Mutations in one of the five eukaryotic initiation factor 2B genes (EIF2B1-5) were first described in childhood ataxia with cerebral hypomyelination—vanishing white matter syndrome. The syndrome is characterized by (i) cerebellar and pyramidal signs in children aged 2–5 years; (ii) extensive cavitating leucoencephalopathy; and (iii) episodes of rapid deterioration following stress. Since then a broad clinical spectrum from congenital to adult-onset forms has been reported, leading to the concept of eIF2B-related disorders. Our aim was to describe clinical and brain magnetic resonance imaging characteristics, genetic findings and natural history of patients with adult-onset eIF2B-related disorders (after age 16). The inclusion criteria were based on the presence of eIF2B mutations and a disease onset after the age of 16 years. One patient with an asymptomatic diagnosis (age 16 years) was also included. Clinical and magnetic resonance findings were retrospectively recorded in all patients. All patients were examined to assess clinical evolution, using functional, pyramidal, cerebellar and cognitive scales. This multi-centric study included 16 patients from 14 families. A sex ratio imbalance was noted (male/female = 3/13). The mean age of onset was 31.1 years (range 16–62). Initial symptoms were neurologic (n=11), psychiatric (n=2) and ovarian failure (n=2). Onset of the symptoms was linked to a precipitating factor in 13% of cases that included minor head trauma and delivery. During follow-up (mean: 11.2 years, range 2–22 years) 12.5% of the patients died. Of the 14 survivors, 62% showed a decline in their cognitive functions, and 79% were severely handicapped or bedridden. One case remained asymptomatic. Stress worsened...
clinical symptoms in 38% of the patients. Magnetic resonance imaging findings consist of constant cerebral atrophy, extensive cystic leuкоencephalopathy (81%), corpus callosum (69%) and cerebellar (38%) T<sub>2</sub>-weighted hyperintensities. All families except one showed mutations in the EIF2B5 gene. The recurrent p.Arg113His-elf2B<sub>8</sub> mutation was found in 79% of the 14 elf2B-mutated families, mainly at a homozygous state. The family with a mutation in EIF2B2 had the relatively prevalent p.Glu213Gly mutation. elf2B-related disorder is probably underestimated as an adult-onset inherited leuкоencephalopathy. In this late-onset form, presentation ranges from neurologic symptoms to psychiatric manifestations or primary ovarian failure. Cerebral atrophy is constant, whereas the typical vanishing of the white matter can be absent. Functional and/or cognitive prognosis remains severe. Molecular diagnosis is facilitated for these forms by the screening of the two recurrent p.Arg113His-elf2B<sub>8</sub> and p.Glu213Gly-elf2B<sub>8</sub> mutations, positive in 86% of cases.

**Keywords:** elf2B-related disorders; CACH/VWM; adult-onset leuкоodystrophies

**Abbreviations:** CACH/VWM = childhood ataxia with cerebral hypomyelination—vanishing white matter; elf2B = eukaryotic initiation factor 2B

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### Introduction

The childhood ataxia with central hypomyelination (CACH)/vanishing white matter (VWM) syndrome (MIM 603896) has been described as the most prevalent childhood inherited leuкоencephalopathy with a recessive mode of transmission (Schiffmann et al., 1994; van der Knaap et al., 1997). This clinico-MRI entity was initially individualized in young children. After a usually normal initial development, patients aged 2–5 years experienced a neurologic deterioration characterized by cerebellar ataxia, mild spasticity and relatively mild mental decline. Additional episodes of acute deterioration after febrile infections or minor head trauma often occurred with subsequent partial recovery, leading to death usually after 2–5 years of disease evolution. MRI revealed a diagnostic pattern with symmetric, diffuse involvement of the white matter (WM) of the cerebral hemispheres with typical CSF-like signal intensity. Increasing degrees of WM vanishing were observed over time. Neuropathologic findings consist of caviting orthochromatic leuкоodystrophy with rare myelin breakdown and relative sparing of axons. Diffuse vacuolation results in a spongiform to cavitated appearance of the WM (Schiffman et al., 1994; van der Knaap et al., 1997). Increased density of oligodendrocytes with abundant ‘foamy’ cytoplasm contrasting with scarce dystrophic astrocytes has been considered to be the most specific neuropathologic hallmark of the disease (Rodriguez et al., 1999, Wong et al., 2000). Using a positionning cloning strategy, mutations in the five genes encoding the five subunits of the eukaryotic initiation factor 2B (elf2Bα, β, γ, δ and ε) have been identified (Leegwater et al., 2001; van der Knaap et al., 2002). The elf2B factor is a ubiquitously expressed protein that is a key regulator of the protein synthesis through its nucleotide guanine exchange activity (GEF activity), particularly under cellular stresses such as endoplasmic reticulum (ER) stress or viral infection (van der Voorn et al., 2005; Fogli and Boespflug, 2006).

The use of MRI- or neuropathology-based criteria to select patients with undetermined leuкоodystrophies for elf2B genes analysis has demonstrated a broad clinical spectrum of elf2B-mutated patients: from congenital forms with rapid death (van der Knaap et al., 2003) to adult-onset forms with slow neurologic progression (Biancheri et al., 2003), justifying the

generic designation ‘elf2B-related disorders’ or ‘elf2B-pathies’ (Fogli et al., 2004; Boespflug-Tanguy et al., 2008).

For a clearer delineation of the neurologic presentation and long-term evolution of adult-onset forms of elf2B-pathies, we report the clinical picture, MRI presentation and follow-up of a cohort of 16 elf2B-mutated patients with disease onset after the age of 16 years.

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### Patients and Methods

Patient inclusion criteria were (i) disease onset after the age of 16 years; and (ii) mutation in one of the EIF2B1-5 genes.

Written informed consent was obtained from all patients. They were tested by direct sequencing of the coding regions of the EIF2B1-5 genes. The exons and flanking intron DNA of the genes EIF2B1, 2, 3, 4 and 5 were amplified by PCR as previously described (Fogli et al., 2002).

Clinical and MRI findings were retrospectively reviewed by two independent experts (O.B.T. and P.L). Age at disease onset was defined as that at first clinical manifestation in symptomatic patients. Classification of psychiatric symptoms was based on DSMIV criteria. Diagnostic criteria of ovarian failure were based on primary amenorrhoea or secondary amenorrhoea lasting for >6 months, associated with elevated gonadotrophin levels before the age of 40 years. Precipitating factors underlying clinical manifestations were sought in each patient.

All the survivors were interviewed and clinically examined in 2008. A full record of the disease course since onset or diagnosis in asymptomatic cases was obtained during this visit. Standardized scales were used to evaluate cognitive functions (MMSE, BREF, Dubois et al., 2000), functional global handicap level: EDSS score (Noseworthy, 1994), Barthel and FIM (Keith et al., 1987), cerebellar dysfunction (SARA, Schmitz-Hübsch et al., 2006), and spasticity (SPRS, Schüle et al., 2006). In addition, for global assessment of long-term evolution, patient status was classified on a five-point scale adapted from Peters et al. (2003): 0, no functional handicap and no neurologic signs; 1, mild coordination or gait difficulties not requiring assistance; 2, moderate learning or neurologic abnormalities requiring support or intervention in a few areas, able to walk with assistance; 3, severe learning or neurologic abnormalities requiring support in many areas, wheelchair-bound; 4, individual requiring constant supervision, confined to bed or loss of cognitive abilities; 5, death.
Progression of the disease was classified using the multiple sclerosis rating as asymptomatic, relapsing remitting, or primary or secondary progressive. Follow-up duration was defined as the time between disease onset and last clinical evaluation or the patients' death.

MRI study consisted of T1, T2 and FLAIR sequences. Analysis focused mainly on (i) location and extent of the abnormal WM signal; (ii) presence of WM cavitations assessed by low signal intensities on FLAIR sequences; (iii) widening of lateral ventricles and subarachnoid spaces; and (iv) corpus callosum, cerebellum and brainstem atrophy.

The statistical chi-squared test was used to evaluate dimorphism between groups.

Results

Fifteen patients with an age of onset >16 years of eIF2B-related disorders were selected. In addition, we included one asymptomatic patient at the age of 16 years when a brain MRI was performed subsequently to a previous diagnosis of CACH/VWM in her brother at age 14. Two affected siblings were observed in two distinct families. Only three patients were male, indicating a marked sex imbalance in this mild severity group of eIF2B-pathies.

Initial clinical symptoms

The mean age of onset was 31.1 years (range 16–62 years, SD 10.4). The initial symptoms were neurologic in 11 patients (69%), mainly gait disturbances with spastic paraparesis, and (or) cerebellar ataxia and rare cognitive decline (Table 1). Psychiatric symptoms (depression and schizophrenia) were isolated over 2 and 5 years in two patients. Ovarian failure preceded the neurologic symptoms in two cases. In only two patients (12.5%), stress triggered the clinical onset of the disease.

Clinical disease evolution

Deceased patients

Two patients (12.5%) died in their thirties after a stress-induced deterioration. Patient 1189-2, a female aged 35 years, depressed since age 33, had a minor head trauma without initial loss of consciousness, which rapidly led to a profound comatous state related to intractable diffuse brain edema, resulting in death 8 months later. Patient 871, a female aged 33 years, with a mild tetraparesis and early menopause since age 27 years, died rapidly from an intractable status epilepticus following a brief generalized seizure. These two patients were excluded from our subsequent natural history survey due to lack of reliable evaluation before death.

Neurologic and functional evaluation

Fourteen patients were available for neurologic and functional evaluation at a mean age of 42.4 years (range 23–65 years) and a mean follow-up time of 11.2 years, (range 2–22 years). Disease evolution was progressive in 11 patients: primary in nine and secondary in two patients.

Three patients (23%) were still able to walk without support when evaluated at a mean age of 27 years (range 23–32 years) and after a mean disease evolution of 5.7 years (range 5–7 years). Their age at disease onset was 21.3 years (range 16–27 years). Patient 76, initially asymptomatic, remained asymptomatic with normal cognitive functions at age 23 years after a 7-year follow-up.

Eleven patients (79%) lost independent walking at a mean age of 46.7 years (range 16–62). In this group, the mean follow-up (12.7 years, range 3–22 years) and the mean age at disease onset (34 years, range 16–62 years) were higher than in the autonomous group of patients. Clinical evaluation showed mild ataxia and spasticity scores with a mean SRA at 19.9/100 (8–40) and SPRS at 26/100 (10–52), respectively. However, the high mean values observed with the EDSS [7.1/(range 5–9.5)], the MIF [83.1/(range 19–140)] and the Barthel [54.1/(range 0–100)] scales demonstrated the severity of the handicap.

Cognitive evaluation

Cognition was impaired in eight patients (62%) with a mean MMSE score of 16.7 (range 0–27) and a mean BREF score of 8.25 (range 0–15). Mean age at evaluation and at disease onset was identical in the groups of normal and cognitive-impaired patients [40.5 years (range 23–57 years) versus 43.9 years (range 26–65) and 29.2 years (range 16–52 years) versus 32.8 years (range 17–62 years), respectively]. However, motor handicap was milder in the normal group (six patients) than in the cognitive-impaired group (eight patients) of patients: in the normal group, there were no bedridden patients and two autonomous against three bedridden patients and only one autonomous in the cognitive impaired group. Interestingly, the precipitating role of stress was observed only in two patients with a cognitive decline (Cases 1386 and 1501).

Stress as onset trigger or aggravating factor

Stress-induced factors were found in 38% patients of our series. An abnormal stress response precipitated death in the two deceased cases already described; a benign head trauma induced an irreversible brain oedema in one and a short generalized seizure was followed by an intractable status epilepticus in the other. Onset trigger factors were observed in two patients with initial spastic signs: benign head trauma (Patient 948) and delivery (Patient 1467). Aggravating factors were noted during disease evolution in two other patients. Patient 1386 had suffered from ovarian failure since age 21 years, with no neurologic symptoms for 5 years. She presented with epileptic seizures at age 26 followed by a progressive cerebellar ataxia. Patient 1501 presented with an insidious, slow cognitive decline since age 17 years. Her neurologic status remained stable for 10 years. After a minor head trauma at age 27, she presented with a deep coma, lasting a few days, from which she awoke with a permanent right lower limb weakness. At age 28, she became wheelchair-ridden after a single generalized seizure. At age 29, she became aphasic and became bedridden after a fall and minor head trauma without loss of consciousness.
Table 1  Clinical evaluation of the 16 eIF2B-mutated patients

| No.   | Sex | Age (years) | First symptoms | Age (years) | Follow-up | Provoking factors | Type | Cognitive decline | Associated signs | Clinical evaluation | OF | Neurology | Walking | MMSE | BREF | EDSS | SARA | SRPS | MIF | BARTHEL | Scale |
|-------|-----|-------------|----------------|--------------|------------|-------------------|------|-------------------|------------------|--------------------|----|-----------|---------|-------|-------|-------|-------|-------|------|-------|-------|-------|-------|
| 1189-1| F   | 46          | CA             | 42.5         | 3.5 y      | No                | PP   | Yes               |                  | CA                 |    | H         | 23      | 12    | 7.5   | 21.5  | 26    | 25    | 76   | 3     | PA     |
| 1189-2| F   | 35          | Depression     | 33           | 2 y        | Yes: Trauma       | D, 35 y | No               | E (generalized)   | Coma               |    | A         | NA      | NA    | NA    | NA    | NA    | NA    | NA    | 5     | PA     |
| 871   | F   | 33          | Pyra           | 27           | 6 y        | Yes: Seizures     | D, 33 y | No               | E (generalized), Epileptic status | Py                 | A   | NA       | NA      | NA    | NA    | NA    | NA    | NA    | NA    | 5     | EM, 30yo |
| 1348* | M   | 32          | Psychosis      | 27           | 5 y        | No                | CIS  | No               |                  | Py, CA             |    | A         | 28      | 9     | 3     | 1     | 1     | 100   | 147   | 1     | –      |
| 1386* | F   | 26          | 36             | 21           | 5 y        | Yes: Seizures     | SP   | Yes              | E (generalized)   | CA                 |    | A         | 25      | 15    | 2     | 1     | 1     | 100   | 124   | 1     | IN     |
| 76*   | F   | 23          | AS             | 16           | 7 y        | No                | AS   | No               |                  | NI                 |    | A         | 27      | 14    | 0     | 0     | 0     | 100   | 133   | 0     | Nl     |
| 948*  | F   | 52          | 36             | 30           | 22 y       | Yes: Trauma       | SP   | Yes              | E (partial)       | Py, CA             |    | H         | 21      | 6     | 6.5   | 22    | 18    | 75    | 72    | 3     | EM, 31yo |
| 1304-1| M   | 57          | ParaP          | 52           | 5 y        | No                | PP   | No               |                  | SPG, CA            |    | H         | 23      | 11    | 6     | 8     | 22    | 100   | 139   | 2     | –      |
| 1304-2| M   | 55          | ParaP          | 46           | 9 y        | No                | PP   | No               |                  | SPG, CA            |    | H         | 10      | 8     | 8     | 26    | 35    | 15    | 32    | 3     | Nl     |
| 1309  | F   | 37          | CA, Py         | 16           | 21 y       | No                | PP   | No               |                  | SPG, CA            |    | H         | 27      | 16    | 6     | 10.5  | 21    | 100   | 136   | 2     | Nl     |
| 1467  | F   | 44          | ParaP          | 34           | 10 y       | Yes: Delivery     | PP   | Yes              |                  | SPG, H             |    | 27       | 15     | 5.5   | 5     | 10    | 100   | 140   | 2     | Nl     |
| 1388  | F   | 41          | CA, mild ParaP | 21           | 20 y       | No                | PP   | Yes              | E (generalized)   | CA, mild SPG       |    | B         | 18      | 14    | 8     | 25.5  | 30    | 35    | 68    | 3     | Nl     |
| 1436  | F   | 38          | CA, CD         | 35           | 3 y        | No                | PP   | Yes              | E (generalized)   | CA, SPG            |    | B         | 4       | 0     | 9     | 36    | 36    | 0     | 22    | 4     | EM, 35yo |
| 1501  | F   | 39          | CD             | 17           | 22 y       | Yes: Trauma       | SP   | Yes              | E (generalized)   | STG                |    | B         | 0       | 0     | 9.5   | 40    | 52    | 0     | 21    | 4     | EM, 11yo |
| 1292  | F   | 39          | EM             | 18           | 21 y       | No                | PP   | No               |                  | SPG, CA            |    | H         | 27      | 15    | 6.5   | 9.5   | 23    | 95    | 135   | 3     | EM, 18yo |
| 1665  | M   | 65          | CD             | 62           | 3 y        | No                | PP   | Yes              |                  | SCW                |    | H         | 15      | 4     | 5     | 15    | 13    | 50    | 73    | 3     | –      |

*Already reported in Fogli et al., 2003, Denier et al., 2007 or Peter et al., 2008.

a,b,f CA = Cerebellar ataxia; Py = Pyramidal symptom; IN = Infertility; AS = asymptomatic; ParaP = paraparesis; CD = cognitive decline; EM = Early Menopause.
b PP = primary progressive; D = death; CIS = clinical isolated symptom; SP = secondary progressive.
c E = epilepsy.
d STG = tetraplegia; SCW = subcortical walking; SPG = spastic paraplegia.
e H = Handicapped; A = Autonomous; B = Bedridden; NA = not available.
f OF = ovarian failure; PA = Primary amenorrhoea; N = normal 0: normal values of the corresponding score; y = years; yo = years old.
Associated symptoms

Of the 13 females, 62% had ovarian failure. Two had primary amenorrhoea. Six had later manifestations at mean age 29.5 years (range 22–35 years): early menopause in five patients and infertility in one. The neurologic symptoms always preceded the ovarian failure, except for case 1386. Pelvic ultrasonic exploration was performed in three out of the 13 females; ovarian atrophy was noted only in the case with early menopause. No correlation was found between ovarian failure and disease severity or duration.

Half of the patients presented epileptic seizures that were partial in only one case. Occurrence of seizures caused a major deterioration of the clinical status in three cases, leading to death in case 871 and permanent loss of cognitive or motor functions in cases 1386 and 1501, respectively.

MRI findings

MRI was available in all patients (mean age 38.7 years, range 16–65 years). The supratentorial WM showed a diffuse abnormal signal characterized by a T2-weighted hyperintensity and T1-weighted hypointensity relative to cortical signals, in all cases.

Cystic breakdown of the WM was found on the FLAIR sequences in 13 out of 16 patients (81%) (Fig. 1A and B). The three patients without WM cavitations (Cases 1189-2, 76-1 and 1304-1) were of different ages at the time of MRI analysis, that is 16, 35 and 55 years, respectively. In contrast, the sister of patient 1304-1 (1304-2) had a cystic leucoencephalopathy on the MRI performed at the age of 50 years. Cerebral atrophy was consistently found in patients, and was not correlated with disease severity or age.

Corpus callosum was involved in all patients except one. Abnormalities consisted of atrophy in 13 patients and T2-weighted and FLAIR hyperintensities in 11 patients (Fig. 1C–G).

The cerebellum was likewise involved. Cerebellar atrophy was observed in 12 patients, affecting the lobes or the vermis, whereas abnormal WM signal of the lobes was noted in only six cases (Fig. 1D). Brainstem was more rarely involved, including atrophy in four patients and T2-weighted hyperintensities in one patient.

Finally, Case 1304-1, analysed at the age of 55 years, had a non-specific, extensive, supratentorial leucoencephalopathy without a cystic aspect, sparing the corpus callosum, associated with an isolated cerebellar atrophy.

Genetic findings

The two pairs of siblings included in our study were from non-consanguineous families (families 1189 and 1304) (Table 2). Patient 871, born of consanguineous parents, had eight siblings who died between ages 1 month and 16 years but without sufficient clinical information to determine their status. Case 76 had a brother with a previous CACH/VWM diagnosis. A total of 12 patients were without family history. Fifteen patients from 13 unrelated families showed mutations in the EIF2B5 gene and one patient in the EIF2B2 gene. The recurrent c.338G>A mutation in the EIF2B5 gene (p.Arg113His) was found in

10 patients (71%) of our EIF2B-mutated families with an age of onset after 16 years, including nine at a homozygous state. In the only compound heterozygote patient for this recurrent mutation, the second mutation was also an arginine/histidine substitution, but at position 299. The three remaining EIF2B5-mutated families
were also compound heterozygotes for missense mutations affecting arginine or histidine residues. In one of these families (family 1388), the second mutation creates a stop codon leading to a corresponding truncated eIF2B subunit. These results are in line with the previous observation that nonsense eIF2B mutations are never found at a homozygous state. The only patient mutated for the eIF2B2 gene was compound heterozygote for two missense mutations, one corresponding to the recurrent c.638A>G mutation (p.Glu213Gly-eIF2B2). Hence, detection of the two p.Arg113His-eIF2B and p.Glu213Gly-eIF2B2 mutations allowed diagnosis in 13/16 (81.2%) of our eIF2B-mutated patients, corresponding to 79% (11/14) of our eIF2B-mutated families with an age of onset >16 years.

**Discussion**

CACH/VWM disease related to eIF2B mutations is considered as one of the most severe causes of inherited childhood leukoencephalopathy (van der Knaap et al., 1999). The frequency of clinical onset after age 16 years (adult forms) has been previously reported as <5% of patients with only nine cases reported before 2004 as single cases or associated with larger cohorts of eIF2B-mutated patients (Prass et al., 2001; Fogli et al., 2003, 2004; Gallo et al., 2004; Ohtake et al., 2004; Vaidya et al., 2004; van der Knaap et al., 2004). To date, 163 eIF2B-mutated patients for whom disease onset was known have been reported (Fogli et al., 2003, 2004; Ohtake et al., 2004; van der Knaap et al., 2004; Vaidya et al., 2004; San Antonio-Arce et al., 2007; Denier et al., 2007; Matsui et al., 2007; Peter et al., 2008; Wu et al., 2009). When we pooled our patients with these 163 patients reported to date, the total of 177 patients comprised 25 (15%) with an onset after age 16 years against 39 (22%) before the age of 2 years, 82 (46%) between ages 2 and 5 years and 31 (18%) between ages 5 and 16 years. However, diagnosis in adulthood probably remains underestimated.

Surprisingly, we found only three males in our series of 16 adult-onset patients. Two of them showed the oldest ages of disease onset at 52 years (patient 1304) and 62 years (patient 1665), respectively. When we considered the pool of 177 known eIF2B-mutated patients, we confirmed a statistically significant sex ratio imbalance only in the group with age at disease onset beyond 16 years (three males/22 females, \( \chi^2 = 10.59, P < 0.005 \) versus 22/17 in the group aged <2 years, 39/43 in the group aged 2–5 years and 18/13 in the group aged 5–16 years). This difference may be explained by better disease recognition in females after puberty due to the association with ovarian dysfunction and (or) by a higher susceptibility of females to disease expression. Data suggest that the WM susceptibility to eIF2B mutations may result from both an abnormal glial maturation and the sensitivity of glial cells to eIF2B dysfunction during life (Fogli et al., 2004; Dietrich et al., 2005; van der Knaap et al., 2006). Differences in myelin density, oligodendrocyte turnover and myelin breakdown between male and female (Cerghet et al., 2006; Schmithorst et al., 2008; Yang et al., 2008) may account for a higher susceptibility of the female WM to mild eIF2B mutations. The impact of ovarian hormone deprivation on glial cell functions (Carrer and Cambiasso, 2002; Garcia-Segura and Melcangi, 2006) may also contribute to the larger number of symptomatic eIF2B-mutated females compared with males during adulthood.

Clinical and imaging patterns and long-term outcome of adult forms remain largely unknown. To our knowledge, our series is the largest ever reported. The highest age of clinical onset previously reported was 40 years (Ohtake et al., 2004). In our series, the first clinical symptoms appeared after age 40 years in 25% of the patients, with a maximum of 62 years. In contrast with the childhood onset form of CACH/VWM, which usually begins with spastic-cerebellar ataxia symptoms (Hanefeld et al., 1993,
van der Knaap et al., 1998), the first manifestations of elf2B-related disease with age of onset >16 years, show a broader range of clinical presentations. Initial symptoms were mostly neurologic (69%), including spasticity and (or) cerebellar syndrome, but also seizures and dementia as previously mentioned in single case reports by Ohtake et al. (2004), Prass et al. (2001) and van der Knaap et al. (1998, 2004). Extra neurologic initial symptoms were observed in 31% of our cases including: psychiatric symptoms, such as depression and psychosis (Gallo et al., 2004), and manifestations of ovarian failure (Fogli et al., 2003; van der Knaap et al., 2004). Unexplained isolated ovarian failure (including primary amenorrhea, infertility and early menopause), in the absence of any neurologic or psychiatric manifestations, can thus reveal an elf2B-related disorder and calls for investigation by brain MRI (Biancheri et al., 2003; Fogli et al., 2003). Lastly, as observed in one of our patients, asymptomatic forms can be discovered in at-risk relatives by brain MRI (van der Knaap et al., 2004).

Stress was found to be an onset trigger or aggravating factor in 38% of our elf2B-mutated adult patients just as in forms with clinical onset below 16 years old (Fogli and Boespflug-Tanguy, 2006). The stress shows a wide range of severity from benign fall or head trauma to acute fright (Kaczorowska et al., 2006; van Kollenburg et al., 2006), sun bathing (van der Knaap et al., 1998), pregnancy, delivery, seizures or infections. In our series, these were always associated with cognitive loss and usually with a more severe functional handicap, sometimes leading to death.

The 50% occurrence rate of epileptic seizures that we observed justifies a systematic EEG checking for epileptic activity in cases of rapid cognitive or behavioural changes. Epileptic activity indicates unfavourable prognosis in terms of death or severe sequelae, probably reflecting the severity of the neuronal insult.

CACH/VWM with age of onset <2 years is considered as more severe than adult forms of the elf2B-related disorders, leading to death in few months or years (Fogli et al., 2004). Analysis of our large series of elf2B-related disorders showed that in the 20 forms with an age of onset <2 years, 50% of the patients died and 40% were bedridden after a mean of 3 years of disease evolution, whereas in the 42 forms with an age of onset 2–5 years, 26% died and 26% were bedridden after a mean disease evolution of 6 years. In the 16 patients with an age of onset 5–16 years, 19% of patient deaths were observed after a mean disease follow-up of 9 years and only 6% were bedridden. The present study shows that forms with age of onset >16 years are also serious diseases, given that they caused death in 12.5% of our patients, and that most of them became handicapped or bedridden and half developed a cognitive loss after a mean 11 years of follow-up. Thus, forms with an age of onset >5 years share a slower disease progression than the forms with an age of onset <2 years. After age 5 years, severity of the disease tends to be less closely correlated with age at disease onset and a greater difference in disease severity is observed for affected patients within the same family, as reported here for Patients 1189-1 and 1189-2. This confirms that environmental factors largely modulate disease evolution in forms with onset after age 5 years.

Our series allowed a better delineation of the MRI presentation of elf2B-related disorders with an age of onset >16 years. 80% of our patients presented with the typical MRI patterns consisting of diffusely abnormal cerebral WM (T1-weighted hypointensity, T2-weighted hyperintensity), associated with cystic changes (decreased FLAIR signal) including the corpus callosum. No abnormal signal was observed in the grey matter, including cortex, thalamus and globus pallidus in all of our patients. Cerebral atrophy was always observed, reflecting a progressive WM volume loss. Cystic breakdown of the WM was absent in three of our 16 patients, including one patient aged 55 years with a non-specific extensive leucoencephalopathy, sparing brainstem, corpus callosum and cerebellum. Absence of any evidence of vanishing WM on MRI was already reported in two elf2B-mutated patients, but at a younger age, that is 18 and 16 years, respectively (Fogli et al., 2003; van der Knaap et al., 2004). Cavitations can appear on serial MR examinations (van der Knaap et al., 2004; Mascalchi et al., 2006). Our series confirms that even in the end stage of the disease, cerebral hemispheric WM may not have vanished.

Mutations in elf2Bc were present in 93% of our elf2B-mutated families (13/14). Also, 71% of the families (10/14) had a recurrent p.Arg113His-elf2Bc mutation; all except one at a homozygous state. The 78% (25/32) of p.Arg113His-elf2Bc allele frequency found in the present series is much higher than the 36% previously reported by us taking into account patients with an age at disease onset >5 years (Fogli et al., 2004). On the other hand, in this last series, the p.Glu213Gly-elf2Bβ mutation considered also as a recurrent ‘mild mutation’ was found in 21% of the mutated allele compared with only in 3% of the present series. This confirms the utility of first searching for these two mutations in routine diagnosis. Using this simple technique, the percentage mutation detection in affected families with age of onset >16 years reached 86% in our series. In case of negativity, the direct sequencing of the elf2B5 coding regions will detect the remaining mutations. The arginine 113 is not conserved among species; the mouse and rat protein has a histidine residue at the homologous position, suggesting that the p.Arg113His substitution in humans leads to milder effect on the elf2B function.

In conclusion, adulthood elf2B-related disorder is probably more frequent than was initially thought, particularly in females. Lack of neurological symptoms and of vanishing of the WM on MRI can delay diagnosis. Detection of the p.Arg113His-elf2Bc mutation is of high diagnostic value and must be easily performed in adult leucoencephalopathies with a non-specific diffuse supratentorial abnormal WM signal. Functional and cognitive prognosis is severe although long-term survival is more frequent than in infantile forms.

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References


