

A Review of Infantile Vanishing White Matter Disease and A New Mutation

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INTRODUCTION

Vanishing white matter disease (VWM) also called childhood ataxia with central hypomyelination or eukaryotic initiation factor 2B (eIF2B)-related disorder, is an autosomal recessive leukoencephalopathy. The course is progressive with additional stress-provoked episodes of rapid deterioration. VWM is caused by mutations in the genes EIF2B1–5 encoding the subunits of eIF2B. eIF2B is indispensable for translation initiation and regulation of protein synthesis under different conditions, including cell stress⁽¹⁾.

Characteristic neuropathologic findings include a marked decrease in volume of white matter, diffuse loss of myelin fibers, dysmorphic astrocytes and cystic degeneration of white matter^(2,3). Astrocytic dysfunction constitutes the basis of VWM pathology⁽⁴⁾.

VWM phenotypes may range from a congenital form to a infantile form (onset age 1 year), an early childhood onset form (onset age 2-4 years), a late childhood/juvenile onset form (onset age 5-15 years), and an adult onset form (onset age >15years)⁽⁵⁾. Clinical symptoms and diseases severity are correlated with age at disease onset. The risk of rapid disease evolution and death is higher in the group with the youngest age at disease onset and lower in the group with the oldest age at disease onset⁽⁶⁾.

The disease was formerly known as a disease of young

children. VWM exists with cerebellar ataxia and less prominent spasticity. Stresses act as provoking factors with respect to the onset of the disease and to the episodes of major and rapid neurologic deterioration, which typically characterize the clinical course. Out of these events, the disease runs a slowly progressive course and is eventually fatal⁽³⁾. VWM has a wider clinical spectrum. Milder variants have been reported with onset in adolescence and adulthood. The initial clinical signs in adults consist of seizures, spasticity, cerebellar syndrome, dementia, depression, psychosis, and manifestations of ovarian failure⁽⁷⁾. VWM occurring in association with primary ovarian failure is described as ovarioleukodystrophy⁽⁸⁾.

VWM may also have a severe infantile or antenatal onset. Prenatal forms of disease are defined by reduced fetal movements, oligohydramnios, primary microcephaly, growth failure, congenital contractures, hepatosplenomegaly, renal hypoplasia, cataracts, pancreatitis, in addition to ovarian dysgenesis and leukoencephalopathy⁽⁹⁾.

Two brothers are presented here whose diseases symptoms appeared in early infantile period with strabismus. The index case had been found novel heterozygous mutation in the gene *EIF2B5*. In addition the relevant literature for individuals with infantile vanishing white matter disease (single case reports to case series) had been reviewed. The aim of this article is to highlight

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the features of the infantile form of the disease and to alert physicians to consider this entity when caring for children presenting with similar cases.

METHODS

Patient Description

Case 1 (index case)

A three and half-month-old boy was evaluated for strabismus. His right eye had inward deviation since two months of age. He was the second child of healthy and nonconsanguineous parents and was born at 37 weeks of gestation. His birth weight was 2.600 g. The pregnancy and delivery were uneventful. He stayed two days in hospital for meconium aspiration. In the early infantile period, his developmental milestones were within normal limits. He had an elder brother who died of a progressive neurological disease. Physical examination on admission showed his weight was 6.8 kg (%50-75), length was 60 cm (%25-50), and head circumference was 41.3 cm (%75-90). Bilateral inward deviation of eyes was noticed. Deep tendon reflexes were absent. The other neurological findings were normal. Routine laboratory examination gave normal results. He died at 6 months old with respiratory insufficiency and hypersomnia.

The laboratory information of Case 1

Lactate: 1.15mmol/L, creatine kinase: 642 u/L (N:30-200). Brain magnetic resonance imaging (MRI) disclosed on T2-weighted MR images, the cerebral white matter, including the subcortical arcuate fibers, was hyperintense as were the internal capsule and cavum septum pellucidum (Fig. 1a). Generally thalamus, caudate nucleus, and lentiform nucleus were spared. Less severe signal intensity changes were seen in cerebellar dentate nucleus, posterior of the pons and bulbus. MR spectroscopy from the white matter indicated a minimal increasing in N-acetylaspartate value.

The exons and flanking intronic regions of the *EIF2B5* gene were analyzed by sequence analysis at a genomic level in the patient. The exons 7 and 10 of *EIF2B5* were analyzed by sequence analysis in the father and mother. It was found that the patient was heterozygous for the following two variants in the gene *EIF2B5*: c.956A>G, p.Tyr319Cys and c.1546+1G>T, p.?. The father carries

the c.1546+1G>T, p.? variant. The mother carries the c.956A>G, p.Tyr319Cys variant. Neither variant has been observed in other patients with VWM.

The mutation c.1546+1G>T affects a highly conserved nucleotide in the splice donor site of exon 10 in *EIF2B5* and is expected to affect RNA splicing. The consequences of the splicing defect are however not known and therefore the effect on the protein level is indicated with a question mark (p.?). The net effect is that the mutation reduces the level of full length eIF2B encoding mRNA and protein.

The variant c.956A>G, p.Tyr319Cys affects a highly conserved amino acid up to Baker's yeast (considering 13 species). There is a large physicochemical difference between Tyr and Cys (Grantham distance is 194 [scale from 0-215]). The variant is predicted to affect protein function by SIFT and PolyPhen (as part of the Alamut software).

Case 2

He was the big brother of Case 1. His data performed at outside institutions was reviewed. He was hypotonic since birth. He did not obtain head control and sitting. He laughed at her mother at three months. At the same time strabismus was appeared. His laughing began to decrease at four months. He could not move his hands after four months. Additionally he began to get much sleep after four months. The patient did not react to the sound after 5-6 months. He admitted to hospital at five and half months old for hypersomnia. Percutaneous endoscopic gastrostomy was initiated at 11 months old. Tonic seizures were shown at the last 2-3 months. Optic atrophy was found bilaterally at one year old. He spent his life mostly in hospitals after five and half months old. He died at 14 months old with respiratory insufficiency.

The laboratory information of Case 2

TSH, FT4, folic acid, creatine kinase, tandem mass spectrometry (amino acids and acylcarnitines profile), biotinidase deficiency analysis, urinary cyanide nitroprusside test (cystinuria homocystinuria screening), urinary fast blue B test (methyl malonic aciduria screening), urinary organic acids, urinary reductant substance, NH₃, ASPA gene analysis, EEG were normal. Vit B12: 115 pg/ml (N: 120-505), lactate: 3.9 mmol/L (N: 0.5-2.2). The results before death ALT: 234 u/L (N: 10-40),

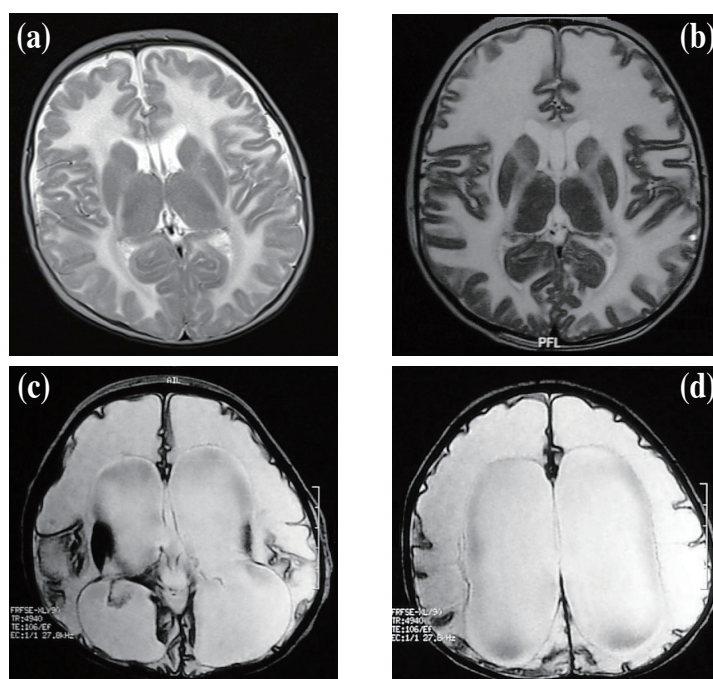


Figure 1. Axial T2-weighted images of the patients. The brain MRI at the ages of 4 months of case 1 shows diffuse bilateral symmetrical hyperintense signal changes of the white matter and prescence of cavum septum pellucidum (a). The brain MRI at the age of 6 months of case 2 at the level of the basal ganglia displays diffuse bilateral symmetrical hyperintensity of the white matter and cavum septum pellucidum (b). Image of case 2 acquired one year old demonstrates enlargement of the white matter lesion with involvement of the thalami and the globus pallidus (c), and the image acquired at the level of centrum semiovale indicates all cerebral white matter has vanish similar to cerebrospinal fluid, just the fluid, the wall of the dilated lateral ventricles and very thin cortex are left (d).

AST: 316 u/L (N: 9–80) (previous results of transaminases were normal), creatine kinase: normal, creatine kinase MB: 265 u/L (N: 0–25). Initial cranial MRI revealed that the cerebral hemispheric WM was symmetrically and generalized abnormal and cavum septum pellucidum. The WM had hypointensity on T1-weighted and hyperintensity on T2-weighted images (Fig. 1b). Subsequent brain MRI showed dilated lateral ventricles, progressive expansion of the white matter lesion with involvement of globus pallidus and the thalami, where the signal intensity of the lesion was the same as that of cerebrospinal fluid (Fig. 1 c-d).

RESULTS

The review of the literature identified 15 previous reports summarizing 20 individuals with infantile VWM ranging from single case reports to case series^(2,6,9-21).

There were two pairs of affected siblings. Clinical, radiological and genetic summaries of the 22 cases including our cases are presented in the Table 1.

There are eight female (36.4%), 14 male (63.6%) patients. The disease appeared in the first 6 months in two girls (25%), in 7–12 months in six girls (75%). The disease appeared in the first 6 months in eight boys (57%), in 7–12 months in six boys (43%).

A total of 15 children died (68.1% of all). Six patients in the one year old (40% of deads), five patients in the two years old, two patients in 3, one patient in 4, and one patient in 10 years old died. Seven patients (male/female 4/3) were alive. Eight cases were dead in six months. Three cases were died in 7–12 months. A hyper acute course was shown in two cases⁽¹²⁾. They died within 10 days of onset of acute neurological symptoms.

Onset of the symptoms was linked to a precipitating factor in 50% of cases. 8 children had suffered from

Table 1. Clinical and genetic evaluation of the infantile VWM patients

Author, Year	Gender/ Age onset (month)	Age exitus (month)	Provocative factors	Initial motor development	Clinical presentation	Clinical course	Last features	Mutated gene in EIF2B	Mutation on genomic DNA	Amino acid change
Francalanci 2001, Fogli 2002 Neurology, Fogli 2004	*F/11	18	URTI	N	Loss motor abilities, irritability	P	Nistagmus, tetraplegia, dystonia, opisthotonus feeding difficulties	<i>EIF2B5</i>	G925C/ G925C homozygous missense	V309L/ V309L
Francalanci 2001, Fogli 2002 Neurology, Fogli 2004	*F/10	13	Infection	N	Loss motor abilities, irritability	RR	NS	<i>EIF2B5</i>	G925C/ G925C homozygous missense	V309L/ V309L
Fogli 2002 Ann Neurology	*F/7	7	Febril illness	Delay	Acute neurological deterioration	Acute P		<i>EIF2B5</i>	G584A/ G584A homozygous missense	R195H/ R195H
Fogli 2002 Ann Neurology	*M/5	5	Febril illness	Delay	Acute neurological deterioration	Acute P		<i>EIF2B5</i>	G584A/ G584A homozygous missense	R195H/ R195H
Fogli 2002 Ann Neurology	F/4	14	NS	Delay	Developmental delay	P	Decerebrate, nonresponsive state	<i>EIF2B5</i>	G584A/ G584A homozygous missense	R195H/ R195H
Rosemberg 2002	F/7	Alive	NS	N	Loss motor abilities, irritability	P	Hypertonia, optic atrophy, microcephaly	Not done		
van der Knaap 2003	M/5	7	Vaccination, URTI	NS	Developmental delay, hypotonia	P	Hypertonia, coma, respiratory insufficiency	<i>EIF2B5</i>	1289T-A 1340C-T heterozygous	V430A S447L
van der Knaap 2003	M/6	9	Febril illness	NS	Hypotonia, loss of head control	NS	Coma, irregular breathing episodes	<i>EIF2B5</i>	1484A-G homozygous	Y495C
van der Knaap 2003	M/4,5	25	Infections	NS	Chronic and episodic neurological deterioration	P, RR	Hypotonia, cerebellar ataxia, coma	A mutation was not found		
Fogli 2004	M/10	12 ?	NS	Delay	Motor signs	P	NS	<i>EIF2B5</i>	C967T/ C1280T	P323S/ P427L
Fogli 2004	F/10	9.8 years ?	NS	Delay	Motor signs	P	NS	<i>EIF2B5</i>	T166G/ G944A	F56V/ R315H
Alsalem 2012	F/10	Alive	NS	Poor feeding	Failure to thrive, hypotonia	NS	NS	<i>EIF2B2</i>	c.803G> A homozygous missense	p.C268Y. NM_ 014239.3
Unal 2012	M/10	Alive	Infection, vaccination	Poor weight gain, hypotonia	Hypotonia, weakness	P, RR	Developmental delay, hypotonia, weakness, ptosis	<i>EIF2B2</i>	c.817A>C c.939_948del heterozygous	p.Lys273 Gln p.Asp314 ProfsX23
Shimada 2012, Hata 2014	M/10	4 years	Gastro- enteritis, bronchitis	N	Convulsion	P	Central apnea, palate movement disorders	<i>EIF2B2</i>	c.254T>A V85E missense	

Table 1. Clinical and genetic evaluation of the infantile VWM patients (continue)

Author, Year	Gender/ Age onset (month)	Age exitus (month)	Provocative factors	Initial motor development	Clinical presentation	Clinical course	Last features	Mutated gene in EIF2B	Mutation on genomic DNA	Amino acid change
Takano 2015	F/4	Alive	Vaccination	Delay	Convulsion	P	Spastic tetraplegia, shallow breathing, feeding difficulty	<i>EIF2B5</i>	c.584G>A c.1223T>C compound heterozygous	R195H I408T
Woody 2015	M/10	Alive	NS	N	Convulsion	P	Fully dependent, optic atrophy, feeding difficulty, hypopituitarism	<i>EIF2B5</i>	241G>A(E81K) Additionally 784G>A(D262N) heterozygous missense	
Shimada 2015	M/8	Alive	Infection	N	Drowsiness, poor sucking	NS	Spasticity, developmental delay	<i>EIF2B2</i>	c.254T>A compound heterozygous	p.V85E
Zhang 2015	M/4	42	NS	Delay	NS	NS	NS	<i>EIF2B4</i>	c.691G>A	p.Gly 231Ser
Zhang 2015	M/7	13	NS	Delay	Convulsion	NS	NS	<i>EIF2B5</i>	c.1340C>T c.1340C>T	p.Ser 447Leu p.Ser 447Leu
Gungor 2015	M/3	Alive	NS	NS	Convulsion	NS	Mental and motor retardation, optic atrophy, cataract	<i>EIF2B4</i>	c.1091G>A (p.R364Q) homozygous	p.Arg 374Cys
Our case	*M/3	14	NS	Delay, hypotonia	Strabismus	P	Optic atrophy, seizure, respiratory insufficiency, hypersomnia	Not done		
Our case Index case	*M/2	6	NS	N	Strabismus	P	Respiratory insufficiency, hypersomnia	<i>EIF2B5</i>	c.956A>G c.1546+1G>T compound heterozygous	p.Tyr 319Cys p.?

*: Familial form. Two affected children in the same family, URTI: Upper respiratory tract infection, N: Normal, NS: Not stated, F: Female, M: Male, P: Progressive, RR: Relapsing remitting,?: Real age of dead is unknown

febrile illness or infections (respiratory, gastroenteritis) before the onset of the disease. Two patients had a history of infection and vaccination before the beginning of the disease. One patient had a history of vaccination also.

Initial motor development was delay in nine patients, hypotonia was reported in two patients, poor weight gain and poor feeding was reported in one patient (totally 50%). The clinical presentation characteristics were as follows. Six of the patient had motor symptoms (loss of abilities).

Five had convulsion. Four had hypotonia. Three had neurological deterioration. Two patients had strabismus.

The illness had a progressive course in 13 patients. Two had progressive and relapsing relapsing course. One had relapsing relapsing course. Last (final) features were found as tetraplegia, dystonia, coma, hypertonia, respiratory insufficiency, hypotonia, nystagmus, optic atrophy, ptosis.

Genetic studies showed that 13 patients (65% of

genetic studies) had *EIF2B5* mutation, 4 cases (20%) had *EIF2B2* mutation, and 2 cases (10%) had *EIF2B4* mutation. Any mutation was not found in one patient (5%). Gen analysis was not performed in two. One patient with *EIF2B2* mutation died at 4 years old (%25), three were alive also. 11 patients with *EIF2B5* mutation died (%85), two patients were alive.

The MR findings can be summarized as follows. The cerebral hemispheric WM is symmetrically and generalized abnormal. The WM had hypointensity on T1-weighted images. The hyperintensity of WM was noticed on T2-weighted images. The cystic degeneration of WM was reported in four patients^(6,18,21). Only two patients with the abnormal white matter have the stripe-like pattern on axial fluid attenuation inversion recovery or sagittal T1-weighted images so typical of VWM⁽⁹⁾.

MR spectroscopy (MRS) had studied in three cases. The Brazilian group reported that MRS using PRESS sequence demonstrated decreased N-acetylaspartate/creatine ratio and normal choline/creatine ratio in the parietooccipital white matter associated with the detection of a lactate peak⁽¹³⁾. A mild decrease in metabolites was found at Unal's study⁽¹⁵⁾. MRS from the white matter indicated a minimal increasing in N-acetylaspartate value in our case.

DISCUSSION

The precise incidence and prevalence of VWM is unknown, but it may be one of the more common leukodystrophies⁽²²⁾. It may affect people of all ages, including neonates and adults⁽³⁾. Infantile form is one of the fewer forms of the VWM. Infantile form constituted 8.2% of the 85 cases with mutation proved VWM. Early childhood form 57.6%, late childhood/juvenile form 29.4%, adult form 4.7% respectively⁽⁶⁾.

In our study sex difference seems an interesting property of infantile VWM. The male/female ratio is 14/8 (1.75). Contrastly, Labauge et al observed thirteen females in the 16 adult-onset patients and verified a statistically significant sex ratio imbalance only in the group with age at disease onset beyond 16 years in the pool of 177 known *EIF2B*-mutated patients⁽⁷⁾. But we do not know the sex ratio of the infantile group in that serie. Larger case series must be studied before it can be concluded that infantile

VWM has sex difference in favor of male patients.

The infantile VWM gives the impression that it begins more early in male patients than female ones. Also van der Lei et al reported that within the entire group of *EIF2B5*-mutated patients (males/females 60/63), differences were found between males and females concerning average age at onset and average age at loss of unsupported walking in the sense that females did better. But there were no differences between males and females in survival. They concluded that females tended to do better than males⁽¹⁾.

Mortality rate of the cases in Table 1 is 68.1% and half of the cases died within one year of onset. Mortality rate and shortness of the onset-death period confirms that death is higher and course is severe in the group with the youngest age at disease onset⁽⁶⁾. Mortality rates according to VWM phenotypes were found in Fogli's serie as; 100% for infantile form, 30.6% for early childhood form, 12% for late childhood/juvenile form, 25% for adult form⁽⁶⁾. Black reported fourteen cases with a leukoencephalopathy that affected native North American Cree and Chippewyan indigenous population infants in northern Quebec and Manitoba in 1988⁽²³⁾. Probably Cree leukoencephalopathy and VWM are the same diseases. Because in three patients of two Cree families, a homozygous missense mutation was found in the *EIF2B5* gene in 2002. A hyper acute course was shown in two cases. They died within 10 days of onset⁽¹²⁾. Cree leukoencephalopathy is a rapidly fatal infantile autosomal recessive leukodystrophy. Median survival from onset to death was 5.5 months. The death happened before 21 months in all cases and the median age at death was 11.0 months⁽²³⁾.

The cases in Table 1 showed that the illness was mostly progressive. But the course may be remitting relapsing character. Progressive course were noticed 63.2% of the cases with early childhood onset form in Fogli's series⁽⁶⁾.

Eleven of the 18 patients in Table 1 with reported history had antecedents (totally 61%). Initial motor development was delay in nine, hypotonia was reported in two patients, poor weight gain and poor feeding was reported in one patient. The most of the patients reported by Black had mild motor delay or hypotonia prior to their neurological deterioration⁽²³⁾. Preillness abnormalities were found 22.4% of the cases with early childhood onset form

in a case serie⁽⁶⁾.

Stress is known to be an onset trigger and/or aggravating factor in VWM cases. The stress shows a wide range of severity from benign fall or head trauma to acute fright, sun bathing, pregnancy, delivery, seizures or infections⁽⁷⁾. During episodes of rapid deterioration hypotonia, irritability, vomiting, and epilepsy ensue or significantly increase. Consciousness is also impaired, ranging from somnolence to unexplained coma, and death may occur⁽³⁾. There were provocative factors at least in half of the infantile VWM cases in the Table 1. Those were mainly reported febrile illness, infections and vaccination. Black reported that there were signs of an infectious illness, usually an infection of upper respiratory tract, at the onset of neurological deterioration in all cases with Cree leukoencephalopathy. Additionally one of her patients received a vaccine prior to deterioration⁽²³⁾.

The loss of abilities, convulsion, hypotonia, neurological deterioration, strabismus were found as mainly clinical presentations respectively in this study. The stupor, limb hypertonia, seizure, eye deviation, hyperventilation were reported as initial presentations in the cases with Cree leukoencephalopathy⁽²³⁾. In all cases in the Fogli's series with an age at disease onset < 2 years, the disease was revealed by motor signs (hypotonia, ataxia, spasticity), which were acute in 60% of cases, often associated with coma or seizures⁽⁶⁾.

The strabismus was the presenting sign of our case and his brother. The strabismus was not stated in the other patients in Table 1. Although eye deviation was reported as initial presentation in 10 of the 11 cases with Cree leukoencephalopathy⁽²¹⁾. The optic atrophy is the most common reported eye related sign^(13,18,21). Four patients in Table 1 had optic atrophy. The other ophthalmological manifestations which may seen in VWM are opsoclonus⁽²⁴⁾ and cataract^(9,21).

The MRI is an effective tool for establishing the diagnosis of the VWM. The MR findings are related with white matter which is diffusely and symmetrically abnormal. Also the common imaging features of infantile VWM seem as diffuse hypointensity on T1-weighted and hyperintensity of WM on T2-weighted images. Only two patients did the MRI display the classic appearance of VWM which had abnormal white matter have the stripe-like pattern on axial FLAIR or sagittal T1-weighted

images⁽⁹⁾. The cystic degeneration of WM was reported in four patients^(6,18,21). Probably in course of time, increasing amounts of WM vanished and were replaced with cerebrospinal fluid; cystic breakdown of the WM is seen on FLAIR or proton density images⁽⁵⁾.

A few biochemical markers have been identified for VWM. However, in view of the high specificity and sensitivity of MRI images, there is restricted need for such biomarkers in MR spectroscopy at common clinical practice⁽³⁾.

Since the five initiative genes were specified in 2001-2002, over 250 patients and 150 mutations have been reported⁽²⁰⁾. The proportions of VWM attributed to mutations *EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, *EIF2B5* were reported as 2%, 13.6%, 9.1%, 10.6%, 64.7% respectively⁽⁵⁾. In this review the mutations of infantile VWM proportions were found as 68.4% for *EIF2B5* mutation, 21% for *EIF2B2* mutation, and 10.5% for *EIF2B4*. The patients with *EIF2B5* mutation had worst prognosis from ones with *EIF2B2* mutation.

The VWM related mutations have been revealed in affected individuals of different ethnic origins such as Chine, European, Turk, Japan, North American Indian^(9,11,15,17,20). Approximately 10% of families with VWM detected by clinical criteria and MRI do not exist an identifiable mutation on sequence analysis of *EIF2B1-EIF2B5*, suggesting the possibility of causative mutations in other genes⁽⁵⁾. Affected individuals are homozygotes or compound heterozygotes for mutations. Approximately 90% are missense mutations most often affecting nonconserved amino acid residues. Frameshifts and nonsense mutations are unusual and have been notified only in the compound-heterozygous state. Heterozygous mutations always affect the same gene^(3,25). A minority of patients with eIF2B-related disorders presents with homozygous mutations in an *EIF2B* gene (28%). The predominance of patients have individual or low incidence mutations in the compound heterozygous state⁽²⁵⁾.

It was stated formerly that the phenotype-genotype correlation was restricted because there was broad phenotypic variability between patients with the same mutations⁽³⁾. But the patients homozygous for p.Arg113His have a milder clinical properties⁽¹⁾. This mutation was not encountered in patients with infantile VWM.

The characteristics of the out cases showed some

differences. The big brother had preillness motor delay and hypotonia, and suffered optic atrophy and seizures. But her life was longer about one year from his brother. These features showed that intra-familial phenotypic heterogeneity might be seen in infantile onset VWM. Intra-familial phenotypic heterogeneity was noticed in cases with childhood onset and adult type formerly. External precipitating factors and/ or other genetic factors may contribute for some of the differences observed^(26, 27).

CONCLUSIONS

Infantile VWM is a grave disease. Half of the patients are dead in two years. The patients may exhibit motor delay, hypotonia in preclinic era. The strabismus may be the presenting sign of the disease. The disease belongs to mostly *EIF2B5* mutations. The disease with *EIF2B2* mutations seems better course than *EIF2B5* mutations.

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