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WHEN THE SKIN IS SILENT: INITIAL NEUROLOGICAL MANIFESTATIONS OF TUBEROUS SCLEROSIS COMPLEX IN CHILDREN

KEY WORDS: Tuberous sclerosis complex; epilepsy; infantile spasms; cortical tuber; developmental delay; genetic epilepsy

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ABSTRACT

Background: Tuberous sclerosis complex (TSC) is a multisystem genetic disorder in which neurological involvement, particularly epilepsy and neurodevelopmental impairment, accounts for substantial morbidity. Classical cutaneous manifestations are important diagnostic clues, but neurological abnormalities may become clinically apparent before recognizable neurocutaneous signs. **Objective:** To describe the initial neurological phenotypes that led to consideration of TSC in children without recognizable neurocutaneous markers at initial neurological evaluation. **Materials and Methods:** We retrospectively reviewed six children evaluated in a pediatric neurology practice for early-onset epilepsy, developmental abnormalities, or paroxysmal neurological events. Clinical phenotype, electroencephalography, magnetic resonance imaging, and molecular genetic findings were reviewed. **Results:** The six children demonstrated a heterogeneous neurological spectrum. Epileptic manifestations predominated and included infantile spasms and focal seizures. Developmental and behavioral abnormalities were also observed. Electroencephalography demonstrated epileptiform abnormalities across the cohort, with patterns including epileptic spasms-associated abnormalities, focal discharges, and sleep-activated centrotemporal discharges. Magnetic resonance imaging demonstrated abnormalities compatible with TSC in several patients, including cortical tubers and subependymal nodules, whereas one child had a normal study. Molecular testing identified TSC1 or TSC2 variants, although variants of uncertain significance were present in two children. The latter finding illustrates the limitations of interpreting genetic results without clinical and radiological correlation. **Conclusion:** Neurological manifestations may bring children with TSC to medical attention before classical neurocutaneous features are recognized. Early consideration of TSC in children with characteristic epileptic and neurodevelopmental phenotypes may facilitate appropriate neuroimaging, genetic evaluation, surveillance, and treatment.

INTRODUCTION

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder characterized by the development of hamartomatous lesions involving the brain, skin, kidneys and other organs. Neurological involvement is a major determinant of morbidity and includes epilepsy, developmental impairment, intellectual disability, autism spectrum disorder and other behavioral and psychiatric manifestations.[1,2]

Epilepsy is among the most frequent neurological manifestations of TSC and commonly begins during infancy or early childhood.[3] Infantile spasms are particularly important because they may be the first recognizable manifestation and are associated with subsequent developmental and epileptic encephalopathy.[1,4] The epilepsy phenotype may subsequently evolve into focal seizures, often related to the presence of cortical tubers and other structural abnormalities.[1,7]

The neuropsychiatric consequences of TSC extend beyond epilepsy. The term Tuberous Sclerosis-Associated Neuropsychiatric Disorders (TAND) encompasses a broad spectrum of behavioral, psychiatric, intellectual, academic and neuropsychological manifestations.[1,5] These manifes-tations can substantially affect educational attainment, quality of life and family burden.[10]

The molecular basis of TSC involves pathogenic variants in TSC1 or TSC2, resulting in dysregulation of the mammalian target of rapamycin pathway.[2] Increasing understanding of this pathway has resulted in targeted therapeutic approaches, including mammalian target of rapamycin inhibition for selected manifestations of TSC.[2,8]

The classical clinical recognition of TSC is often facilitated by cutaneous manifestations such as hypomelanotic macules and facial angiofibromas. However, the absence of readily recognizable skin findings can make the diagnosis challenging when the child presents primarily with epilepsy or developmental concerns. This diagnostic problem is particularly relevant to pediatric neurologists, who may encounter the neurological phenotype before the multi-system nature of the disorder becomes apparent.

We describe six children in whom neurological manifestations prompted evaluation for TSC in the absence of recognizable neurocutaneous markers at initial presentation. The series illustrates the range of neurological phenotypes and, importantly, the need for cautious interpretation of genetic variants of uncertain significance.

MATERIALS AND METHODS

Study design

This was a retrospective descriptive case series of six children evaluated in a pediatric neurology setting.

Case selection

Children were selected when the initial clinical problem was neurological and classical neurocutaneous markers of TSC were not recognizable at the time of initial neurological assessment.

Clinical assessment

The clinical records were reviewed for age at neurological presentation, seizure phenotype, developmental and behavioral manifestations, neurological examination, electroencephalographic findings, brain magnetic resonance imaging and molecular genetic results.

Genetic assessment

Molecular findings were interpreted according to the classification provided in the respective genetic reports. Particular attention was given to the distinction between pathogenic/likely pathogenic variants and variants of uncertain significance. A TSC2 VUS was not considered independently diagnostic of TSC.

Ethical considerations

The study involved retrospective review of anonymized clinical

information. Written informed consent for publication of anonymized clinical information should be obtained from the parents or legal guardians of the children before submission. Institutional ethics committee requirements should be documented according to the policies of the treating institution.

RESULTS

Six children were identified with neurological presentations that preceded recognition of neurocutaneous manifestations.

Neurological phenotype

The principal presenting neurological manifestations were epilepsy, developmental abnormalities and paroxysmal neurological events.

Two children presented with infantile spasms, representing the earliest epileptic phenotype in the series. Other children presented with focal seizures, while one older child presented with recurrent paroxysmal episodes consisting of headache, vomiting, fainting and transient unresponsiveness. Thus, the clinical spectrum ranged from early infantile epileptic manifestations to childhood focal epilepsy and less specific paroxysmal neurological events.

Developmental and behavioral phenotype

Developmental abnormalities were documented in several children. These included global developmental delay, speech/language impairment and behavioral abnormalities. Features suggestive of autism spectrum disorder were noted in one child.

The coexistence of epilepsy and developmental or behavioral abnormalities is clinically relevant because these features fall within the broad spectrum of TAND described in children with TSC.[1,5]

Electroencephalographic phenotype

All six children had abnormal EEG findings documented during evaluation.

The EEG phenotypes were heterogeneous. Children with infantile spasms demonstrated abnormalities compatible with epileptic spasms, while those with focal epilepsy showed focal epileptiform discharges. The older child with paroxysmal events demonstrated frequent sleep-activated bicentrotemporal epileptiform discharges.

This heterogeneity emphasizes that there is no single EEG phenotype that should be regarded as diagnostic of TSC.

Neuroimaging phenotype

Brain MRI demonstrated abnormalities compatible with TSC in several children, including cortical tubers and subependymal nodules. In contrast, the child with later childhood paroxysmal events had a normal MRI.

Cortical tubers are particularly relevant to the epilepsy phenotype because their structural and cellular abnormalities can contribute to epileptogenesis. Recent MRI-EEG work has further explored the relationship between cortical tuber subtypes and interictal epileptiform activity.[7]

Molecular phenotype

Molecular testing demonstrated variants involving TSC2 in five children and TSC1 in one child.

The molecular findings comprised pathogenic, likely pathogenic and uncertain variants. The presence of TSC2 VUS findings in two children highlights an important diagnostic issue: a VUS should not be equated with a molecular diagnosis of TSC. In such cases, clinical criteria, neuroimaging, segregation studies and longitudinal assessment become particularly important.

Overall phenotype

The six cases therefore illustrate a broad neurological spectrum:
Infantile spasms - focal epilepsy - developmental and behavioral manifestations - later paroxysmal neurological events.

The key common feature was that the neurological presentation prompted the diagnostic evaluation before classical neurocutaneous manifestations were recognized.

DISCUSSION

The principal observation from this case series is that the neurological phenotype of TSC may become clinically apparent before the skin provides a diagnostic clue. This has practical implications because epilepsy and developmental abnormalities are often encountered by pediatric neurologists before the child undergoes systematic multisystem evaluation for TSC.

Epilepsy is a central component of the neurological phenotype of TSC.[3] In our series, epileptic manifestations included infantile spasms and focal seizures, reflecting the established spectrum of TSC-associated epilepsy.[1] Infantile spasms are particularly important because they may occur very early in the disease course and are associated with developmental and epileptic encephalopathy.[4]

The importance of early seizure recognition extends beyond seizure control. Persistent epileptic activity during critical periods of brain development may contribute to adverse neurodevelopmental outcomes, and contemporary approaches to TSC increasingly emphasize the possibility of modifying the developmental trajectory by recognizing and treating epilepsy early.[4]

Cortical tubers and epileptogenesis

The structural substrate of epilepsy in TSC is complex. Cortical tubers are characteristic lesions and are thought to constitute important epileptogenic substrates.[1,7] The relationship between a particular tuber and an electroclinical seizure focus, however, is not always straightforward because epileptogenic networks may extend beyond the visible structural lesion.

The recent MRI-EEG study by Kimura et al. further emphasizes the relationship between cortical tuber subtypes and interictal epileptiform discharges.[7] In our series, the presence of cortical tubers in several children with epilepsy supports the relevance of structural brain abnormalities to the neurological phenotype.

At the same time, the normal MRI in one child illustrates an important clinical limitation. A normal initial MRI does not necessarily exclude an epilepsy syndrome or genetic diagnosis, particularly when the clinical phenotype is evolving. The interpretation of imaging must therefore remain integrated with the electroclinical and genetic findings.

TAND and developmental morbidity

Another important feature of the present series was the presence of developmental and behavioral abnormalities in several children. TSC should not be conceptualized solely as a disorder of seizures and structural brain lesions. Neuropsychiatric manifestations are an integral part of the disease phenotype.[1]

The TAND framework provides a useful approach to identifying behavioral, psychiatric, intellectual, academic and neuropsychological difficulties.[1] The recent pediatric study by Fu et al. demonstrated a substantial burden of TAND manifestations among Chinese children with TSC and drug-resistant epilepsy, reinforcing the need for systematic neuropsychiatric assessment.[5]

For pediatric neurologists, this has two implications. First, developmental surveillance should begin at diagnosis rather than waiting for school-age difficulties to emerge. Second, seizure control alone should not be considered an adequate measure of neurological outcome. Cognitive, behavioral, language and social development should form part of longitudinal follow-up.

Genetic Testing: Opportunity and Potential Pitfall

Genetic testing has substantially changed the diagnostic pathway for TSC. Advances in molecular genetics and neuropathology have improved understanding of the TSC1/TSC2 –mTOR pathway and facilitated targeted therapeutic strategies.[2]

However, our series also demonstrates the potential problem of overinterpreting genetic findings. A heterozygous TSC2 VUS in a child with epilepsy does not establish TSC in the absence of appropriate clinical or radiological evidence. This is particularly relevant to case 6, in whom the TSC2 finding was uncertain and MRI was normal.

This distinction is important for genetic counseling. Pathogenic or likely pathogenic variants in an appropriate clinical context can substantially strengthen the diagnosis, whereas VUS findings require cautious interpretation and should not be used as the sole basis for disease labeling or family counseling.

Why the absence of skin findings matters

The absence of recognizable neurocutaneous markers may create a false sense of reassurance. The traditional concept of TSC as a neurocutaneous disorder can lead clinicians to search for skin manifestations before pursuing a neurological-genetic diagnosis.

Our cases suggest the reverse approach may sometimes be more appropriate: the neurological phenotype should trigger consideration of TSC even when the skin examination is unrevealing.

This is particularly relevant for infants with epileptic spasms, children with early-onset focal epilepsy and children with epilepsy accompanied by unexplained developmental abnormalities.

Therapeutic implications

Early recognition is clinically relevant because treatment options for TSC-associated epilepsy have expanded. Understanding of the mTOR pathway has led to targeted therapeutic strategies, including everolimus for selected patients with TSC-associated epilepsy.[2,8]

For children with drug-resistant epilepsy, epilepsy surgery may also be considered after appropriate presurgical evaluation. Surgical strategies such as tuberectomy and related approaches form part of the treatment spectrum in selected patients with focal epileptogenic lesions.[9]

Therefore, early recognition of TSC is not merely diagnostic. It can potentially alter the trajectory of epilepsy management, developmental surveillance, genetic counseling and multidisciplinary care.

Clinical message

The key clinical lesson from this series is not that every child with early epilepsy should undergo indiscriminate genetic testing. Rather, a combination of early-onset epilepsy, characteristic EEG abnormalities, developmental concerns and suggestive MRI findings should increase suspicion for TSC even when the skin examination is nondiagnostic.

The clinician should then integrate clinical examination, MRI and genetic findings rather than allowing any single component to dominate the diagnostic process.

LIMITATIONS

This study has several limitations. First, the sample size was small and the series was retrospective, limiting generalizability. Second, the cases were identified from a pediatric neurology practice and therefore may be subject to referral bias toward children with more prominent neurological manifestations.

Third, the absence of neurocutaneous markers was assessed at initial presentation; some cutaneous manifestations may emerge later with age or may be subtle and require expert dermatological examination. Longitudinal assessment is therefore important.

Fourth, two children had variants of uncertain significance, and these genetic findings should not be interpreted as equivalent to confirmed molecular diagnoses. In particular, the TSC2 VUS in the child with normal MRI requires cautious interpretation and longitudinal reassessment.

Finally, the small cohort does not permit genotype-phenotype correlations or conclusions regarding prognosis. The purpose of the series is instead to highlight a diagnostic phenotype and generate a clinically relevant hypothesis.

Future Directions

Prospective multicenter studies are needed to determine how frequently neurological manifestations precede recognizable neurocutaneous features in children with TSC.

Longitudinal follow-up from the first neurological presentation could help determine:

1. when cutaneous manifestations become clinically recognizable;
2. whether specific early seizure phenotypes predict later neurodevelopmental impairment;
3. whether early EEG abnormalities predict epilepsy severity;
4. how cortical tuber characteristics relate to seizure networks; and
5. whether early genetic diagnosis facilitates earlier targeted therapy and improved developmental outcomes.

Future studies should also incorporate systematic TAND assessment because neurological and neuropsychiatric outcomes extend well beyond seizure control.[5]

CONCLUSION

Tuberous sclerosis complex may first present as a neurological disorder before it becomes clinically recognizable as a neurocutaneous syndrome. In this six-child series, infantile spasms, focal epilepsy, developmental abnormalities and paroxysmal neurological events were among the initial presentations.

The absence of obvious neurocutaneous markers should therefore not exclude TSC when the neurological phenotype and/or neuroimaging raises suspicion. Early integration of clinical assessment, EEG, MRI and appropriately interpreted genetic testing can facilitate diagnosis and enable timely epilepsy management, developmental surveillance, genetic counseling and multidisciplinary care.

Table 1. Clinical and Neurological Characteristics of the Six Children

Case	Age at presentation	Principal neurological presentation	EEG phenotype	MRI	Genetic finding	Interpretation
1	1 y	Infantile spasms	Spasms-associated epileptiform abnormality	Subependymal nodules	TSC2 VUS	Clinical/imaging correlation required

2	5 y	Focal seizures with develop-mental/behavioral concerns	Focal epileptiform discharges	TSC-compatible abnormalities	TSC2 likely pathogenic	Strong TSC association
3	8 y	Infantile spasms evolving to focal epilepsy	Focal epileptiform discharges	Cortical tubers ± subependymal nodules	TSC2 pathogenic	Genetically confirmed TSC
4	2 y	Developmental delay/behavioral or autistic features with epilepsy	Epileptic encephalopathy pattern	TSC-compatible cortical abnormalities	TSC2 likely pathogenic	Strong TSC association
5	2 mo	Early-onset focal seizures	Focal epileptiform activity	[Insert verified MRI finding]	TSC1 pathogenic	Genetically confirmed TSC
6	9 y	Headache, vomiting, fainting and transient unrespon-siveness	Sleep-activated bicentrotemporal discharges	Normal MRI	TSC2 VUS + OPA1 VUS	TSC not established ; diagnostic dilemma

Abbreviations: MRI, magnetic resonance imaging; TSC, tuberous sclerosis complex; VUS, variant of uncertain signi-ficance.

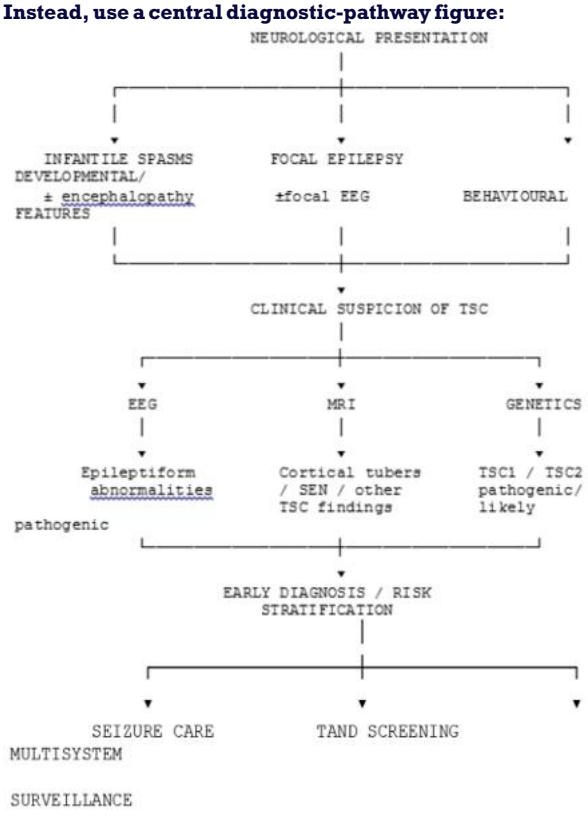
Important: I would keep the phrase "TSC not established; diagnostic dilemma" in the table unless case 6 subsequently fulfills clinical diagnostic criteria. This is much safer scientifically than counting the child as a confirmed TSC case.

FIGURE 1

When the Skin is Silent: Neurological Route to the Diagnosis of TSC

For the actual journal figure, I recommend not using the earlier vertical pyramid, because it incorrectly suggests a severity or temporal progression from infantile spasms ɑ focal epilepsy →behavioral abnormalities → paroxysmal events. Those are different phenotypes, not necessarily stages of one disease.

Instead, use a central diagnostic-pathway figure:



A separate small grey box at the bottom/right:

Diagnostic caution: TSC1/TSC2 VUS + nondiagnostic clinical/MRI findings ≠ confirmed TSC.

Figure legend

Figure 1. Neurological route to recognition of tuberous sclerosis complex. The children in the present series came to neurological attention through heterogeneous presen-tations including infantile spasms, focal epilepsy, developmental /behavioral abnormalities and paroxysmal neuro-logical events. In the absence of recognizable neurocutaneous mark-ers, integration of electroence phalo-graphy, brain magnetic resonance imaging and molecular genetic findings may facilitate recognition of TSC. A variant of uncertain significance should not be considered diagnostic in isolation.

This figure is conceptually stronger because it communicates the actual novelty of your series: neurological presentation →diagnostic suspicion →multimodal evaluation →diagnosis, rather than implying a false disease progression.

Key Messages

- TSC may first present neurologically before recognizable neurocutaneous manifestations appear.
- Infantile spasms and focal epilepsy should prompt consideration of TSC, particularly when accompanied by developmental abnormalities or characteristic MRI findings.
- EEG and MRI are complementary diagnostic tools in children with suspected TSC.
- TSC1/TSC2 variants of uncertain significance should not be interpreted as diagnostic in isolation.
- Early recognition provides an opportunity for timely epilepsy management, TAND screening, genetic coun-seling and multisystem surveillance.

REFERENCES

I would retain your 10-reference list, but there is one important issue: references 8 and 9 as originally supplied are incomplete bibliographic records, so I would not submit them in their present form. AIAN requires references to be appro-priately formatted, and incomplete citations are an avoidable editorial problem. The journal's instructions also specify fewer than 30 references.

Using the bibliographic information you supplied, the list is:

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