A Twelve-Year Follow Up of a Patient with Van der Knaap Syndrome: Case Report

Van der Knaap Sendromu Tanılı Bir Hastanın 12 Yıllık İzlemi

Mustafa SEÇKİN,[a]
Fazıl GELAL,[b]
Yaprak SEÇİL,[a]
Yeşim BECKMANN[a]

Clinics of
[a]Neurology,
[b]Radiology,
İzmir Katip Çelebi University
Atatürk Training and Research Hospital,
İzmir

Geliş Tarihi/*Received:* 26.03.2013
Kabul Tarihi/*Accepted:* 28.09.2013

Yazışma Adresi/*Correspondence:*
Mustafa SEÇKİN
İzmir Katip Çelebi University
Atatürk Training and Research Hospital,
Clinics of Neurology, İzmir,
TÜRKİYE/TURKEY
seckin.dr@gmail.com

ABSTRACT Van der Knaap Syndrome is a dysmyelinating disease characterized by congenital megalencephalic leukoencephalopathy. We present the clinical and magnetic resonance imaging findings of a female patient with van der Knaap syndrome during 12 years follow up period. The natural history of the disease is discussed in the view of the literature. Our patient represents one of the oldest follow up patients with van der Knaap disease in the literature and one of those who has been followed up for the longest period. The patient had cognitive, pyramidal and cerebellar symptoms in her first presentation. It was striking that clinical findings worsened in the third decade and at the beginning of fourth decade patient suffered from new findings characterized by extrapyramidal symptoms including prominent dystonia in upper extremities and mild choreiform movements in lower extremities. During 12-year follow up worsening of the MRI findings were in correlation with the clinical deteroriation.

Key Words: Magnetic resonance imaging; seizures

ÖZET Van der Knaap sendromu konjenital megalensefalik lökoensefalopati ile karakterize dis miyelinizan bir hastalıktır. Burada, van der Knaap sendromu tanılı bir kadın hastanın 12 yıllık izlemine ait klinik ve manyetik rezonans (MR) bulguları sunulmaktadır. Hastalığın doğal seyri literatür eşliğinde tartışılmıştır. Hastamız, literatürdeki van der Knaap sendromu tanılı hastalar arasında en yaşlı ve en uzun süre takip edilen olgularından birisi olma özelliğini taşımaktadır. Olgumuzda ilk klinik değerlendirme sırasında kognitif, piramidal ve serebellar semptomlar mevcuttu. Olgumuzun üçüncü dekadda klinik bulgularında kötüleşme oldu, dördüncü dekadda ise mevcut bulgulara üst ekstremitelerde belirgin distoni ve alt ekstremitelerde koreiform hareketlerle karakterize yeni ekstrapiramidal semptomlar eklendi. Oniki yıllık izlem sırasında MR bulgularındaki kötüleşme klinik kötüleşme ile koreleydi.

Anahtar Kelimeler: Manyetik rezonans görüntüleme; nöbetler

Turkiye Klinikleri J Case Rep 2013;21(4):193-8

Van der Knaap Syndrome is a dysmyelinating disease characterized by congenital megalencephaly and leukoencephalopathy. Diffuse swollen white matter, spongious changes and subcortical cysts in the anterior temporal region are seen as a result of dysmelinating process early in the course of the disease. The disease is known to have a slow progression.[1] During childhood, motor and intellectual functions remain mostly preserved despite diffuse white matter involvement.[2,3] By aging the disease may progress, however the lack of sufficient number of long follow-up studies prevent a better understanding of the real burden of the disease. In this case study, we presented the natural history including clinical and MRI

findings of a patient with van der Knaap syndrome during a follow up period of twelve-years and showed that despite mild course during childhood and adolescence, the clinical findings worsened in the third decade and the patient became wheelchair-dependent.

CASE REPORT

A female patient presented for the first time in 1997 and then in 2007 and 2009. In her history, she had congenital motor-mental retardation and macrocephaly. Macrocephaly was evident in the first year of life and she was able to walk independently only after she was 2 years old. Her ataxia and difficulty in gait were mild in the childhood, and showed little progression until first visit to our clinic at the age of 19 when she was still able to walk alone. She started to have generalized tonic-clonic epileptic seizures at the age of five without a history of trauma. Seizures repeated in every 5 or 6 months and continued for 2 or 3 years and they were never treated. Then, a seizure free period followed until the first visit.

At the age of 19 in 1997, she presented with a generalized tonic-clonic (GTC) seizure. Neurological examination revealed macrocephaly, mental retardation, mild dysarthria, hyperreflexia, cerebellar ataxia and bilateral positive Babinski sign. In the brain MRI, cerebral white matter was diffusely involved with relative sparing of parietal and occipital lobes. White matter was swollen and showed low signal on T1-weighted images. Frontotemporal involvement was more severe and there was mild atrophy with accompanying subcortical cysts in bilateral anterior temporal lobes which were approximately 2 cm in diameter. Basal ganglia and thalami were spared. Mildly increased signal was noted in both cerebral pedincules, cerebellar white matter and ventral pons, showing lesser degree of involvement (Figure 1). In order to differentiate the disease from metabolic white matter abnormalities, a number of laboratory tests were conducted. Routine blood tests and metabolic screening for 24-hour samples of urine amino acids, mucopolysaccharides and organic acids were normal. Cerebrospinal fluid (CSF) lactate analysis was

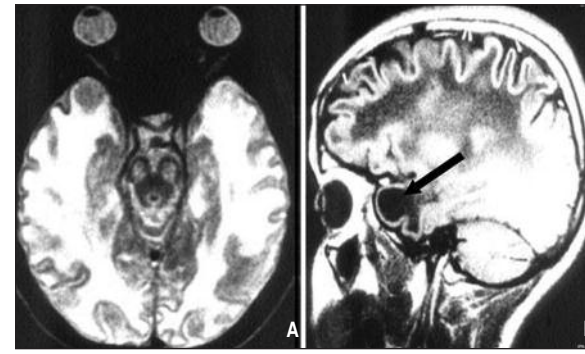

FIGURE 1: The patient with van der Knaap syndrome in the first presentation at 19 years.
A. TSE T2 axial image shows diffusely swollen hyperintense white matter and serebral pedincle involvement.
B. T1-weighted sagittal image shows temporal lobe cyst (arrow), frontoparietal white matter involvement with hypointensity, relative sparing of the parietooccipital white matter.

normal. Based on neurological examination and imaging findings and by the exclusion of metabolic and mitochondrial white matter abnormalities using blood, urine and CSF laboratory tests, she was diagnosed as having van der Knaap disease. She was given antiepileptic drugs (AEDs) but she never used them regularly.

For the next ten years, she had not visited any doctor. Then, she visited our department at the age of twenty-nine years. During this ten-year period without medical attention, her parents reported that her gait and speech worsened slowly but gradually and eventually she became unable to walk. Epileptic seizures were not frequent until 29 years of age when she started to have weekly GTC seizures. In her second visit in 2007, she was awake but had difficulty in cooperation, she had severe dysarthric speech, spastic quadriparesis, trunk ataxia and bilateral extremity ataxia. Babinski sign was bilaterally positive. She had macrocephaly with 63 cm of head circumference. When compared to the initial neurological examination, her ataxia and dysarthria showed severe progression, she became unable to sit and stand alone because of trunk ataxia and her speech became incomprehensible because of dysarthria. She had hyperreflexia and mild spasticity in the first presentation; however, in the second visit she turned out to have severe spasticity with accompanying contractures in the lower extremities. Mood and personality

changes became more evident compared to the initial visit. She became agressive and unable to sleep.

Brain MRI showed no difference when compared to the MRI obtained ten years earlier, other than mild increase in cerebral atrophy and the appearance of tiny frontal subcortical cysts (Figure 2). Diffusion weighted images obtained in 2007, showed increased diffusion in the involved white matter. Magnetic resonance spectroscopy (MRS) revealed inositol peak and a decrease in N-acetile aspartate/Creatine (NAA/Cr) ratio (Figure 3). Routin blood and urine chemistry was normal. The patient was given valproic acid 1000 mg/day for the history of epilepsy and ketiapine 200 mg/day for psychiatric sypmtoms. She had no seizures in the hospitalization period but the other neurological findings continued.

In 2009 at the age of 31, the patient presented for the third time. She still had poor compliance to the medication. Although she had been taking only half dose of recommended AED (Valproic acid 500 mg/day), she had no seizures and her electroencephalogram was normal. Neurological examination revealed little or no change in mental status but more severe spasticity with bilateral clonus in lower extremities. Progression in dysartria and ataxia was evident when compared to the previous examinations. Dysphagia, prominent dystonia in upper extremities and mild choreiform movements in lower extremities were the new findings of the follow-up neurological examination. Her neuropsychiatric sypmtoms continued. The brain MRI, when compared to the one obtained two years earlier, showed minimal increase in diffuse cerebral atrophy and slightly enlarged temporal and frontal subcortical cysts (Figure 4).

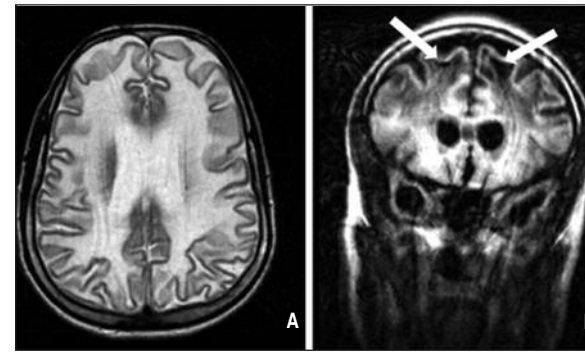

FIGURE 2: Ten years later, at the age of 29 years, brain MRI showed no difference when compared to the previous scan, other than mild increase in cerebral atrophy and the appearance of tiny frontal subcortical cysts (arrows in B). White matter shows diffuse hyperintensity on T2 weighted axial image **(A)**, bilateral temporal cysts persist on coronal FLAIR image **(B)**.

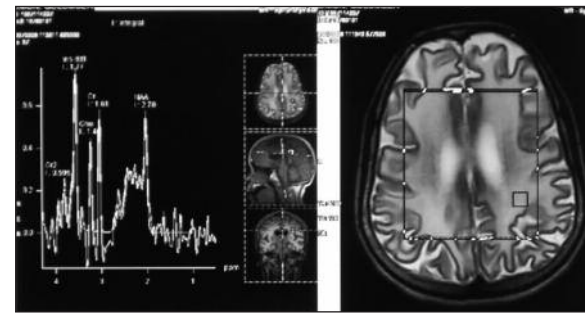

FIGURE 3: MRS, at 29 years of age, shows inositol peak and a decrease in NAA/Cr ratio.

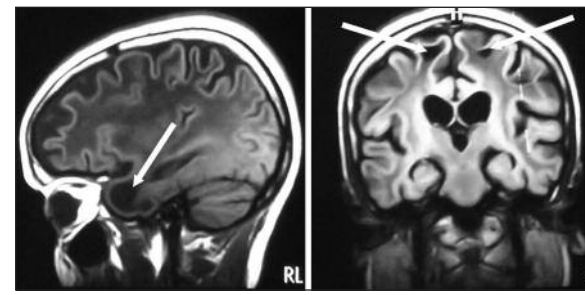

FIGURE 4: MRI, when compared to the one obtained two years earlier, showed minimal increase in diffuse cerebral atrophy and slightly enlarged temporal and frontal subcortical cysts (arrows on A, T1 weighted sagittal and B, FLAIR coronal images).

DISCUSSION

Van der Knaap Syndrome is a slowly progressing disease which is characterized by diffuse leukoencephalopathy and cystic degeneration of the white matter in the brain.[1,2] The presence of cystic degeneration of the white matter can be confirmed by FLAIR and diffusion-weighted imaging.[3] The brain is immature at the time of birth and most of the myelinization process is completed in postnatal 2 years. The negative effects on this process result in dysmyelinating diseases such as Pelizaeus-Merzbacher disease, Alexander disease, Krabbe dis-

ease, Canavan disease and van der Knaap syndrome. Currently no biological markers of van der Knaap syndrome has been shown in urine, blood or CSF. Since patients with van der Knaap syndrome may only present with macrocephaly and minimal or no other neurological findings, the diagnosis is largely based on MRI findings and exclusion of other diseases. Laboratory tests including urine, blood and CSF analysis are necessary to differentiate van der Knaap syndrome from metabolic and mitochondrial diseases. Our patient had macrocephaly within the first year of life and neurological deterioration was slow. She had diffuse cerebral white matter abnormalities and anterior temporal cycts in MRI. Other causes of megalencephaly and dismyelinization were excluded by laboratory tests. The findings were compatible with van der Knaap syndrome diagnostic criteria.[1-5]

Otosomal recessive inheritance is thought to be responsible for the disease.[1] The genetic studies suggest that the gene causing the disease is located on the chromosome 22q and the mutations of MLC1 gene located on this chromosome results in miscoding of the membrane proteins.[6,7] The main pathogenesis of the disease is not known, one of the possibilities suggested is the vacuolisation between myelin lamels, dismyelinisation and enlargement of extracellular space.[1,8]

Knowing the natural history of van der Knaap syndrome is essential for evaluating the clinical course of a patient and to be provident for the possible clinical progression. Natural history of the disease has been identified by some authors via follow-up studies of the patients with van der Knaap syndrome.[9-12] In this paper, we discuss the clinical course and MRI findings of a patient with van der Knaap syndrome relying on the data of 12 years follow-up.

Despite severe white matter degeneration, functional loss is mild and the clinical course has a slow progression. Mental and motor development is normal or mildly delayed initially in most cases.[12] Except for macrocephaly, development abnormalities are usually noticed by the families at about 2 or 3 years. In one study, the patient had delay in walking until 21 months and inability to speak until 36 months.[9] Inability in walking was reported to be observed until 18 months and 3 years in two siblings.[10] All the patients reported had ataxic gait and drop attacks of varying severities.[9-13] Our patient was able to walk independently at two years of age and her gait was mildly ataxic and accompanied by drop attacks. Macrocephaly is usually evident in the first year of life, as shown in our patient. Mental function deteriorates slower than motor function and patients usually maintain their cognition despite severe motor deterioration.[9-14] In some of these patients, mental status has been reported to be good enough to attend school and complete basic schooling.[12,13] Our patient never attended to a school because of her parents' neglect, but she could comprehend and communicate with other people until late twenties. Almost all children have epileptic seizures in early childhood (range between 1,5 and 14 years) which are usually precipitated by a minor head trauma and sometimes seizures fascilitate the deterioration of clinical course.[9,10,15] Seizures are mostly generalized tonic-clonic and sometimes partial with secondary generalization and usually easy to control with medication.[12] In our patient, the first seizure was observed at about 5 years. Although not treated regularly, she never had severe and frequent seizures until 29 years of age, which were then easily controlled with low doses of (500 mg/day) valproic acid. Pyramidal dysfunction and cerebellar ataxia result in gait disturbance. The severity of the clinical course has a variable range; some patients have a more severe clinical course and maintain their ability to walk only for a few years or never achieve independent walking and some maintain the ability to walk independently into their forties, although many children become completely wheelchair dependent at the end of the first decade or in the second decade of life.[10-12] Pascual-Castroviejo et al reported a 28 years old patient with van der Knaap syndrome who was still able to ambulate independently, while having an older sister (32 years old) with van der Knaap syndrome becoming dependent to wheelchair at the age of 7.[10] Tu et al.

reported a patient with mild clinical course who was followed between 32 months and 5 years of age.[9] Our patient became unable to ambulate at the end of the third decade. Behavioural problems and neuropsychological symptoms such as motor and vocal tics, compulsive behavior, perseveration, acquired stuttering may accompany mental deterioration.[16] Our patient was agressive and unable to sleep in her second presentation at the age of 29 years.

During clinical course of van der Knaap syndrome, slow progression period may precede a subsequent period with worsening of the neurological condition. After clinical worsening, some patients may have a stable period or even have tendency to improve.[10,11] Sethi and Sethi reported a patient who was diagnosed as having van der Knaap syndrome at the age of 4 years with a story of generalized tonic clonic seizures. Fourteen years of follow-up yielded slow progression, reduction in demyelination and paradoxical radiological and clinical improvement.[11] The clinical course in our patient showed a slow progression in the first 5 years of life. Her neurological status was stable until she was 19 years old and she experienced a more severe progression in the third decade which resulted in inability to ambulate. In her third presentation at the age of 31, it was noted that progression in neurological status continued in the previous 2 years. Worsening in spasticity and new extrapyramidal findings were accompanied by minor MRI changes in the third presentation.

Because the disease has been known for a relatively short time, little information is available about average life span. Some individuals have died in their teens or twenties while others are alive in their forties.[12] No serious systemic disease was observed in 24 years follow-up of two siblings and they were reported to be alive in their ages of 28 and 32.[10] Our patient is 31 years old and she does not have any serious health problems other than neurological abnormalities. The ages of the oldest patients reported ranged between 32 and 49. Our patient represents one of the oldest follow up patients with van der Knaap syndrome in the literature.[10,17-19]

Hemispheric white matter is diffusely involved and swollen, gray matter structures are spared. Frontal and temporal lobe cysts may appear early in the course of the disease but it has also been reported that subcortical cysts may be absent in the early years of life.[1,9] MRI studies demonstrate homogeneous cerebral hemispheric white matter changes with high signal intensity on T2 weighted images. Slow progression of white matter abnormalities is the typical MRI finding even in long term follow-up periods.[10] Over time the white matter swelling decreases and cerebral atrophy ensues and subcortical cysts may increase in size and number, however it was also reported that cerebral white matter abnormalities decrease over time and the signal intensity of cerebral white matter becomes less abnormal.[12] In some cases MRI changes may have a stable course after second or third decade and even radiological improvement as a result of reduction in degree of demyelination is noted.[10,11] MRI findings of our patient revealed a slow progression in 12 years follow-up and increase in size and the number of the subcortical cysts was noted in the third presentation to our clinic when she was 31 years old. During 12 years follow-up worsening of the MRI findings were in correlation with the clinical deteroriation.

In previously reported cases of van der Knaap syndrome, MR spectroscopy revealed decreased NAA/Cr ratios and high levels of choline and myo-inositol as compared with healthy persons. It is known that these results indicate neuronal loss and decreased neuronal and function. Corresponding changes in these metabolites as well as in their ratios appear to be in conformity with the slowly progressive nature of van der Knaap syndrome.[1,3,10] The MRI and MRS findings of our patient were concordant with the literature.

Most case reports and follow-up studies of van der Knaap syndrome involve young individuals giving little information about the natural history of the disease in the late years.[13,14,16] Extrapyramidal symptoms may accompany other clinical findings as the disease progresses.[20] Our patient represents one of the oldest follow up patients with van der Knaap disease and one of those who has been fol-

lowed up for the longest period. It was striking that cognitive, pyramidal and cerebellar symptoms worsened in the third decade and at the beginning of the fourth decade patient suffered from new findings characterized by extrapyramidal symptoms including prominent dystonia in upper extremities and mild choreiform movements in lower extremities. During 12 year follow-up, worsening of the MRI findings were in correlation with the clinical deteroriation. We believe that this paper will help readers to understand the natural history of van der Knaap syndrome.

REFERENCES

1. van der Knaap MS, Barth PG, Stroink H, van Nieuwenhuizen O, Arts WF, Hoogenraad F, et al. Leukoencephalopathy with swelling and a discrepantly mild clinical course in eight children. Ann Neurol 1995;37(3):324-34.
2. Gelal F, Callí C, Apaydín M, Erdem G. van der Knaap's leukoencephalopathy: report of five new cases with emphasis on diffusion-weighted MRI findings. Neuroradiology 2002;44(7): 625-30.
3. Sener RN. van der Knaap syndrome: MR imaging findings including FLAIR, diffusion imaging, and proton MR spectroscopy. Eur Radiol 2000;10(9):1452-5.
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.
5. Kinney HC, Brody BA, Kloman AS, Gilles FH. Sequence of central nervous system myelination in human infancy. II. Patterns of myelination in autopsied infants. J Neuropathol Exp Neurol 1988;47(3):217-34.
6. Topçu M, Gartioux C, Ribierre F, Yalçinkaya C, Tokus E, Oztekin N, et al. Vacuoliting megalencephalic leukoencephalopathy with subcortical cysts, mapped to chromosome 22qtel. Am J Hum Genet 2000;66(2):733-9.
7. Leegwater PA, Yuan BQ, van der Steen J, Mulders J, Könst AA, Boor PK, et al. Mutations of MLC1 (KIAA0027), encoding a putative membrane protein, cause megalencephalic leukoencephalopathy with subcortical cysts. Am J Hum Genet 2001;68(4):831-8.
8. Harbord MG, Harden A, Harding B, Brett EM, Baraitser M. Megalencephaly with dysmyelination, spasticity, ataxia, seizures and distinctive neurophysiological findings in two siblings. Neuropediatrics 1990;21(3):164-8.
9. Tu YF, Chen CY, Huang CC, Lee CS. Vacuolating megalencephalic leukoencephalopathy with mild clinical course validated by diffusion tensor imaging and MR spectroscopy. AJNR Am J Neuroradiol 2004;25(6):1041-5.
10. Pascual-Castroviejo I, van der Knaap MS, Pronk JC, García-Segura JM, Gutiérrez-Molina M, Pascual-Pascual SI. Vacuolating megalencephalic leukoencephalopathy: 24 year follow-up of two siblings. Neurologia 2005;20 (1):33-40.
11. Sethi PK, Sethi NK. Megalencephalic leukoencephalopathy with subcortical cysts. Indian J Pediatr 2004;71(5):473-5.
12. van der Knaap MS, Boor I, Estévez R. Megalencephalic leukoencephalopathy with subcortical cysts: chronic white matter oedema due to a defect in brain ion and water homoeostasis. Lancet Neurol 2012;11(11):973-85.
13. Hari Krishnan K, Leema Pauline C, Kumaresan G, Vasantha Mallika TK. Megalencephalic leukoencephalopathy with subcortical cysts. Indian Pediatr 2005;42(1):60-3.
14. Chandrashekar HS, Guruprasad AS, Jayakumar PN, Srikanth SG, Taly AB. Megalencephalic leukoencephalopathy with subcortical cysts: MRI and proton spectroscopic features. Neurol India 2003;51(4):525-7.
15. Yalçinkaya C, Yüksel A, Comu S, Kiliç G, Cokar O, Dervent A. Epilepsy in vacuolating megalencephalic leukoencephalopathy with subcortical cysts. Seizure 2003;12(6):388-96.
16. Sugiura C, Shiota M, Maegaki Y, Yoshida K, Koeda T, Kitahara T, et al. Late-onset neuropsychological symptoms in a Japanese patient with megalencephalic leukoencephalopathy with subcortical cysts. Neuropediatrics 2006;37(5):286-90.
17. Blattner R, Von Moers A, Leegwater PA, Hanefeld FA, Van Der Knaap MS, Köhler W. Clinical and genetic heterogeneity in megalencephalic leukoencephalopathy with subcortical cysts (MLC). Neuropediatrics 2003;34(4): 215-8.
18. Singhal BS, Gursahani RD, Udani VP, Biniwale AA. Megalencephalic leukodystrophy in an Asian Indian ethnic group. Pediatr Neurol 1996;14(4):291-6.
19. Singhal BS, Gorospe JR, Naidu S. Megalencephalic leukoencephalopathy with subcortical cysts. J Child Neurol 2003;18(9):646-52.
20. Takanashi J, Sugita K, Kohno Y. Vacuolating leukoencephalopathy with subcortical cysts with late onset athetotic movements. J Neurol Sci 1999;165(1):90-3.