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## Association Between Factor V Leiden Mutation and the Hemiconvulsion, Hemiplegia, and Epilepsy Syndrome: Report of Two Cases

### ABSTRACT

The factor V Leiden mutation is the most common hereditary cause of venous thrombosis in our population. In the pediatric population, it has been associated with cerebrovascular thrombosis, cerebral palsy, and prosencephaly in neonates. We present two children with hemiconvulsion, hemiplegia, and epilepsy syndrome in whom the cause is likely attributable to the factor V Leiden mutation. We suggest that patients presenting with hemiconvulsion, hemiplegia, and epilepsy syndrome should be routinely investigated for factor V Leiden, and, if positive, careful consideration should be given to therapeutic and prophylactic anticoagulation as this may improve long-term outcome. (*J Child Neurol* 2002;17:713-717).

Factor V Leiden or FVR506Q, is a mutant protein with a point mutation in the gene encoding for factor V that results in a single

amino acid substitution at the ARG506 specific cleavage site for activated protein C. This renders factor V Leiden resistant to proteolytic inactivation by activated protein C and results in an increased generation of thrombin and a life-long predisposition to thrombosis.<sup>1,2</sup> This autosomal dominant condition is most commonly seen in Caucasian populations, occurring in 5 to 6% of the general population with a mean allelic frequency of 2.7%.<sup>3</sup> Factor V Leiden is found in 20 to 60% of patients with venous thrombosis,<sup>2</sup> and heterozygous carriers of the factor V Leiden protein have a three- to seven-fold increased risk of venous thrombotic events,<sup>4,5</sup> whereas homozygotes have an 80-fold increased risk.<sup>6</sup> Factor V Leiden alone is not thought to cause thrombosis<sup>7</sup> and probably represents a mild thrombophilic state; however, studies have shown that factor V Leiden becomes a significant risk factor for thrombosis in combination with other prothrombotic factors.<sup>8,9</sup>

There is a recognized significant association between factor V Leiden and cerebrovascular thrombosis in the pediatric population.<sup>10</sup> The factor V Leiden mutation has been found to have a higher prevalence in pediatric cases of stroke.<sup>11</sup> In children, it has been implicated in arterial and venous thrombosis, cerebral palsy, and prosencephaly in neonates.<sup>10</sup> Its association with other neuropathologic conditions is undetermined, and there has been no association with hemiconvulsion, hemiplegia, and epilepsy syndrome reported in the literature. We present two children with hemiconvulsion, hemiplegia, and epilepsy syndrome and factor V Leiden mutation. Given that venous thrombosis is considered as the principal cause of hemiconvulsion, hemiplegia, and epilepsy syndrome,<sup>12</sup> we suggest that consideration be given to early investigation for activated protein C resistance and factor V Leiden mutation in these subjects, with the prospect of commencing therapeutic and prophylactic anticoagulation.

### Case Report

#### Patient 1

This 5-year-old girl was referred at 18 months for the investigation and treatment of a persistent, postictal right hemiparesis following febrile partial status epilepticus. Her previous medical history showed a normal gestation, delivery, and development. She had experienced two previous episodes of prolonged febrile seizures. Her family history was negative for epilepsy, febrile seizures, and coagulopathies.

Two days prior to her referral, the patient was found by her sister to be unresponsive, warm to the touch, and having a convulsion characterized by deviation of the head and eyes to the right with generalized tonic-clonic movements. The convulsion persisted for approximately 1 hour, initially involving all four limbs and then becoming lateralized to the right. The temperature recorded on the way to the hospital was 38.5°C. On arrival, she was found to have a right hemiplegia with ipsilateral facial weakness. She was subsequently transferred to our pediatric neurology ward for management of her illness. Physical examination revealed an afebrile, somnolent child with hypotonia and weakness of the right side (grade IV power, Medical Research Council scale). She had a central facial palsy with decreased sensitivity and Babinski reflex on the right. There was a lack of visual response to appropriate external stimuli on the right side; however, direct and consensual light reflexes were present and normal bilaterally. Deep tendon reflexes were difficult to evoke in the upper limbs and normal in the lower limbs bilaterally.

Routine laboratory investigations and cerebrospinal fluid analysis were normal. A repeat computed tomographic (CT) scan showed a hypodensity of the left thalamus with cerebral edema localized to the left hemisphere (Figure 1). Magnetic resonance imaging (MRI) showed an increase in signal intensity in the left thalamus with a mild hyperintense signal in the

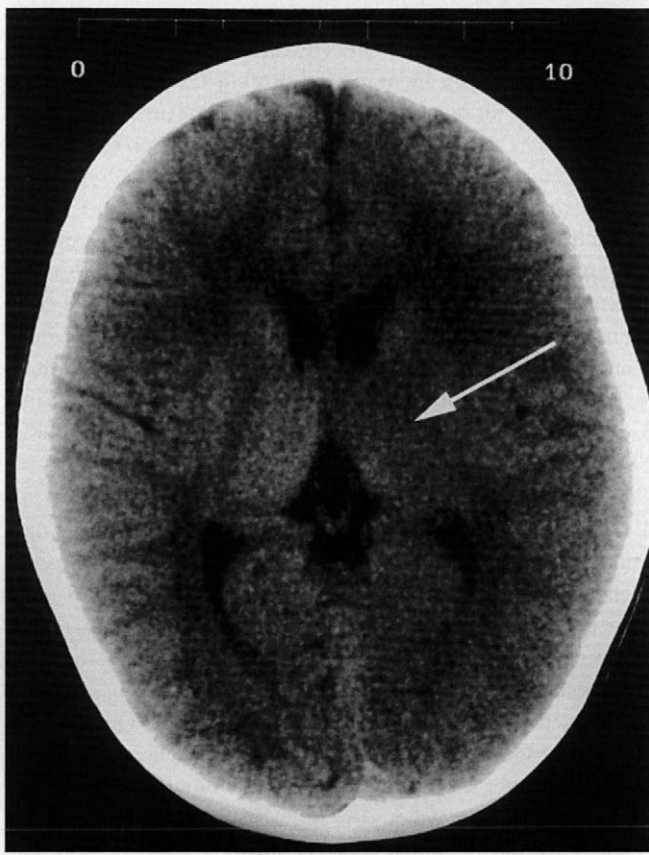


Figure 1. Cerebral computed tomographic scan from patient 1 demonstrates hypointense signal of the left thalamus (arrow) and flattening of the gyri, narrowing of the sulci, and loss of gray- and white-matter differentiation localized to the left hemisphere.

right thalamus (Figure 2). Cerebral magnetic resonance angiography and echocardiography were normal. The electroencephalogram (EEG) was characterized by diffuse slow-wave activity on the left in the range of 3 to 4 Hz. Hematologic investigations uncovered the factor V Leiden mutation, and the patient, her mother, and two sisters were found to be heterozygous carriers of the mutant gene. She was prescribed valproic acid for control of her seizures and was referred for physiotherapy and occupational therapy. Over the years, she has developed a diffuse progressive atrophy of the left hemisphere (Figure 3). Now, at age 5 years, she is left-handed and walks well, but with a tendency to stumble easily. She has good language comprehension but has limitations in her expressive speech. Repeat interictal EEGs have been normal. Seizures are well controlled except for those recurrences associated with fever, including another febrile status epilepticus, with no new neurologic deficit.

### Patient 2

This is a 13-year-old girl who first presented at age 11 years following a complex partial seizure with secondary generalization complicated by a post-ictal hemiplegia on the right side and an expressive dysphasia. Her past medical history revealed a normal gestation and labor. Apgar scores at birth were 10 at 1 minute, 10 at 3 minutes, and 10 at 5 minutes. She was diagnosed at 2 months of age with a congenital torticollis. At the initial consultation, she was noted to have a mild hyperreflexia, hypertonia, and weakness on the left side. There were no other developmental or cognitive deficits, and her condition resolved completely with physiotherapy. At 8 months of age, she was discharged from the clinic.

At 11 years old, she had her first convulsive episode. The convulsions started with clonus of her right upper limb that subsequently became gen-

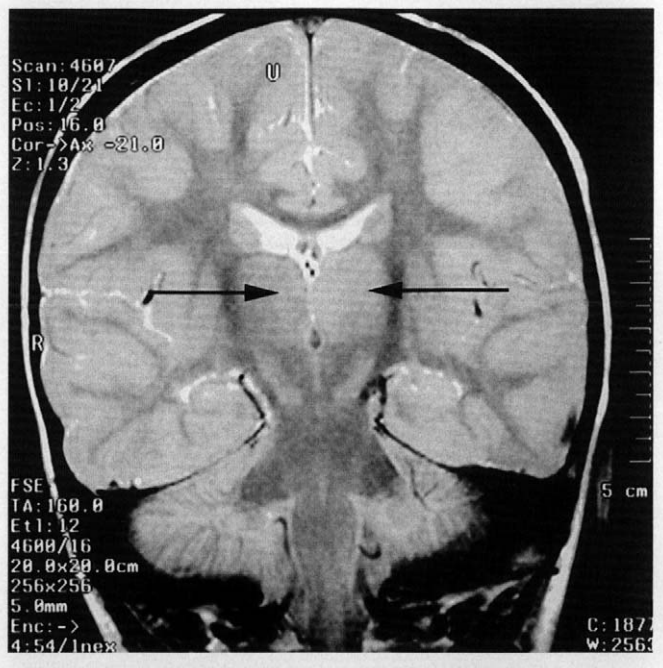


Figure 2. T<sub>2</sub>-weighted magnetic resonance image from patient 1. Coronal section demonstrates bilateral thalamic hypersignality left > right (arrows).

eralized. On arrival at the hospital, she had an axillary temperature of 37°C. She was aphasic with a right hemiparesis involving the upper more than the lower limbs. A CT scan was normal. She was started on valproic acid and was subsequently transferred to pediatric neurology. Physical examination on arrival showed weakness, hyperreflexia, and a hemianopia on the right side. She also had an expressive aphasia.

Routine laboratory investigations, electrocardiography, echocardiography, and a repeat CT scan were normal. Cerebral MRI, magnetic resonance angiography, and single-photon emission computed tomographic (SPECT) scans were normal. An EEG done on admission showed a slow-wave abnormality predominantly on the left with an abundance of epileptiform activity originating from the left centrotemporal region. She was found to be a heterozygous carrier of the factor V Leiden mutation and to be homozygous for the *MTHFR* C677T mutant gene. She subsequently recovered well in hospital, and a repeat EEG showed a disappearance of the epileptiform activity; however, the slow-wave abnormality persisted. She was discharged on carbamazepine controlled release 300 to 400 mg for control of her seizures. Her only residual motor deficits were mild weakness of her right hand accompanied by an impediment of verbal expression. She was not treated initially for her thrombophilia. She was readmitted for a second episode of hemiparesis and aphasia following a generalized tonic-clonic convulsion. The episode had a partial onset starting with clonus of the right upper limb. Although MRI/magnetic resonance angiography continued to be negative, she was suspected of having a left-sided cerebrovascular accident and was anticoagulated and started on preventive long-term warfarin therapy. A routine EEG showed spikes located at T<sub>3</sub> on the left on a background of generalized slow-wave activity with left-sided predominance. This focus was confirmed by video EEG as the ictal onset zone (Figure 4). Subsequent MRI and interictal SPECT showed small changes in the nuclei of the gray matter of the left cerebral cortex associated with mild left cerebral hemiatrophy (Figure 5). The patient has had no recurrence of hemiparesis since being started on warfarin approximately 2 years previously, and the seizures are well controlled on carbamazepine.

### Discussion

Hemiconvulsion, hemiplegia, and epilepsy is a rare syndrome first described by Gastaut et al in 1959<sup>12</sup> and characterized by an

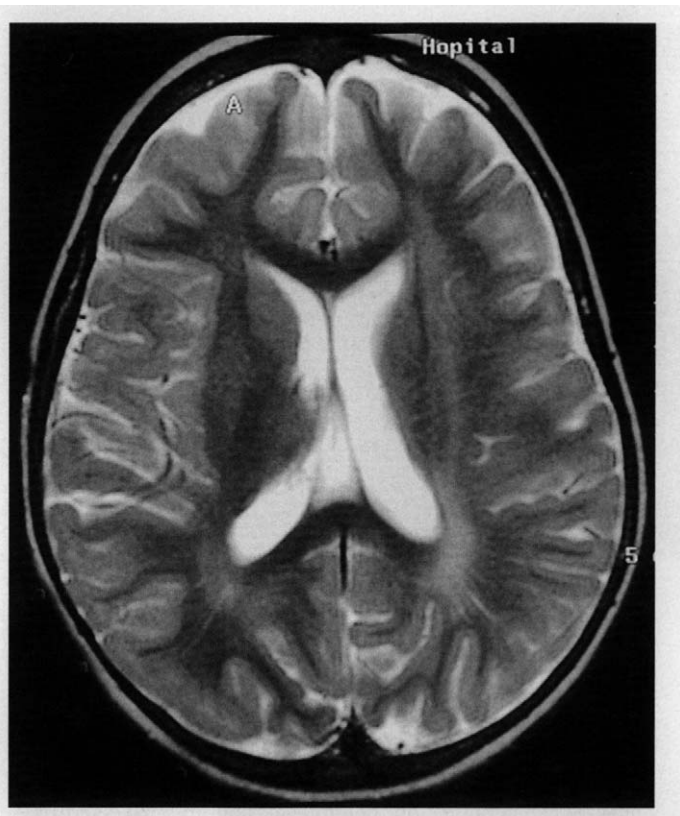


Figure 3. T<sub>2</sub>-weighted magnetic resonance image from patient 1. Axial section demonstrates diffuse gray- and white-matter atrophy and hypersignal localized to the left hemisphere.

initial acute episode of hemiconvulsions followed by hemiplegia that generally first appears between the ages of 6 months and 4 to 6 years.<sup>13</sup> Studies have shown that greater than 90% of cases occur before the age of 2 years, with a median age of approxi-

mately 16 months.<sup>12,13</sup> Rarely do patients present after the age of 6 years; however, presentations between the ages of 6 and 11 years, as in our second patient, can occur.<sup>13,14</sup> In 47 to 75% of cases, the acute hemiplegia and hemiconvulsions are precipitated by a febrile related illness and there is a recognized association between hemiconvulsion, hemiplegia, and epilepsy syndrome and a family history of seizures, a past history of prolonged febrile seizures, or previous convulsive episodes.<sup>12,13,15,16</sup> Most often, hemiconvulsion, hemiplegia, and epilepsy occurs, as in the two children of this report, in previously neurologically normal subjects.<sup>12</sup> Fundamental to the diagnosis of hemiconvulsion, hemiplegia, and epilepsy syndrome is the initial occurrence of hemiconvulsions, which are principally described as starting with deviation of the head and eyes to one side followed by clonic unilateral rhythmic limb movements, as in our patients.<sup>12</sup> Hemiconvulsions can precede or follow generalized tonic-clonic convulsions and can be associated with atypical presentations that include bilateral clonus with predominance of one side or unilateral clonus that can switch sides; in the latter, the hemiplegia always supervenes on the side that was affected second.<sup>17</sup> These hemiconvulsions tend to have a long duration and will evolve into status epilepticus if left untreated.<sup>12,13,16</sup>

The convulsive episode is then followed by an acute hemiplegia, which, in most cases, occurs on the side expressing the hemiconvulsions but can occur on the opposite side.<sup>17</sup> Aphasia, mainly of the expressive type, and hemianopia, as seen in our patients, have been previously reported.<sup>13</sup> Their occurrence depends on the side of the lesion and the severity of the cerebral edema and cerebral hemiatrophy associated with this syndrome.

In the acute stage, CT or MRI findings in hemiconvulsion, hemiplegia and epilepsy syndrome are cerebral edema with unilateral predominance followed by the development of cerebral hemiatrophy and ventricular dilatation in the convalescent stage.<sup>14,16,18</sup> In

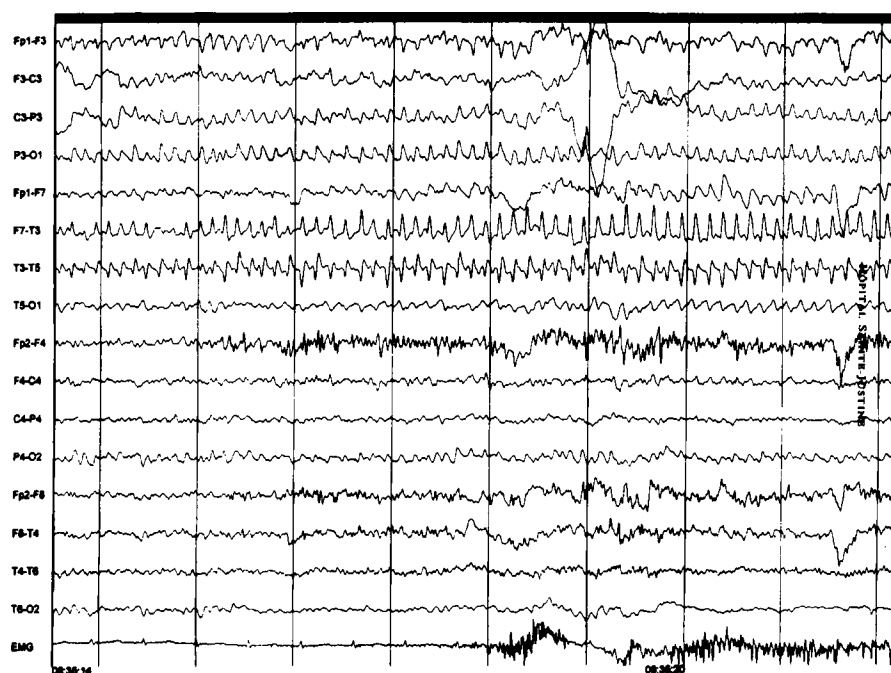


Figure 4. Electroencephalogram of patient 2. Bipolar montage demonstrates left temporal rhythmic seizure activity during a typical convulsion.



Figure 5. A, T<sub>2</sub>-weighted magnetic resonance image from patient 2. Axial section demonstrates very mild atrophy of the left cerebral cortex. B, Interictal single-photon emission computed tomographic scan from patient 2. Axial section demonstrates diffuse hypoperfusion despite minimal atrophy involving the left cerebral cortex.

our study, in the acute phase, patient 1 had thalamic lesions with no obvious cerebral hemiatrophy and patient 2 had no abnormality. A study of 23 cases of cerebral hemiatrophy attributable to both hemiconvulsion, hemiplegia, and epilepsy syndrome and Dyke-Davidoff-Masson syndrome has shown that ipsilateral thalamic atrophy had its highest association with a febrile related event, whereas cortical changes were shown to be more prevalent in patients without prolonged febrile convulsions.<sup>16</sup> As previously reported, the absence of cerebral edema found in the second patient is a common finding in hemiconvulsion, hemiplegia and epilepsy syndrome.<sup>18</sup>

Approximately two-thirds of patients with acute hemiplegia and hemiconvulsions go on to develop epilepsy<sup>12-14</sup> after a variable period ranging from 1 month to as high as 20 years<sup>13,14</sup>—hence the name hemiconvulsion, hemiplegia, and epilepsy syndrome. The epilepsy causes partial motor, complex partial, generalized tonic-clonic, myoclonic, or multiple seizure types that vary with age.<sup>12-14,17</sup> Seizures of temporal lobe origin are described as occurring most commonly; however, other epileptogenic localizations are reported, including suprasylvian, parietal, frontal, and multifocal abnormalities.<sup>12,17</sup> In our report, interictal EEG and video-EEG monitoring localized the origin of the seizures to the temporal lobe in patient 2, whereas localization has not been confirmed in the first child. However, given its association with prolonged febrile convulsions, the epilepsy is most likely to be of temporal lobe origin.<sup>15,19</sup> Both of our cases were discharged on anticonvulsants and are relatively well controlled.

The most common acute EEG findings in hemiconvulsion, hemiplegia, and epilepsy syndrome are bilateral slow waves with highest amplitude ipsilateral to the side of the hemiplegia, which improves with arrest of the seizures.<sup>12</sup> Subsequent epilepsy and EEG abnormalities most often occur ipsilateral to the hemiatrophy but can occur contralaterally or bilaterally if the hemiatrophy is pronounced.<sup>14</sup> In our report, the first child's EEG demonstrated the classic findings, whereas in the second, the slow waves and epileptiform

activity were identified bilaterally, with greatest frequency and highest amplitude over the involved side.

Cerebral venous thrombosis is thought to be the principal cause of hemiconvulsion, hemiplegia, and epilepsy syndrome. Cerebral arterial thrombosis, encephalitis, subdural hematoma, and other progressive neurologic disorders have also been implicated.<sup>12-15</sup> In our study, factor V Leiden mutation was diagnosed genetically by polymerase chain reaction amplification of DNA followed by digestion with restriction enzyme *MnI*. We were unable to positively identify cerebrovascular thrombosis in both of our cases, and this is in keeping with several other studies of patients with hemiconvulsion, hemiplegia, and epilepsy syndrome.<sup>12-15</sup> Despite the lack of confirmatory evidence of thrombosis on MRI/magnetic resonance angiography, we suggest that patients presenting with acute hemiconvulsions and hemiplegia should be investigated for factor V Leiden mutation. A positive finding increases the likelihood of thrombosis as the cause and allows for consideration of anticoagulation to prevent recurrence or progression.<sup>20</sup>

Recurrence of thrombosis is another important consideration. Heterozygous carriers of the factor V Leiden mutation alone have been shown in several studies not to be at a significantly increased risk of recurrence of venous thrombotic events as compared with those patients without an identifiable coagulopathy,<sup>21-24</sup> but they are thought to be at an increased risk in combination with other prothrombotic states, including a febrile illness or other thrombophilic factors.<sup>20</sup> In our report, patient 1 had febrile status epilepticus, whereas patient 2 had a combination of factor V Leiden mutation and *MTHFR C677T* mutation as contributing factors. In its homozygous form, the *MTHFR* mutation is a known cause of hyperhomocysteinemia and, as such, is thought to be an independent risk factor for venous and arterial thrombosis.<sup>25</sup> Case-control studies have not been able to prove conclusively that patients with hyperhomocysteinemia owing to the *MTHFR* gene mutation or patients with a combi-

nation of factor V Leiden mutation and *MTHFR* are at an increased risk of thrombosis or recurrence.<sup>26,27</sup> One case-control study has found evidence, in a small number of patients, that the combination of *MTHFR* and the factor V Leiden mutation can unfavorably affect the clinical course of transient ischemic attack or minor stroke.<sup>28</sup> In light of these data, we propose that perhaps the initiation of acute anticoagulation and long-term warfarin therapy in our second patient may account for her better outcome with milder cerebral hemiatrophy as compared with the first patient.

### Conclusion

The two children reported argue in favor of a link between factor V Leiden mutation and hemiconvulsion, hemiplegia, and epilepsy syndrome. However, the high incidence of factor V Leiden mutations in our population requires that our findings be interpreted with caution. Over the past 5 years, the only other case of hemiconvulsion, hemiplegia, and epilepsy syndrome diagnosed at our institution was attributable to Rasmussen's encephalitis. We believe that a genetic abnormality in the coagulation cascade should be ruled out in every child presenting with hemiconvulsions and hemiatrophy. In the presence of a positive finding, the initiation of therapeutic and long-term prophylactic anticoagulation should be carefully considered as this may improve long-term outcome.

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Received April 2, 2002. Accepted for publication May 13, 2002.

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