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Sturge-Weber Syndrome: A comprehensive review of clinical features, optimized diagnosis and management strategies

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Abstract

Introduction: Sturge-Weber Syndrome is a rare neurocutaneous disorder characterized by facial port-wine birthmarks, leptomeningeal angiomatosis, and associated neurological, ophthalmological, and dermatological symptoms. The condition's variable presentation poses challenges for diagnosis, management, and long-term care. Advances in imaging, genetics, and targeted therapies are reshaping the landscape of Sturge-Weber Syndrome treatment.

Aim of Study: This review aims to summarize current knowledge on the clinical manifestations, diagnostic approaches, differential diagnoses, and treatment options for Sturge-Weber Syndrome, with a focus on the management of neurological, ophthalmological, and dermatological symptoms.

Material and methods: A comprehensive review of the literature on Sturge-Weber Syndrome was performed using the PubMed database.

Results and Conclusions: Sturge-Weber Syndrome is a complex disorder requiring a multidisciplinary approach to management. Neurological complications, particularly epilepsy, are a major concern, often necessitating pharmacological or surgical interventions. Ophthalmological issues, especially glaucoma, pose challenges across all age groups, with tailored treatments offering varying success. Dermatological symptoms, such as port-wine stains, benefit significantly from early pulsed dye laser therapy, often enhanced by adjunctive treatments like topical rapamycin. Emerging therapies, including sirolimus and aspirin, show promise in reducing complications. Advances in imaging techniques and targeted treatments offer hope for improved management, while lifelong

monitoring remains essential. Further research into the pathophysiology and therapies for Sturge-Weber Syndrome is critical to developing personalized and effective treatment strategies, ultimately improving patient outcomes.

Keywords: Sturge-Weber syndrome, port wine birthmark, glaucoma, seizures

1. Introduction

Sturge-Weber syndrome (SWS) is a rare, congenital neurocutaneous disorder characterized by a combination of dermatological, neurological, and ophthalmic manifestations. SWS affects both genders equally and is the third most common neurocutaneous syndrome after neurofibromatosis and tuberous sclerosis (1, 2). The condition results from somatic mutations in the GNAQ or the GNA11 gene, leading to abnormal endothelial cell signaling during embryonic development (3, 4).

The associated features of SWS include a facial port-wine birthmark (PWB), leptomeningeal vascular malformations, and glaucoma. The neurological manifestations of SWS are often severe and include strokes, seizures, cerebral atrophy, and intellectual impairments (5). While diagnosis is typically straightforward when the characteristic features are present, it can pose a challenge in neonates with no neurological manifestations (6). Lifelong, multidisciplinary medical care involving neurologists, ophthalmologists, dermatologists, neuropsychologists, and rehabilitative therapists, alongside standardized neuroimaging and cross-center studies, is crucial for diagnosing, monitoring disease progression, and guiding future clinical trials. (5, 7). The aim of this review is to provide a comprehensive overview of Sturge-Weber syndrome, focusing on the clinical features, pathogenesis, diagnostic challenges, and the importance of lifelong multidisciplinary care.

2. Pathogenesis

The discovery of a somatic activating mutation in the GNAQ gene (loqus 9q21.2) has been pivotal in understanding the pathogenesis of SWS and related vascular malformations (8). Somatic GNAQ mutations, predominantly p.R183Q, were identified in most capillary malformations (CM) with additional novel mutations (p.R183L and p.R183G) found in other cases, while some showed no detectable mutations. The variant allele frequency, ranging from 1% to 18%, supports the mosaic nature of SWS (5, 9).

GNAQ encodes the alpha subunit of the guanine nucleotide binding protein (Gαq), which activates phospholipase Cβ (PLCβ), by linking G-protein-coupled receptors (GPCR) (10). Upon GPCR activation, guanosine diphosphate (GDP) is released, and guanosine triphosphate (GTP) binds to GNAQ, leading to its activation via dissociation from the Gβγ complex. Leading to downstream effects on cellular growth and differentiation (9). The process is terminated through hydrolysis of GTP to GDP by GTPase-activating proteins (GAPs) (11). The R183Q mutation disrupts GTPase activity, preventing Gαq inactivation leading to persistent activation and promoting unchecked tumoral and vascular proliferation (12).

Recent reports of GNA11 gene variants have expanded the phenotypic spectrum of SWS. Patients with GNA11 mutations exhibit distinctive clinical features that differentiate them from classical SWS, including different presentation of CM and milder neurological manifestations (13).

In conclusion, variants in the GNAQ or GNA11 genes result in abnormal gain-of-function signaling pathways, leading to enhanced activity in endothelial cells during embryonic development. This aberrant signaling drives capillary overgrowth, impaired endothelial cell differentiation, and progressive dilation of immature venule-like vasculature (4). The embryological link between the ectoderm forming the frontonasal skin and the neural folds

forming the parieto-occipital brain regions supports the association between facial PWB and leptomeningeal angiomatosis. Abnormal endothelial cell differentiation in PWB regions further underscores these malformations (12).

3. Epidemiology

Sturge-Weber syndrome occurs with an estimated frequency of 1 case per 20,000–50,000 live births. The condition affects both males and females equally, regardless of race. It is one of the more common disorders among the group of neurocutaneous syndromes, ranking behind neurofibromatosis and tuberous sclerosis in prevalence (1, 2).

4. Characteristics of Sturge-Weber Syndrome

Sturge-Weber syndrome is a rare neurocutaneous disorder characterized by dermatological, neurological, and ocular manifestations. Key features include vascular malformations such as a port-wine birthmark on the facial skin and capillary and venous malformations in the brain, known as leptomeningeal angiomatosis (8). These malformations are typically unilateral and occur on the same side as the facial PWB. Additionally, SWS is associated with an increased risk of glaucoma, which may present at birth or develop later in life (14).

An early clinical classification of SWS was provided by the Roach scale, dividing SWS into three types:

Type I: Presence of facial capillary malformations and leptomeningeal angiomatosis; glaucoma may also be present (classic form of SWS).

Type II: Facial capillary malformations without brain involvement; glaucoma may occur.

Type III: Isolated leptomeningeal angiomatosis; glaucoma is rarely observed (1, 15).

While this classification was useful in the early stages of research, it is now considered imprecise. It suggests that all patients with facial capillary malformations, without brain or ocular involvement, belong to Type II, which is not always accurate. Current approaches allow for a more precise assessment of brain and ocular involvement risks by considering the location and extent of facial capillary malformations. The clinical course of SWS is highly variable and unpredictable, making its diagnosis and management challenging and requiring an interdisciplinary approach (14).

1. Neurological symptoms

The neurological manifestations of SWS are diverse, often severe, and significantly impact patients' quality of life. Common symptoms include strokes, stroke-like episodes, seizures, cerebral atrophy, calcifications, hemiparesis, visual field deficits, and intellectual impairments (5).

Seizures are the most common presenting symptom, typically appearing in infancy as focal motor or complex partial seizures (5). They arise from cortical irritability caused by cerebral vascular malformations, mediated through mechanisms of hypoxia, ischemia, and gliosis (1). Affecting 75–80% of patients overall and up to 93% of those with bilateral cerebral involvement Some infants may present with early handedness, hemiparesis or visual gaze preference instead of acute seizure (5).

Stroke-like episodes present as transient hemiparesis with or without speech impairments. The episodes are common in younger patients, most with onset before the age of 5. Seizures and head trauma, such as falls or blows to the head, were identified as the most common triggers (5, 16). These episodes closely resemble ischemic strokes clinically, but their course is variable, and brain magnetic resonance imaging (MRI) rarely reveals permanent infarctions, though they can lead to lasting neurological deficits (17). Recovery from these episodes was generally observed, with a median recovery time of 24 hours, although the range varied significantly (1 minute to 4392 hours) (16).

Headaches and migraines are prevalent in SWS, and in adult patients, often have a greater impact on quality of life, than seizures (18). They are frequently accompanied by visual or sensory-motor aura and can escalate into stroke-like episodes. These episodes are believed to result from vasomotor disturbances near the vascular malformation, triggering cortical spreading depression and oligemia (19).

Behavioral challenges are also common in SWS. Approximately 50% of patients report significant behavioral difficulties, 26% experiencing sleep disturbances, 40% of patients are affected by attention deficit hyperactivity disorder (20, 21). Autism spectrum disorder is more prevalent in patients with bilateral brain involvement. Notably, the severity of epilepsy does not appear to significantly influence behavioral problems (21, 22).

Neurological impairments in SWS are primarily due to venous strokes, seizures, migraines, or progressive brain injury, which are often detectable on imaging studies (5). Intellectual and language impairments are prevalent, with the severity of these deficits correlating with the extent of brain involvement. (22).

The presence of a facial port-wine birthmark is associated with more severe neurological outcomes, such as intellectual and language impairments (23). In contrast, patients without a PWB tend to experience later seizure onset and more favorable cognitive outcomes, which may reflect later mutation timing during fetal development, affecting fewer brain regions (22).

2. Dermatological symptoms

Sturge-Weber syndrome is characterized by the presence of facial capillary malformations visible at birth (24). Capillary malformations are the most common type of vascular malformation, affecting approximately 0.3% of the population (25). Most skin lesions in SWS have a characteristic appearance and location. These malformations, known as port-wine birthmarks, most commonly appear on the forehead, eyelids, or temples and are pink-red to purple in color (26). They may have a blotchy or geographic pattern and sometimes extend to the mucous membranes (14, 26).

In SWS, facial vascular lesions follow a specific anatomical distribution and are associated with an increased risk of leptomeningeal and ocular involvement. The likelihood of brain involvement ranges from 20–50%, depending on the size, location, and extent of skin involvement (24), while the risk of leptomeningeal or ocular involvement is estimated at 7–28% (18). The highest risk of central nervous system abnormalities is associated with extensive, bilateral facial involvement, covering one half of the face and forehead, often including the upper eyelid. Additional risk factors include midline port-wine birthmarks and lesions covering more than 50% of the adjacent half of the forehead (26, 27).

Over time, skin lesions in SWS may darken, taking on a deep red or purple hue characteristic of port-wine birthmarks. When the jaw or lips are involved, there may be overgrowth of soft and bony tissues, which is observed in two-thirds of patients by age 50. As the skin thickens with age, progressive vascular dilation may result in blistering or nodules on the surface of the lesions (28).

The phenotype of SWS has been expanded to include findings described in the less common GNA11 variant, which differs from the classical GNAQ-related SWS (13, 29). Capillary malformations in the GNA11 variant may appear pale pink with a reticular pattern and are sometimes accompanied by other pigmented skin changes of varying severity, such as nevus anemicus (mixed vascular lesions), café-au-lait spots, or dermal melanocytosis. Vascular malformations related to the GNA11 mutation tend to darken to purple more slowly than those associated with the GNAQ mutation (13).

Approximately 10% of patients with characteristic CNS or ocular manifestations of SWS do not present with skin lesions (30).

3. Ophthalmological symptoms

Glaucoma is the most common ophthalmological complication in patients with SWS, occurring in 30–70% of cases, especially when capillary malformations involve both the upper and lower eyelids (12). The condition typically occurs on the same side as the facial port-wine birthmark or leptomeningeal angiomatosis. It may present as congenital or acquired glaucoma (1, 7), with most cases (60%) developing during infancy, while the remaining 40% emerge in childhood or early adulthood (7, 31).

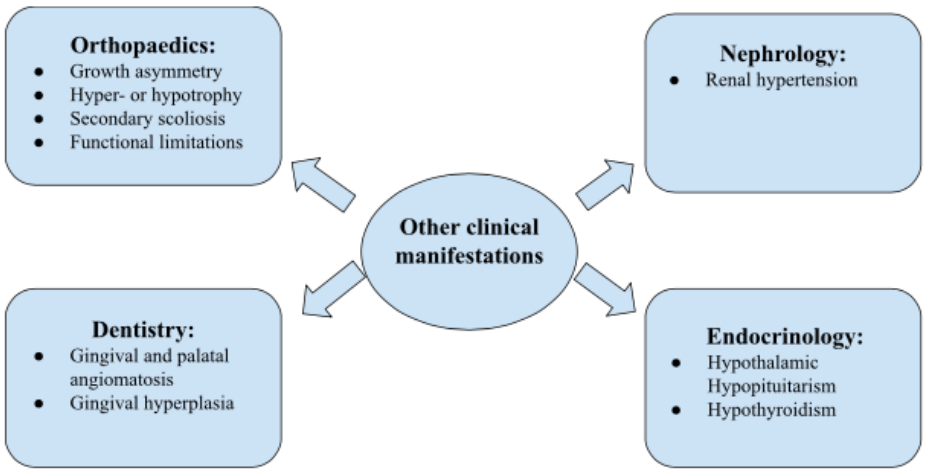
Glaucoma is a disorder that leads to optic nerve damage caused by elevated intraocular pressure. If untreated, it may result in permanent and complete vision loss (5). Open-angle glaucoma is the most common form observed in SWS patients. It can manifest as vision loss, conjunctival redness due to dilated vessels, ocular pain, excessive tearing, and, in infants, enlargement of the eyeball (32). Although rare, glaucoma can be bilateral, even in cases where the port-wine birthmark is unilateral (18).

In addition to glaucoma, SWS patients may experience other ocular complications. One of the more common conditions is choroidal hemangioma (CH), a benign vascular tumor found in 40–50% of SWS patients. These lesions are typically diffuse but may also be focal and generally occur on the same side as the facial PWB (33). Other complications include conjunctival vascular malformations (localized or diffuse), dilated retinal vessels, and persistent episcleral vessels, all of which exhibit a distribution consistent with the location of the PWB. Moreover, ocular melanocytosis, iris mammillations, and abnormalities such as cilio-retinal or hemi-retinal artery occlusion have been reported. Heterochromia iridum, characterized by differences in iris coloration, is another significant finding that increases the risk of glaucoma development up to 45% (34).

4. Symptoms from other organs

In addition to the characteristic neurological, dermatological, and ophthalmological manifestations of SWS, patients may also present with symptoms from other organ systems. Other clinical manifestations are illustrated in *Figure 1*.

Figure 1. **Other clinical manifestations of Sturge-Weber Syndrome (13, 35-38)**.



5. Diagnostics

The diagnosis of Sturge-Weber syndrome is typically straightforward in individuals presenting with a port-wine nevus, glaucoma, clinical signs of cerebral involvement, and confirmatory neuroimaging. However, diagnosis becomes more challenging in neonates with a facial PWB but no neurological symptoms. In such cases, initial imaging may fail to detect abnormalities, requiring follow-up scanning in uncertain cases (6).

1. Gadolinium-enhanced MRI remains the gold standard for diagnosing brain involvement in Sturge-Weber syndrome, effectively detecting leptomeningeal enhancement, abnormal venous drainage, cortical atrophy, and other abnormalities (18). While Susceptibility-Weighted Imaging (SWI) and Fluid-Attenuated Inversion Recovery (FLAIR) offer superior sensitivity for pial vascular abnormalities, normal MRI results in low-risk patients may reduce the need for additional screening (39-41).
2. Electroencephalography (EEG) is a cost-effective tool for detecting cortical involvement and subclinical seizure activity. Prolonged video EEG may be essential for diagnosing non-convulsive status epilepticus in SWS patients with altered mental status (27, 42).
3. Transcranial Doppler (TCD) imaging shows promise as a non-invasive tool for monitoring disease progression, with lower flow velocities correlating with worse neurological outcomes in SWS patients (41).
4. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) provide valuable insights into disease progression in Sturge-Weber syndrome, detecting subtle metabolic and perfusion changes associated with cognitive decline and seizure activity (43).

5. Computed tomography (CT) remains useful for identifying structural abnormalities like calcifications and cortical atrophy, although is not routinely recommended for children with new-onset SWS-related seizures or neurological symptoms due to its low diagnostic yield and risks of radiation exposure (7, 27).

Children with high-risk facial PWB, particularly those involving the hemifacial, forehead, or median regions are at increased risk for SWS with brain involvement. Such patients should undergo baseline evaluation by a pediatric neurologist and periodic follow-ups (44). Early screening of asymptomatic infants under 3 months of age shows high sensitivity and specificity for detecting leptomeningeal angiomatosis (40).

Routine follow-up MRIs are not recommended for children with SWS who exhibit stable clinical symptoms, controlled seizures, and no neurocognitive decline, as the potential risks outweigh the benefits (42). However, additional MRI may be warranted in cases of new or progressive neurological symptoms, uncontrolled seizures, stroke-like episodes, or new-onset migraine. Pre-surgical MRI in drug-resistant epilepsy cases is crucial for assessing the extent and severity of brain involvement, aiding in tailored surgical planning (18, 42).

Ultimately, the choice of imaging modality depends on individual patient factors, with pre- and post-contrast MRI sequences being preferred for post-symptomatic evaluation (39).

Additional modalities for assessing disease impact include neuropsychological evaluations, the SWS neuroscore, disability scoring, and various developmental assessment tools, offering a multifaceted approach to understanding functional and neurological outcomes (45).

Patients with Sturge-Weber syndrome require lifelong monitoring by multidisciplinary teams to assess disease progression in the skin, eyes, and brain. Standardized neuroimaging and a stronger clinicopathological understanding are needed, along with uniform tissue banking and clinical data collection for cross-center to support future clinical trials (7).

6. Differential diagnostics

Differential diagnosis of SWS includes conditions such as Blue Rubber Bleb Nevus Syndrome, Klippel-Trenaunay-Weber Syndrome, Posterior fossa abnormalities, Hemangiomas, Arterial anomalies, Cardiac, Eye, and Sternal anomalies (PHACES) Syndrome and Wyburg-Mason Syndrome. Key distinguishing factors include the clinical history, specific physical examination findings and characteristic brain MRI features. While these conditions may present with overlapping vascular malformations or neurocutaneous manifestations, the distinctive patterns of involvement, such as the presence of leptomeningeal angiomatosis in SWS, allow for accurate differentiation and appropriate management (2).

Differentiating facial PWB from other conditions such as hemangiomas, arteriovenous malformations and Megalencephaly Capillary Malformation Syndrome is crucial for accurate diagnosis. While similarities in clinical presentation can pose challenges, key distinguishing features, including location, growth patterns, and the absence of associated neurological manifestations, can guide differentiation. Genetic testing plays a pivotal role in confirming diagnoses and distinguishing conditions with overlapping features (18, 46).

7. Treatment

1. Treatment of Neurological Symptoms

The management of neurological symptoms in Sturge-Weber syndrome, particularly seizures, primarily involves the use of antiepileptic drugs such as levetiracetam and oxcarbazepine, as well as low-dose aspirin (47). Aspirin at a dose of 3–5 mg/kg/day is especially recommended for children under three years old with involvement of three or more brain lobes. It may also be used in older patients with less extensive changes but who experience hard-to-control seizures, stroke-like episodes, or focal neurological deficits (48). Aspirin has shown potential in reducing the frequency and severity of headaches, seizures, and stroke-like events. Studies indicate that it is safe and well-tolerated in children. While the exact mechanism of its action in SWS remains unclear, observational findings suggest it may be an effective adjunct in managing neurological symptoms. Further research, however, is needed to fully elucidate its role in therapy (47).

Infants treated presymptomatically with low doses of aspirin and antiepileptic drugs demonstrated a lower frequency of seizures and a later age of onset. Since seizures can contribute to cognitive decline and reduced quality of life in SWS patients, presymptomatic treatment could significantly improve long-term outcomes (49).

For seizures resistant to pharmacological therapy, more invasive methods are considered, including focal resection, hemispherectomy, or vagus nerve stimulation (47). The decision to proceed with surgery requires careful deliberation. Patients with unilateral brain involvement are the best candidates for surgical intervention (50). In contrast, those with bilateral brain involvement rarely qualify for surgery due to the high risk of neurological and cognitive complications (51). Hemispherectomy may be used in exceptional cases for patients with severe, debilitating seizures originating from one brain hemisphere, but it is regarded as a palliative treatment (52).

Research has also shown the effectiveness of cannabidiol in treating refractory seizures in SWS patients, but further studies are necessary to explore the use of cannabinoids in this syndrome.(53)

2. Treatment of Ophthalmological Symptoms

Glaucoma in Sturge-Weber syndrome can manifest at different stages of life, with mechanisms and treatment varying according to the patient's age. In infants, glaucoma development is typically associated with both elevated episcleral venous pressure and congenital abnormalities of the trabecular meshwork. In such cases, initial treatment often involves surgical intervention, supported subsequently by medications or laser therapy (54). In older patients, glaucoma is more frequently attributed to isolated increases in episcleral venous pressure with normal anatomy of the ocular drainage system. Initial treatment usually relies on topical or systemic pharmacotherapy. If sufficient control is not achieved, laser or surgical treatment becomes necessary.

Surgical options require careful consideration, as the eyes of SWS patients are more prone to complications both during and after surgery. This susceptibility stems from the increased pressure gradient in the choroidal vessels, which can lead to episcleral hemorrhage or difficult-to-treat serous retinal detachments (54).

3. Treatment of Dermatological Symptoms

Pulsed dye laser (PDL) therapy is considered the gold standard and the first-line treatment for vascular lesions using light-based technologies. The effectiveness of the therapy depends on factors such as vessel depth, the initial color of the lesion, the patient’s skin phototype, and the anatomical location of the lesion. The best results are achieved in frontal lesions, whereas zygomatic and perioral lesions are more challenging to treat. Studies have shown that initiating treatment at a young age, particularly within the first year of life, increases the effectiveness of therapy. Typically, several PDL sessions, usually 7 to 15, are required to achieve the desired therapeutic effect (55). PDL is considered safe for children and, when properly applied, is associated with a low risk of complications. Treatment of periorbital areas, with adequate eye protection, does not worsen existing glaucoma or trigger seizures (56).

If conventional laser therapy does not produce the desired results, PDL can be combined with topical agents such as rapamycin (57) or axitinib (58). Photodynamic therapy with a photosensitizing agent can also be considered (59).

4. Targeted Therapy – A New Approach to SWS Treatment

Sirolimus has shown potential in improving outcomes for vascular tumors, especially those associated with severe coagulopathy, as well as in the treatment of venous and lymphatic malformations. Its efficacy in these conditions, along with the role of the mammalian target of rapamycin (mTOR) pathway in cell growth and proliferation, justifies the use of this drug in treating capillary malformations associated with Sturge-Weber syndrome (60). The side effects of sirolimus are generally mild, with the most commonly reported being hypertriglyceridemia, reduced high-density lipoprotein (HDL) cholesterol levels, oral ulcers, headaches, elevated liver function tests, and personality changes such as behavioral deterioration (61).

The combination of topical rapamycin with PDL therapy has demonstrated the highest effectiveness in both subjective and objective evaluations, including photographic, clinical, and histopathological assessments, compared to laser or topical monotherapy. This therapeutic approach has been deemed particularly effective in pediatric populations (57).

In one case, oral rapamycin combined with aspirin was used as prophylactic treatment in an infant with bilateral facial skin lesions and extensive leptomeningeal involvement. Therapy was initiated at three weeks of age, administering rapamycin (0.8 mg/m²/dose) and aspirin (10 mg/kg/day). By 23 months of age, the child had not experienced any seizures, suggesting the potential effectiveness of this approach in preventing neurological complications of SWS. Further research is needed (62).

8. Conclusions

Sturge-Weber Syndrome presents a unique constellation of neurological, ophthalmological, and dermatological challenges, requiring a comprehensive, multidisciplinary approach for effective management. Early diagnosis and intervention are critical, particularly in addressing neurological complications such as epilepsy and glaucoma, which significantly impact quality of life. Advances in imaging techniques, including MRI and PET, have enhanced diagnostic accuracy and guided treatment planning, while novel therapies like sirolimus and cannabidiol provide promising avenues for refractory cases.

Dermatological management, spearheaded by pulsed dye laser therapy, underscores the importance of early and aggressive intervention to improve cosmetic and functional outcomes. Emerging adjunctive therapies, including topical and systemic rapamycin, reflect the evolving landscape of SWS treatment.

Despite these advancements, SWS remains a lifelong condition necessitating ongoing surveillance and individualized care. Standardized protocols for monitoring and treatment, along with collaborative efforts to understand the disease's genetic and molecular underpinnings, are paramount. Continued research and clinical trials are essential to refine current approaches and explore innovative therapies, ultimately aiming to improve the prognosis and quality of life for patients with SWS.

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Author's contribution

Conceptualization: [KN], [AK], [JG]
Methodology: [KN], [AK], [AŚ], [WN]
Software: [KN], [OK], [AK]
Check: [KN], [AK], [NJ], [NP]
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Data curation: [KN], [NJ], [AH], [WN]
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Writing - review and editing: [AH], [AŚ], [OK], [KN]
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