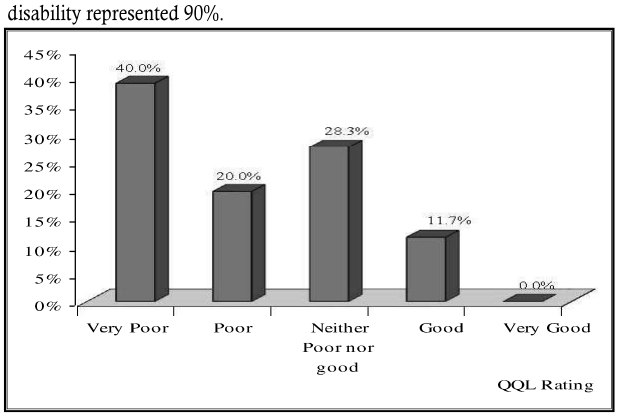

Figure (3) Patients QOL Ranking scores, as regards the degree of Rating.

Discussion:

The average sample size of this study, coupled with comprehensive clinical evaluations and neuroimaging correlatioms, allowed us to define the spectrum of neurobehavioral disorgers linked to cerebellar malformations patients. In the present study Delayed speech was evident in whole studied patients as the mean age at first spoken word was 4.07± 1.86 years and this was a little bit later than that found by Summers et.al., 2017 whose patients began walking at 2.6± 1.3 years.

Motor evaluation using the SARA score clarified that our patients had affected motor functions; with range of 10- 39 and a mean±SD 25.95± 7.53.

All parameters of the SARA score were highly correlated with the cerebellar malformations reflecting its major role in motor functions, except the stance.

Hypertonia also was expressed in 7% of our studied group and this is a lower percentage that was found by Wassmer et.al., 2003 whose percentage was 58% of patients and also comes in agreement of Stefan et.al., 2015 whose patients suffered from hypertonia (n= 6) out of 47 total patients.

Behavior of our studied patients was assessed using CBCL and a mean score of 50±10 is considered normal. Most patients were found anxious(mean of 80.63± 15.15)and had behavioral withdrawal (mean of 80.25± 14.21) and these were clinically significant. Also there was a highly significant correlation between these two behavioral scores and radiologic cerebellar malformation especially with all patients with complete vermin hypoplasia and most patients with joubert syndrome, cerebellar hypoplasia and PCH and this comes in agreement with Villanueva (2012) who had highlighted that cerebellar defects might underlie some of the symptoms in subgroups of patients diagnosed with neurodevelopmental disorders like autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), and schizophrenia.

IQ assessment was done for our studied patients using WAIS- IV FSIQ of 57 in all patients- except those with DWM- would typically reflect extremely Impaired Intellectual Functioning. Most of our studied patients exhibit an extremely low full scale IQ category (40%), followed by 12% showing very low category, similarly their verbal and performance IQ are falling between the very low to extremely low category, except the DWM that showed average intelligence. Interestingly the three IQ categories showed highly significant correlation with the neuroradiologic cerebellar malformations

Quality of life (QOL) Our patients had assessment of QOL using WHOQOL score and demonstrated that the greater percentage rated very poor (40%), neither poor nor good (28.3%), poor (20%), good (11.7%). while patient satisfaction ranged from very dissatisfied (38.3%) to satisfied (13.3%) with dissatisfied (20%) and neither nor (28.3%) in between.

Conclusion:

The cerebellum is finally given the spotlight it deserves, as traditionally the cerebellum has been recognized as a motor organ dominator but our

findings highlight that children with cerebellar malformations experience high prevalence of neurological Cogntive, behavioural in addition to motor impairment as well as poor quality of life due to functional disabilities.

Recommendations:

Further long term studies need to be done to confirm role of cerebellum in higher orders functions. More advanced neuroimaging techniques like (FMRI, PET studies). are needed to demonstrate the cerebellar topography to understand cerebellum engagement in cognition, emotions and behavior. More standardized tests For ASDs are needed to measure and study the relation of the cerebellum malformations with autistic features.

References:

1. Achenbach TM, Rescorla LA. (2001): Manual for the ASEBA school-age forms& profiles. Burlington: Research entre for Children, Youth and Families, University of Vermont, **Psychology**, Vol. 7 No. 9
2. Schmahmann JD, Sherman JC (1998): The cerebellar cognitive affective syndrome. **Brain**. 1998; 121: 561- 79.
3. Tavano, A.& Borgatti, R. (2010): Evidence for a link among cognition, lang- uage and emotion in cerebellar malformations. **Cortex**, 46(7), 907- 918.
4. Stefan G, Katharina K, Thomas K, Joerg W, Giles H Vince (2015): Behavioral disorders and cognitive impairment associated with cerebellar lesions. **Journal of Molecular Psychiatry** (2015) 3: 5
5. Wechsler, D. (2014b): **Wechsler intelligence scale for children- fifth edition technical and interpretive manual**. San Antonio, TX: NCS Pearson.
6. WHOQOL Group (1998): The World Health Organization Quality of Life Assessment (WHOQOL): Development and general psychometric properties. **Social Science and Medicine** (in the press)
7. Summers C, Snow G, Wiggs E, liu A, Toro C, Poretti A, Zein W, Brooks B, Parisi M, Inati S, Doherty D, Vemulapalli M,. Mullikin J, Vilboux T, Gahl W, Aygun M. (2017): Neuropsychological phenotypes of 76 individuals with Joubert syndrome evaluated at a single center. **Amercian journal of human genetics**. DOI: 10.1002/ajmg. a. 38272
8. Villanueva R. (2012): **The Cerebellum and neuropsychiatric disorders** Volume 26, Issue 3, Pages 317- 329.
9. Wassmer E, Davies P, Whitehouse WP, Green SH, (2003): Clinical spectrum associated with cerebellar hypoplasia. **Pediatr Neurol** 2003; 28: 347- 51.