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Original article

EXPLORING THE POTENTIAL ASSOCIATION BETWEEN DANDY WALKER SYNDROME AND ADIE'S PUPIL: A COMPREHENSIVE CASE STUDY AND SYSTEMATIC LITERATURE REVIEW

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ABSTRACT

The purpose of this case report and literature review is to describe a case of Adie's pupil associated with variant Dandy-Walker complex (DWC) and to review the literature on the ocular manifestations of Dandy-Walker syndrome and variant Dandy-Walker syndrome. A literature search was conducted using the Pubmed database following the PRISMA guidelines. Inclusion criteria were radiologically confirmed Dandy Walker or Dandy Walker variant patients with ocular anatomical and functional anomalies. Overall, 48 studies met the inclusion criteria for this review, with a total of 634 patients diagnosed with Dandy-Walker syndrome and variant Dandy-Walker syndrome exhibiting a wide range of ocular manifestations. Microphthalmia was the most frequently reported abnormality, while megalocornea was less frequently reported. Of the 48 studies included, only one reported a case of Adie's pupil associated with variant Dandy-Walker complex, as presented in the case report. Ocular involvement in patients with Dandy-Walker syndrome and variant Dandy-Walker syndrome is rare. The authors present a case of variant Dandy-Walker complex associated with Adie's pupil, which has not been reported in the literature previously. The literature review confirms that ocular manifestations are rare but can occur in patients with Dandy-Walker syndrome and variant Dandy-Walker syndrome. Therefore, it is important for clinicians to evaluate patients with these malformations for possible ocular involvement.

1. Introduction

Dandy-Walker complex (DWC) is a rare congenital malformation of the posterior cranial fossa that occurs during embryonic development of the cerebellum and fourth ventricle. It is estimated to affect 1 in 25,000 to 30,000 newborns [1]. Traditionally, posterior fossa malformations have been classified into classic Dandy-Walker, variant Dandy-Walker (VDW), and megacisterna magna malformations.

The classic Dandy-Walker malformation is characterized by anatomic and neuroimaging findings, such as complete or partial agenesis of the cerebellar vermis, cystic dilatation of the fourth ventricle, and enlarged posterior fossa. Other occasionally associated features include displacement or elevation of the tentorium of the cerebellum, atrophy and occlusion of the foramina of Magendie and Luscka, and hydrocephalus [2]. VDW includes hypogenesis of the cerebellar worm to a lesser degree than the Dandy-Walker syndrome and cystic dilation of the fourth ventricle with a normal posterior cranial fossa.

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Symptoms begin to appear in early childhood, including macrocephaly, spastic paraparesis and hypotonia, intellectual disability, and, less commonly, cranial nerve palsies, ataxia, and strabismus. Dandy-Walker syndrome has been associated with some cerebral malformations, such as agenesis of the corpus callosum, rachischisis, ectopic brain or cerebellar tissue, and cardiovascular, urogenital, and gastrointestinal malformations [3].

Some genetic syndromes and chromosomal abnormalities have been linked to DWC, such as syndrome 3q (genes ZIC1 and ZIC4), trisomy 18, and 6p25 deletion syndrome, characterized by various abnormalities, including anterior ocular segment dysgenesis resembling Axenfeld-Rieger syndrome (ARS), hypertelorism, palpebral, flat nasal bridge, dental abnormalities, congenital heart disease, hearing loss, and the development of intellectual disability [4].

Although several evidences of ocular involvement are reported in the literature, there are few reports of ocular involvement in variant Dandy-Walker syndrome. In our case report, we present a case of variant Dandy-Walker complex associated with Adie's pupil, and we review the literature on the association between the syndrome and other ocular manifestations.

Case Report

A 3-year-old female patient was evaluated for the onset of blurred vision and persistent anisocoria. The patient was born to non-consanguineous parents after an uncomplicated spontaneous birth. Motor developmental milestones were appropriate, while cognitive development was delayed, particularly in the speech areas. The patient had poor vocabulary speech, with fewer than 20 spoken words by age 3 years.

Physical examination revealed no notable changes, except for the presence of anisocoria with the left pupil poorly reactive to light and decreased photomotor effect, which configured as Adie's pupil. An ophthalmological examination revealed hyperopia with accommodative paresis, and vision was preserved in all visual fields. To assess the neurological functional integrity of the visual system, visual evoked potentials were performed, which showed a slight increase in latency times and hypovoltage.

MRI of the brain showed dilatation of the foramen of Magendie with enlargement of the fourth ventricle and subtentorial periencephalic cerebrospinal fluid (CSF) spaces. Additionally, the vermis and cerebellar hemispheres were hypoplastic, consistent with a variant of Dandy Walker syndrome (Figure 1).

Exome sequencing was performed, which identified a mutation of the FOXC1 gene on chromosome 6. The mutation was determined to be a partial loss of function mutation.

Figure 1. 3-year-old patient with VDW and Adie's pupil

2. Methods

A comprehensive literature search was conducted using Pubmed as the database, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (see Figure 2).

The search terms included "eyes," "dandy walker," "dandy walker variant," and "Adie's pupil." Only articles available in the English language were considered. Inclusion criteria were patients with a radiologically confirmed diagnosis of Dandy Walker or Dandy Walker variant, who presented with ocular anatomical and functional anomalies.

Exclusion criteria encompassed articles reporting on patients with Dandy Walker Syndrome without ocular manifestations or patients with ocular involvement where Dandy Walker complex was not clearly defined by radiological diagnosis, as well as patients whose ocular manifestations were the consequence of secondary alterations.

A PRISMA flowchart was used to document the systematic search strategy for assessing the association between Dandy Walker malformation-variant and ocular malformations. The PRISMA model was updated in line with the Creative Commons Attribution License, based on the PRISMA 2020 statement published by Page et al. in BMJ Extension in 2021 (372:n71).

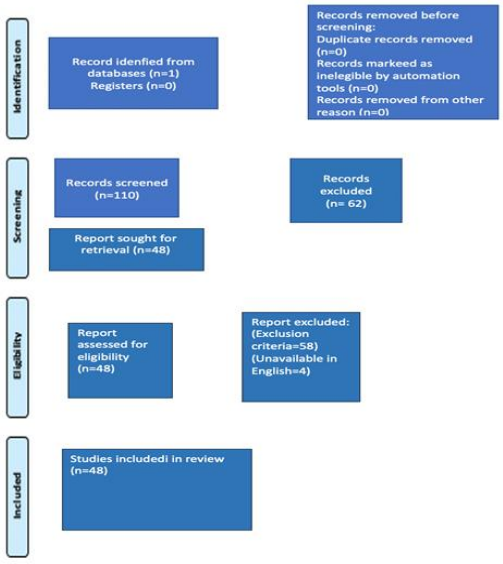

Figure 2. PRISMA flowchart of systematic search strategy for patients with eye abnormalities and dandy walker malformation. Data added to the PRISMA template (from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CT, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.) under the terms of the Creative Commons Attribution License.

3. Results

A total of 110 articles were initially identified through a systematic search of the PubMed electronic database, of which 48 studies met the inclusion criteria for this review (Table 1).

Patients diagnosed with Dandy-Walker syndrome (DWS) and Dandy-Walker variant (DWV) exhibited a wide range of ocular manifestations. Microphthalmia was the most frequently reported abnormality, occurring in approximately 33.3% of cases, while megalocornea was less frequently reported (5%).

Authors & Year	*Study Type*	*Ocular Manifestations*	*Brain Imaging Findings*
Stambolliu E. et al. *2017*	Systematic review	congenital cataract	DW
Singh Charan G. et al. *2021*	Case report	congenital cataracts variant, sclerocornea, iris coloboma	DW
Battaglia Parodi M. et al. *2020*	Case report	Nummular macular retinal depigmentation	DW
A Osman Saatci et al. *2008*	Case report	unilateral orbital cyst (Delleman–Oorthuys syndrome-oculocerebrocutaneous syndrome)	DW variant
Ebrahimiadib N. et al *2017*	Case report	Foveal hypoplasia	DW
Rusu I. et al *2016*	Case report	Strabismus, pathologic myopia measuring, chorioretinal atrophy, pigment mottling in the macula, retinal capillary nonperfusion	DW variant
Young B. et al *2017*	Case report	Salzmann's nodular degeneration (idiopathic corneal degeneration)	DW variant
Srirampur A. et al. *2019*	Case report	Ligneous conjunctivitis	DW
Tranos P. et al. *2016*	Case report	bilateral cystoid macular edema	DW
March W.F. et al. *1974*	Case report	Sclerocornea	DW
Vohra N. et al *1993*	Case report	microphthalmia congenital cataracts ocular colobomas	DW
Poetke M. et al *2002*	retrospective literature review	colobomas optic nerve atrophy, microphthalmos,cryptophthalmus Exophthalmos, glaucoma (PHACE Syndrome)	DW
Aymé S. et al *1989*	case series	retinal dyaplasia abnormal cornea (Fryns Syndrome)	DW
Simsek T. et al. *2010*	case series	retinitis pigmentosa (Uscher syndrome)	DW variant
Kosolapova N.V. et al. 2015	case report	choroidal colobomas, Jeune syndrome	DW
Donahue M.L. et al. *1995*	case report	microphthalmia Interstitial deletion of 8 chromosome	DW variant
Chance P.F. et al. *1999*	review of letterature	Retinopathy Cerebello-oculo-Renal syindrome (Arima syndrome)	DW
Beby F. et al. *2012*	case report	optic disc coloboma (Chromosome 6p25 deletion syndrome)	DW
Ewald O. et al. *2006*	case report	megalocornea	DW
De Crecchio G. et al. *2013*	case series	pathological myopia, posterior staphyloma, vitreal membranes with fenestrations	DW variant
Dobyns W.B. et al. *1989*	review of letterature	Microphthalmia, ocular colobomas, congenital cataracts (Walker-Warburg syndrome)	DW
Lin R.J. et al. *2005*	case series	hyperopia with exotropia ectopic left pupil; Axenfeld anomaly (Terminal Deletion of 6p)	DW DW variant
Nabhan M.M. et al *2017*	case series	Microphthalmia (Walker-Warburg syndrome)	DW
Delahaye A. et al *2012*	case series	Axenfeld–Rieger anomaly glaucoma Corectopia Enophthalmos, hyperopia (6p25 Deletions)	DW
Steiner J.E. et al *2018*	letterature review	posterior staphyloma microphthalmia hypoplasia of the optic nerve(s) or chiasm (PHACE syndrome)	DW
Cursiefen C et al *2000*	Case report	microphthalmus, cloudy cornea,retinal dysplasia (Fryns syndrome)	DW
Schoner K et al *2013*	Case series	anisophthalmia, microphthalmia corneal thinning, iridal fibers adherent to the central cornea, and protrusion of the lens into the anterior chamber (Peters' anomaly)	DW
Caruso P.A. et al *2004*	Case series	Cataract (Smith-Lemli-Opitz syndrome)	DW variant
Boycott et al *2007*	Case series	optic nerve retinal colobomas (Meckel Syndrome)	DW
Chemke J. et al *1975*	Case series	corneal opacities, cataracts	DW
Van Maldergem L. et al *2008*	Case series	corneal dystrophy	DW
Assari R. et al *2017*	Case report	esotropia, hypotropia,abnormal eye movements(PHACE)	DW
Ballarati L. et al *2007*	Case sieries	microphthalmos,coloboma hypoplasia of the optic nerve	DW
Castroviejo P. et al *2005*	Case series	microphthalmia anophthalmia Delleman syndrome	DW
de Azevedo Moreira L.M. et al *2005*	Case report	microcornea, corneal opacity partial trisomy 3q	DW
Pira-Paredes S.M. et al *2017*	Case series	megalocornea Ritscher-Schinzel syndrome	DW
Sakurai E. et al *1996*	Case report	coloboma. microphthalmos sclerocornea	DW
Pagon R.A. et al *1983*	Case report	microphthalmos, megalocornea, Peter anomaly, cataract coloboma, (Warburg syndrome)	DW
Shapiro I. et al *1992*	Case report	cataract Neu-Laxova Syndrome	DW
Pavone L. et al *1986*	Case report	shortened anterior chamber Cataracts	DW
Saatci I. et al *1998*	Case report	microphthalmia, retro-ocular cyst	DW
Frieden I.J. et al *1996*	Case report	Congenital cataract Phace syndrome	DW
Lerone M. et al *1992*	Case report	nystagmus, cataract Oculocerebral syndrome	DW
Balci S. et al *2002*	Case report	megalocornea MMMM syndrome (Neuhäuser syndrome)	DW variant
Charan G.S. et al *2021*	Case report	microphthalmos, congenital cataracts, iris coloboma, sclerocornea	DW variant
Saatci A.O. et al *2008*	Case report	orbital cyst Delleman-Oorthuys syndrome	DW variant
Rusu I. et al *2006*	Case report	severe myopia, tilted optic disks with peripapillary atrophy	DW variant
De Crecchio G. et al *2013*	Case report	pathological myopia, anomalous vitreal fenestrated membranes	DW variant

Table 1. Selected studies of patients with DWS or variant DWS and ocular manifestations

Of the 48 studies included in the quantitative analysis, a total of 55 patients with documented cases of DW and DWV were included. The mean age of the patients was 8.66 years (range 0.25-36 years), with 38 out of 55 patients (69%) being male. DWS was reported in the majority of cases (76%), while DWV was less common (24%). Pathological myopia was the most significant association observed in DWV (42%), followed by congenital cataract (26%), orbital cysts (15%), megalocornea (7%), coloboma (5%), and retinal depigmentation (5%). None of the examined patients exhibited alterations in the autonomic nervous system, which regulates pupillary motility (Table 2 and Figure 3).

Syndrome	Chromosome/gene
Phace	1 q32.1,
Phace	3 q26.32
Phace	3 p11.1,
Phace	10 q24.32
Fryns	15 q26.2 microdeletions
Usher	1 q32-q41
jeune	18 deletion
microphthalmia	8 deletion
Arima	13 q14.13-q32.3
coloboma	6 p25 deletion
Walker-warburg	1p32-p34.
hyperopia with exotropia	6 deletion
Axenfeld–Rieger anomaly ,glaucoma ,Corectopia	6 p25 deletion
Smith-Lemli-Optiz	11 q13
Microcornea, cornal opacity	3 q partial trisomy
Ritscher-Schinzel syndrome	6p Subtelomeric deletions
Warburg	2 microdeletion
Neu-laxova	9 missense mutation
Neuhäuser syndrome	x linked mutation
Delleman-Oorthuys	x-linked mutation

Table 2. Gene/Chromosome and related syndromes mainly involved in DWC/Adie's pupil

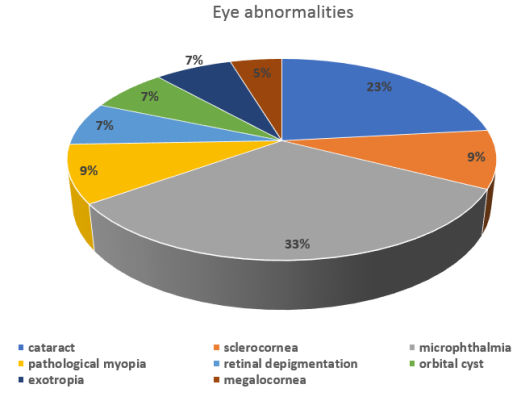

Figure 3. Frequency of ocular anomalies in the Dandy Walker Malformation.

Association between ocular malformations and DWS/DWV was observed in some genetic conditions. In particular, the association between hemangiomas, ocular malformations, and malformations in different organs and anomalies of the posterior cranial fossa in PHACE syndrome was observed in 11% of cases.

The presence of congenital cataract, microphthalmia, and coloboma in patients with DWS (8% of cases) was related to Walker Warburg syndrome. Some aneuploidies, including the deletion of chromosome 6, which is associated with coloboma and microphthalmia, and trisomy of chromosome 3, mainly associated with congenital cataract, were found to be associated with Dandy Walker complex.

Less frequent evidence of ocular malformations was observed in association with DWS/DWV and Usher syndrome, Fryns syndrome, Smith-Lemli-Opitz syndrome, Delleman syndrome, Neuhäuser syndrome, and Neu-Laxova Syndrome.

4. Discussion

Dandy-Walker Syndrome (DWS) is often associated with various comorbidities. According to the literature, there is a significant association between DWS and intellectual disability, learning disabilities, and behavioral disorders, as well as diseases of the circulatory system (such as patent ductus arteriosus, aortic coarctation, ventricular septal defect, and atrial septal defect), skin disorders including neurocutaneous melanosis and hemangiomas, and associations with renal malformations, hypoplastic genitalia, and cryptorchidism.

In contrast to the findings of our systematic review, which suggest that microphthalmia (33%) is the predominant ocular manifestation in DWS, with congenital cataract being the second most common ocular manifestation (23%), Emelina Stambolliu et al. described a different relationship between DWS and eye diseases. In their study, the main manifestation was cataract (20% of cases), followed by microphthalmia (11% of cases), chorioretinal dysplasia atrophy (11.1%), corneal opacity, and myopia (11%)[6].

Ocular abnormalities have been found in patients with chromosomal abnormalities or genetic syndromes, particularly in those with PHACE syndrome, where ocular anomalies and defects of the posterior cranial fossa are associated with hemangiomas, arterial anomalies, cardiac defects, sternal cleft, and supraumbilical raphe syndrome[7-8]. The association between DWS and ocular abnormalities is also frequently described in patients with Walker-Warburg syndrome, a rare form of muscular dystrophy characterized by ocular and cerebral anomalies. In 20% of cases, this syndrome is caused by mutations of the POMT and FKRP genes[9]. The main ocular manifestations described in association with anomalies of the posterior cranial fossa in this syndrome are coloboma, microphthalmia, and congenital cataract.

Chromosome 6 and chromosome 3 are the chromosomes mainly involved in the association between ocular manifestations and DWS[10]. In particular, an association was found between the deletion of chromosome 6 (FOXC1 gene) in patients with radiologically proven DWS/DWV and severe ocular refractive defects (hyperopia with esotropia), coloboma, and congenital glaucoma[11-12].

Ocular abnormalities were also associated with partial trisomy 3q in a two-month-old baby girl with dysmorphic features of the Dup3q phenotype and severe ocular and cerebellar malformations. Lília Maria de Azevedo Moreira et al. described the association between bilateral microphthalmia, microcornea, and corneal opacities in a patient with posterior fossa anomalies, including cerebellar vermis hypoplasia suggestive of Dandy-Walker Syndrome. This patient presented intrachromosomal duplication of distal 3q[13].

Rare pathologies characterized by ocular anomalies can occur in patients with impaired development of the posterior cranial fossa, such as Usher syndrome[14]. This syndrome is characterized by blindness resulting from retinitis pigmentosa (genes involved: MYO7A, USH1C, CDH23, PCDH15, USH1G, locus USH1E, USH2A, GPR98, and DFNB31 CLRN). Primarily neurological disorders, in which DWS/DWV is frequently reported, such as Boucher-Neuhäuser syndrome or Delleman syndrome, manifest ocular abnormalities in their pathological spectrum[15-16].

5. Conclusions

This review highlights the frequent association between classic Dandy-Walker syndrome/variant Dandy-Walker syndrome and ocular anomalies, summarizing the main reported alterations and their relative frequency. Our clinical case, which describes the first association of posterior fossa defects with disorders of the autonomic nervous system that regulates pupillary motility in a girl with variant Dandy-Walker syndrome and Adie's pupil, is the first of its kind in the literature.

In light of this review, we recommend that brain magnetic resonance imaging be performed on patients with ocular anomalies such as microphthalmia, congenital cataract, sclerocornea, and megalcornea, in order to search for malformations of the posterior cranial fossa. It is also advisable to pay close attention to possible ocular anomalies in patients with posterior cranial fossa defects detected by radiological investigations. These recommendations will aid in the diagnostic management of patients and improve their overall care.

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