16p13.11 Microdeletion in a Patient With Hemiconvulsion-Hemiplegia-Epilepsy Syndrome: A Case Report

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Abstract
We describe a patient with hemiconvulsion-hemiplegia-epilepsy syndrome. The pathophysiology of hemiconvulsion-hemiplegia-epilepsy syndrome remains uncertain and there are probably multiple potential contributing factors. Our patient had a chromosomal 16p13.11 microdeletion that confers susceptibility to various types of epilepsy. This is the first report detailing an association of hemiconvulsion-hemiplegia-epilepsy syndrome with a 16p13.11 deletion and identifies another potential causal factor for hemiconvulsion-hemiplegia-epilepsy syndrome.

Keywords
hemiconvulsion-hemiplegia-epilepsy syndrome, 16p13.11 microdeletion, susceptibility loci

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Hemiconvulsion-hemiplegia-epilepsy syndrome was first described in the mid-1950s.¹ It is a rare sequel of prolonged focal status epilepticus. Children are usually younger than age 4 years and have fever-associated seizures. Initial acute cytotoxic edema in the affected hemisphere is followed by hemispheric atrophy. Magnetic resonance imaging (MRI) findings at onset often show hyperintensity of the white matter on diffusion-weighted imaging, predominantly involving the subcortical U-fibers.² After a variable time (between 1 and 2 years), the children develop epilepsy that is often refractory to medication. The pathophysiology is not well understood and a combination of factors seems likely.³

We describe a patient diagnosed with hemiconvulsion-hemiplegia-epilepsy syndrome who was found to have a chromosomal 16p13.11 microdeletion.

Case Report
Our patient was a previously healthy, developmentally normal, nondysmorphic girl born to unrelated parents.

At age 17 months, she had a cluster of 5 febrile convulsions over approximately 3 hours. She was successfully treated with midazolam and phenytoin and made an uncomplicated recovery. An MRI and electroencephalography (EEG) showed no significant abnormality.

At age 23 months, she re-presented with a 45-minute left-sided motor seizure while febrile. This stopped only after several doses of midazolam. She had a prolonged left-sided hemiparesis but was otherwise well. The hemiparesis persisted. On day 3 of her admission, she had a recurrence of high temperatures and associated refractory left-sided motor seizures unresponsive to loading with phenytoin and phenobarbitone. She was admitted to the intensive care unit.

An MRI showed cytotoxic edema affecting most of her right hemisphere with hyperintensity of the subcortical white matter (Figure 1). A lumbar puncture was normal (see below). She became seizure-free with a continuous midazolam infusion. This was stopped after 12 hours. Twenty-four hours later, her seizures returned and levetiracetam was added. Over the next hours, the patient became increasingly obtunded and showed signs of increased intracranial pressure. A computed tomography revealed hemispheric swelling with midline shift (Figure 2).

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and she required life-saving decompressive craniectomy on day 6 after admission.

EEGs before and after craniectomy showed background suppression of the right hemisphere, but no epileptic discharges. An MRI 3 days after her craniectomy showed extensive edema of the entire right cerebral hemisphere, now also involving the deep gray matter, with restriction on diffusion sequences (Figure 3) suggesting infarction.

She made a good recovery of consciousness following the surgical decompression; however, there was persistent dense left-sided hemiparesis.

She remained seizure free for 4 months, but then developed refractory left-sided complex partial seizures. Her seizures occurred up to 7 times daily lasting up to 5 minutes. An MRI 5 months after the initial presentation showed severe atrophy of her right hemisphere (Figure 4).

On follow-up, at age 3 years 2 months, she has a residual spastic left hemiparesis and corresponding homonymous hemianopia. She is able to walk with her ankle foot orthosis and has some function in her left hand. She has some mild cognitive delays. She is seizure free on carbamazepine and clonazepam.

**Diagnostic Workup**

The 16p13.11 microdeletion was detected by comparative genomic hybridization microarray (a 60 k ISCA design oligo array [Bluegnome], v2.5 software with probes mapped to GRCh37(hg19)). The deletion spanned 1.34 Mb (chr16:

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**Figure 1.** On day 3 after presentation (axial diffusion-weighted imaging): Edema of the right cortex and white matter with typical involvement of the subcortical U-fibers. **Figure 2.** On day 6 after presentation (axial computed tomography): Hemispheric swelling and midline shift. **Figure 3.** On day 10 after presentation (axial diffusion-weighted imaging): Edema and restricted diffusion involving the entire right hemisphere. **Figure 4.** At 5 months after presentation (axial T2): Marked atrophy of the right hemisphere.
14,968,878-16,311,041). The 13 genes in the region are as follows:

NOMO1, NPIP, PDXDC1, NTAN1, RRN3, MPV17L, C16orf45, KIAA0430, NDE1, MYH11, FOPNL, ABCC1, and ABC6.

The patient’s mother who is healthy and intellectually normal was found to have the same microdeletion as tested by FISH analysis with the MYH11 probe (Cytocell).

Other normal genetic investigations included SCN1A sequencing and MLPA; testing of exons 4, 5, 16, 17, and 36 of CACNA1A; and testing of the 3 most common POLG mutations (c.1399G>A, c.2243G>C, and c.2542G>A). Metabolic investigations were all normal and included an earlier newborn screening test, blood glucose, ammonia, lactate, blood gas analysis, transferrin isoforms, acylcarnitine profile, plasma amino acids, and urine metabolic screen.

Other negative acute investigations included cerebrospinal fluid, blood, and urine culture; cerebrospinal fluid polymerase chain reaction test for herpes simplex virus types 1 and 2 and varicella zoster virus; a nasopharyngeal aspirate for influenza A, influenza B, respiratory syncytial virus, metapneumovirus, adenovirus, and parainfluenza virus types 1, 2, and 3; and fecal analysis for rotavirus and adenovirus antigens.

Discussion

This is the first case report describing the possible association of hemiconvulsion-hemiplegia-epilepsy syndrome with a 16p13.11 microdeletion.

The 16p13.11 microdeletion was first described in 2007 associated with autism and intellectual impairment. Although it has never been reported in hemiconvulsion-hemiplegia-epilepsy syndrome, several articles have suggested associations with intellectual impairment, autism, attention-deficit hyperactivity disorder (ADHD), schizophrenia, and/or microcephaly. However, it is possible to have the microdeletion and have no intellectual deficits or symptoms. That is, the condition causes a susceptibility to neurodevelopmental conditions and is autosomal dominant with reduced penetrance. Recently, evidence of a male-biased autosomal effect has emerged; males with the microdeletion are more likely to manifest symptoms.

Trobeano et al provide good epidemiologic evidence regarding the frequency of 16p13.11 microdeletions in control populations. They found 4 of the 10 375 (0.04%) individuals with no past psychiatric history in their sample had 16p13.11 microdeletions. A population of patients with either developmental delay/intellectual disability, autism spectrum disorders, ADHD, specific developmental delays such as speech or language delay, or birth defects was also examined (data available in Brain and Body Genetic Resource Exchange database; http://bbgre.org). In that sample, 16 of 10397 (0.15%) had one of the common-sized 16p13.11 microdeletions. The odds ratio between the 2 groups was 4.00 (1.34-11.96) with a P value of .007. Detailed phenotypic data were available from 8 of 16 individuals in the Brain and Body Genetic Resource Exchange and 2 of 8 had seizures.

There is also evidence that 16p13.11 deletions cause a particular predisposition to epilepsy. 16p13.11 deletions were detected in 23 of 3812 (0.6%) patients with a diverse spectrum of epilepsy syndromes and in 0 of 1299 neurologically normal controls. The 23 patients had either partial epilepsy (focus unknown, temporal lobe, or frontal epilepsy), childhood absence epilepsy, or juvenile absence epilepsy. Another study by De Kovel et al found 2 of 3022 (0.2%) controls had a 16p13.11 deletion versus 6 of 1234 (0.5%) patients with idiopathic generalized epilepsy. Four of the 6 patients had childhood absence epilepsy, 1 had juvenile myoclonic epilepsy, and 1 had epilepsy with generalized tonic-clonic seizures. A third study by Mefford et al showed 16p13.11 microdeletions in 4 of 517 (0.77%) patients with epilepsy. Three patients had juvenile myoclonic epilepsy and 1 had childhood absence epilepsy.

In this case report, it is interesting that the patient’s mother also has the 16p13.11 microdeletion but has no symptoms. To many clinicians, this may seem unusual but it illustrates the important point that many chromosomal microdeletion syndromes are autosomal dominant conditions with incomplete penetrance and variable expressivity. There are many examples of such “chromosomal susceptibility loci” (eg, microdeletions or microduplications involving 15q11.2, 15q13.3, 16p11.2, 16p13.13, and microdeletions involving NRXN1, plus many others).

It is difficult to draw conclusions from an isolated case report but the association of 16p13.11 microdeletions with seizures suggests that this chromosomal deletion along with potential modifying factors predisposed to the hemiconvulsion-hemiplegia-epilepsy syndrome in our patient.

There is possibly a synergistic relationship in hemiconvulsion-hemiplegia-epilepsy syndrome between inflammation and seizures that potentiates status epilepticus and promotes cellular damage. Contributing factors in other children may have included focal epileptogenic lesions, venous thrombosis, human herpes virus 6, human herpes virus 7, metabolic conditions, CACNA1A mutations, SCN1A mutations, and head trauma.

This case report provides further support for the concept that multiple additive predispositions and events lead to the phenotype that is hemiconvulsion-hemiplegia-epilepsy syndrome. We await further reports of chromosomal microdeletions or duplications contributing to hemiconvulsion-hemiplegia-epilepsy syndrome.

Authors’ Note

The child described was evaluated and treated at John Hunter Children’s Hospital, Newcastle, Australia. The case was presented as a poster at the Epilepsy Society of Australia meeting in 2012. The title of the poster was “Hemiconvulsion-Hemiplegia Epilepsy (HHE) Syndrome With Therapeutic Decompressive Craniectomy in a 2 Year Old Girl.”

Author Contributions

CIM and BK were both responsible for preparation and submission of the manuscript. RLS, GS, CIM, and JEB were responsible for the care of the patient. RLS also provided guidance with regard to this publication and revised the manuscript. BK was the Clinical Geneticist
overseeing genetic investigations. NLB performed most of the laboratory work.

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**Ethical Approval**
The parents gave consent to the publication of this case report. The parents also gave written consent to the genetic investigations of their child and themselves.

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