

## CLINICAL COMMENTARY

# ILAE neuroimaging task force highlight: Subcortical laminar heterotopia

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**Abstract**

The ILAE Neuroimaging Task Force publishes educational case reports that highlight basic aspects of neuroimaging in epilepsy consistent with the ILAE's educational mission. Subcortical laminar heterotopia, also known as subcortical band heterotopia (SBH) or “double cortex,” is an intriguing and rare congenital malformation of cortical development. SBH lesions are part of a continuum best designated as agyria-pachygyria-band-spectrum. The malformation is associated with epilepsy that is often refractory, as well as variable degrees of developmental delay. Moreover, in an increasing proportion of cases, a distinct molecular-genetic background can be found. Diagnosing SBH can be a major challenge for many reasons, including more subtle lesions, and “non-classic” or unusual MRI-appearances. By presenting an illustrative case, we address the challenges and needs of diagnosing and treating SBH patients in epilepsy, especially the value of high-resolution imaging and specialized MRI-protocols.

**KEYWORDS**

double cortex, epilepsy, neuroimaging, subcortical band heterotopia, subcortical laminar heterotopia

## 1 | CASE PRESENTATION

A right-handed 18-year-old female patient presented to the adult epilepsy center in Erlangen, Germany, with refractory focal epilepsy since the age of 6 years. Her habitual seizures were described either as subtle twitching of the head to the right and/or sudden movements of the left arm. At times she

was aware of an impending seizure due to sensory symptoms in the left arm. Focal to bilateral tonic-clonic seizures were not reported; however, the patient's father mentioned events with stiffening on the left side of the body sometimes leading to falls. Seizures would occur especially in the morning, and no seizures during sleep were noted by the family. Pregnancy, birth, and early development were reported as normal. However,

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learning difficulties developed in primary school and she subsequently attended a special school. Febrile seizures, meningitis or trauma were not reported. A younger sister and an older half-brother were healthy without developmental delay or seizures. A cousin experienced seizures during childhood, being currently seizure free without medication.

Her current anti-seizure medications (ASM) were valproate and topiramate and many were previously tried including carbamazepine, oxcarbazepine, zonisamide, lacosamide, gabapentin, and levetiracetam. Routine scalp EEG showed intermittent right frontal slowing and spike wave patterns. Ictal recordings were not available at this time. MRI at age 6 years had been reported as normal. MRI at age 10 (see [Figure 1A](#)) was reported as showing a lobar dysplasia. Subsequent review suggested there was a “band-like lesion” (see [Figure 1B](#)). Genetic testing at age 10 identified a LIS1-mutation (see below).

## 2 | COMPREHENSIVE INVESTIGATIONS

### 2.1 | Video-EEG

At age 18, video-EEG monitoring over several days recorded numerous of her habitual seizures characterized by short tonic extension of the left arm and turning of the head to the right. Larger seizures were associated with bilateral proximal arm abduction and head/neck flexion, with facial grimace. Some brief seizures showed only subtle head turn to the right with loss of tone in the arms followed by jerks or stiffening. Ictal EEG was often unremarkable, but at times displayed right frontal spike wave patterns and in one seizure showed right fronto-temporal rhythmic theta evolving to bifrontal spike waves. Interictal EEG showed intermittent slowing and frequent interictal epileptiform discharges (IEDs) over right frontal areas (Fp2, F4, Fz), either as single patterns or more frequently as longer runs and polyspikes/polyspike-waves during sleep, occasionally evolving to bilateral synchronous IED but with a right frontal lead. Neuropsychological testing showed reduced abilities over a wide range of cognitive functions.

### 2.2 | Magnetic/electric source imaging

MEG/EEG (WHS3600, 4D-Neuroimaging, San Diego, CA, USA) recordings showed numerous IED with complex topography. Source analysis using dipole localization and distributed source modeling methods (CLARA) yielded diffuse activity in the right inferior frontal gyrus, with additional, potentially propagating activity in frontopolar areas, the frontal operculum and the precentral gyrus.

### Key points

- We present a case with subcortical laminar heterotopia, a rare congenital malformation of cortical development.
- Subcortical laminar heterotopia is characterized by heterotopic gray matter below the orthotopic cortex in laminar formations.
- The malformation is associated with epilepsy and developmental delay.
- No typical semiology or characteristic EEG patterns pose diagnostic challenges.
- Lesions are easily seen on adequate MRI, but atypical or subtle variants may be overlooked.

### 2.3 | MRI investigation in general anesthesia

MRI (Aera 1.5T, Siemens, Erlangen, Germany) included sequences according to the HARNES protocol<sup>1</sup>: Isotropic 3D MPRAGE (TR/TE/FA = 2200/3.79 ms/15°, voxel size 1 × 1 × 1 mm), 3D FLAIR (TR/TE/FA = 5000/333.0 ms/120°, voxel size 1 × 1 × 1 mm) and coronal T2 perpendicular to the hippocampal axis with high in-plane resolution (TR/TE/FA: 5510/96.0 ms/150°, .36 × .36 × 3.7 mm). These images (see [Figure 1D–G](#)) showed distinct pericentral-posterior localized band-like subcortical gray matter (= subcortical laminar heterotopia or SBH), in the right greater than left hemisphere. This abnormality was easier to visualize with MRI-postprocessing ([Figure 1C](#), morphometric analysis program (MAP18),<sup>2</sup>).

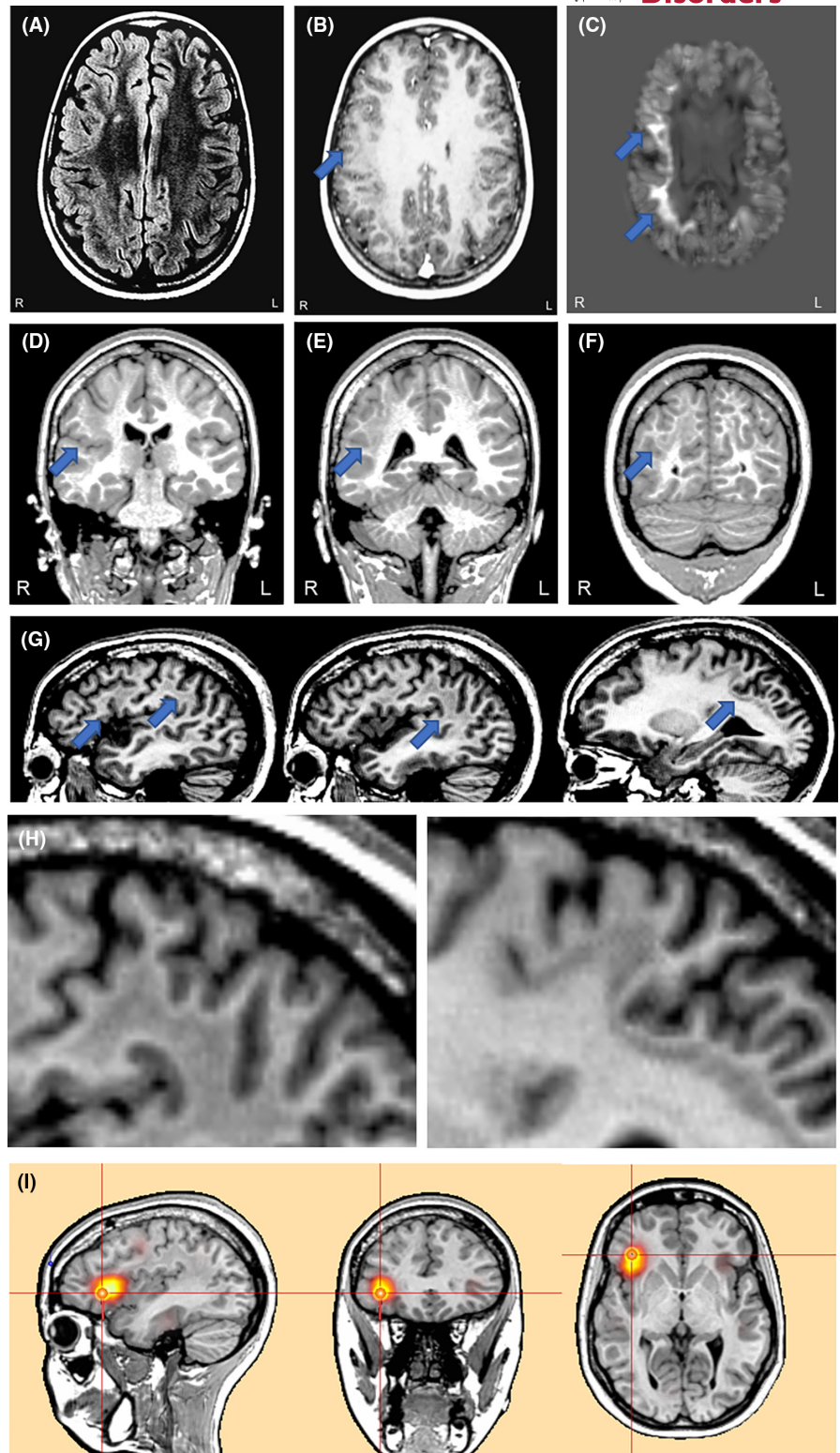
### 2.4 | Genetics

Genetic evaluation according to the original report from age 10 years had yielded an 18-nucleotide deletion in exon 6 of LIS1 (codons 143 to 149; nt429\_446delACGAACTCTTAAAGGACA) leading to deletion of 6 amino-acids of the LIS1-protein with additional exchange of glutamic-acid by aspartic-acid at position 143 (E143\_H149delinsD). This was designated as “not described so far,” but ranked significant and causal, as it would lead to a change within a critical protein site.<sup>3</sup>

### 2.5 | Further treatment course

Epilepsy surgery was not suggested due to the large and bilateral distribution of the lesions, the varying semiology and rather poor post-surgical outcomes previously

**FIGURE 1** Patient MR-Imaging: (A and B) first MRI in childhood not interpreted as subcortical band heterotopia (SBH): (A) FLAIR, (B) T1-MPRAGE. (C) MAP-Analysis indicating band heterotopia right more than left (morphometric analysis program [MAP18], combined z-score map, summarizing features from extension-, junction-, and thickness-maps). (D–F) New MRI, T1-MPRAGE, various coronal planes displaying the SBH. (G and H) Lesion best seen on sagittal T1, laterally appearing as “gray filled” “white matter,” medially as SBH. (H) Zoomed in images on images G left and right. (I) Magnetic source imaging visualizing interictal activity with frontal localization.



reported from literature.<sup>4</sup> Instead, implantation of a vagal nerve stimulator (VNS) was offered and pursued after further ineffective pharmacotherapy regimen, with some improvement of seizure frequency. Her seizures persisted in a pharmacoresistant course. Further optimization of ASM however could minimize impact on alertness and mood, allowing for an acceptable quality of life.

### 3 | DISCUSSION

Despite prior imaging, medically refractory epilepsy and developmental delay, the structural etiology of this patient's epilepsy was not revealed until repeat imaging with updated protocols revealed the subtle structural changes. This highlights the importance of imaging patients with the correct



“epilepsy protocol” sequences, such as the isotropic “3D” T1-weighted and FLAIR sequences with millimetric or submillimetric resolution, as included in the standard HARNESS protocol recommended by the ILAE.<sup>1</sup> It also demonstrates the value of re-imaging patients who have had prior “normal” imaging, with “epilepsy protocol” sequences, particularly if epilepsy is medically intractable or a surgical option is being pursued. In patients with limited cooperation (e.g., due to developmental delay), general anesthesia can improve image quality by reducing motion artifacts. Finally, it shows that when findings from visual inspection of structural MRI are equivocal, post-processing can be helpful to confirm the presence of structural abnormalities.

While volumetric T2-weighted acquisitions such as FLAIR are helpful to highlight epileptogenic lesions such as gliosis and focal cortical dysplasia, some lesions such as subcortical laminar heterotopia are more readily appreciated on T1 weighted images. In MRI evaluation, a main point is to search for aberrant “gray like” signal in the white matter core below the cortical surface (best done on sagittal planes in T1-weighted images, [Figures 1G,H](#) and [2C,D](#)) and/or a seemingly “thickened” cortical band ([Figure 2E,F](#)), as the heterotopic layer can lay very close below the lower border of the cortex with a separating strip of white matter not always apparent at first glance ([Figure 2E–G](#)). Another subtle imaging feature of SBH is an altered cortical folding with the appearance of “coarse” gyration (depending on MRI planes, [Figure 2E,F](#)). In more subtle SBH, the brain might appear normal at first glance due to absence of striking gyral aberrations and/or strict symmetry of the lesion, which increases the chance of remaining undiagnosed.

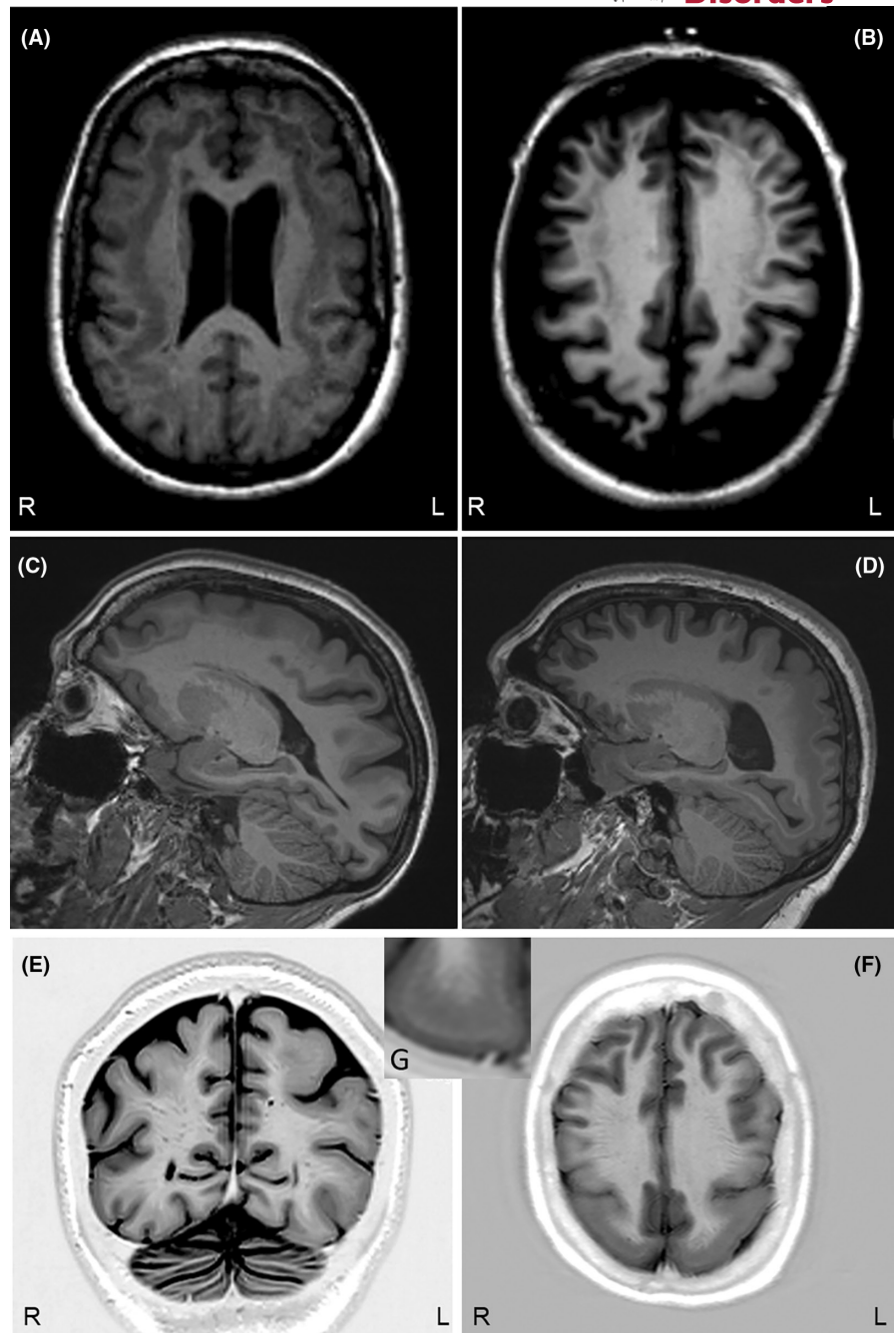
MRI-postprocessing methods such as MAP, which performs a statistical comparison of the given MRI to a database of healthy controls ([Figure 1C](#)), can facilitate the detection of SBH.<sup>2</sup> A grading system has been suggested integrating both imaging and clinical parameters.<sup>5</sup> Neurons within heterotopic laminae are dysfunctional with increased excitability but embedded into complex neuronal circuits.<sup>6</sup> Microscopically, the misplaced band does not represent a true cortex. There are microscopic abnormalities that exceed the MRI-visible lesion.<sup>7,8</sup> Interestingly, fMRI and MEG studies have shown functional activations in heterotopic gray in SBH<sup>9–13</sup> as well as participation in epileptogenicity.<sup>10,14</sup> Humans and animal model data imply seizure origin from superficial cortex<sup>15</sup> and/or parts of the heterotopic lamina.<sup>16</sup>

Laminar heterotopia/SBH belongs to the *agyria-pachygyria-band-spectrum*.<sup>17</sup> Variability is large, ranging from subtle to thick subcortical laminae, to diffuse lissencephaly, with variations in lesion distribution (example shown in [Figure 2](#)). There are some imaging features that may suggest particular genetic etiologies.

An X-linked form due to mutations within the *DCX* gene on the long arm of chromosome X<sup>15,18–21</sup> (encodes doublecortin, stabilizes microtubules), is usually associated with an anteriorly predominant frontoparietal subcortical band in females. Males are much more severely affected, with lissencephaly, epileptic and developmental encephalopathy and severe psychomotor impairment.<sup>16,18</sup> Our patient had posterior distributed bilateral SBH, a pattern associated with mutations in the *LIS1* gene, located on chromosome 17p13.3.<sup>22,23</sup> *LIS1* regulates the protein dynein, which plays a role in movement of neuronal nuclei along microtubules. Mutations are associated with a range of structural abnormalities, including SBH, lissencephaly, and the Miller-Dieker syndrome.<sup>20,22</sup> Since description of *DCX* and *LIS1*, knowledge about molecular genetics in this field has expanded considerably: Tubulinopathies (e.g., *TUBA1A*), present with a range of phenotypes, including SBH, lissencephaly, simplified gyration and polymicrogyria as well as alterations of the cerebellum, corpus callosum, basal ganglia, and brainstem.<sup>24</sup> Mutations directly affect microtubule function impacting neuronal migration in addition to their role in mitosis, axonal transport, and synaptic connectivity.<sup>25</sup> There are a number of genes reported from patients presenting with SBHs<sup>5</sup> (e.g., *RELN*, *ARX*, *DYNC1H1*, *CEP85L*), for which no MRI features specific to genetic etiology have been identified. The majority of SBH-patients are reported female.<sup>26</sup> In some cases, MRI may suggest the involvement of a specific gene, for example, *DCX* in anterior dominating SBH<sup>21,27</sup> or *LIS1* in posterior bilateral SBH, such as in our patient.

Clinical phenotypes in SBH are highly variable and seem to correlate to a lesional extent, for example, distribution/thickness of the bands and associated findings.<sup>15,16,19</sup> While some patients show mild disabilities and/or subtle changes on MRI, patients with bilateral thick laminar heterotopia and/or pachygyria usually exhibit profound cognitive impairment.<sup>18</sup> Epileptic seizures usually begin in childhood, but may not occur until the second or third decade of life in some patients.<sup>15</sup> There is no pathognomonic seizure semiology with both “focal” and “generalized” electroclinical phenotypes reported. While multiple seizure types can occur suggesting multifocal epilepsy, even patients with extensive and bilateral SBH may present with only monomorphic seizures, implicating a unifocal onset that do not necessarily coincide with the most apparent MRI alterations,<sup>4,23</sup> for example, as in our patient ([Figure 1](#)). Correspondingly, ictal and interictal EEG patterns can appear highly focal. However, there are no EEG characteristics to SBH.<sup>28–30</sup> MRIs therefore need to be specifically examined for SBH in patients presenting with a range of epilepsy phenotypes, not just in severe, early onset epilepsy.

**FIGURE 2** Examples of subcortical band heterotopia (SBH) phenotype variation. (A and B) Prominent versus more subtle bilateral SBH. (C and D) Anterior versus posterior dominating SBH, pachygyria in C. (E and F) Aspect of pachygyria and cortical thickening, SBH discernible with detection of separating white matter “strip” (inset G) after detailed analysis.



The majority of patients show a difficult treatment course with persisting seizures. Results of epilepsy surgery are reported to be disappointing: In a study of eight patients undergoing individualized procedures including multiple subpial transections, lobectomy with amygdalohippocampectomy and additional anterior callosotomy in five,<sup>19</sup> only a single patient markedly improved after surgery (Engel 1, “free of disabling seizures”). A recent systematic review<sup>31</sup> reports on non-pharmacological treatment options (surgical approaches and neurostimulation) in 26 patients. Of 21 patients undergoing surgery, only two had an Engel 1 outcome. Due to the very low numbers, robust conclusions

whether some (and which) SBH-patients might benefit from a surgical approach cannot be drawn.

As seizure freedom is rarely achieved by ASM, optimized drug regimen should aim for a good balance between efficacy and potential side effects. In our case, ASM-regime change was able to significantly reduce negative effects on alertness and mood with considerable impact on the patient’s everyday life, although seizure freedom was not achieved. Neurostimulation methods, such as VNS, deep brain stimulation, or responsive neurostimulation may offer further treatment options; however, available evidence on efficacy and optimal techniques is sparse.<sup>23,31</sup>

## 4 | CONCLUSIONS

Subcortical laminar heterotopia/SBH (“double cortex”) is a rare CNS malformation frequently associated with difficult-to-treat focal epilepsy and developmental delay. SBH is characterized by heterotopic gray matter found below the orthotopic cortex in laminar formations, most often bilaterally, sometimes unilaterally.<sup>17</sup> The heterotopic lamina might be easily seen on HARNESS MRI, that is, by clearly visible prominent heterotopic bands separated from the overlying cortex. However, morphology is variable, more subtle lesions exist which can be overlooked or remain undiagnosed over years. Configuration and gyral pattern of overlying cortex may appear normal, but is often altered to varying degrees, described as pachygyria, depending on SBH severity and the underlying genotype.<sup>5</sup> Since there is no typical semiology and no characteristic ictal or interictal EEG patterns, neuroimaging provides the essential diagnostic tool. Distinct diagnosis relies on optimal imaging and review.

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## CONFLICT OF INTEREST STATEMENT

None of the authors have any conflict of interest to declare.

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
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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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**Test yourself**

1. Which sequences are especially useful to detect SBH?
  - A. SWI.
  - B. 3D T1.
  - C. T2.
  - D. DWI.
  - E. FLAIR.
2. What are potential signs of SBH on MRI?
  - A. Altered cortical relief (“pachygyria”).
  - B. Nodules of gray matter next to the ventricles.
  - C. Unusual cortical thickening.
  - D. “Blooming” on SWI.
  - E. Transmantle sign on FLAIR.
3. Mutations of which genes are related to SBH?
  - A. *SCN1A*.
  - B. *CDKL5*.
  - C. *LIS1*.
  - D. *PCDH19*.
  - E. *DCX*.

Answers may be found in the [supporting information](#).