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Review Article

Clinical Characteristics Suggestive of a Genetic Cause in Cerebral Palsy: A Systematic Review

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ABSTRACT

Background: Cerebral palsy (CP) is a clinical diagnosis and was long categorized as an acquired disorder, but more and more genetic etiologies are being identified. This review aims to identify the clinical characteristics that are associated with genetic CP to aid clinicians in selecting candidates for genetic testing.

Methods: The PubMed database was systematically searched to identify genes associated with CP. The clinical characteristics accompanying these genetic forms of CP were compared with published data of large CP populations resulting in the identification of potential indicators of genetic CP.

Resullts: Of 1930 articles retrieved, 134 were included. In these, 55 CP genes (described in two or more cases, n = 272) and 79 candidate genes (described in only one case) were reported. The most frequently CP-associated genes were *PLP1* (21 cases), *ARG1* (17 cases), and *CTNNB1* (13 cases). Dyskinesia and the absence of spasticity were identified as strong potential indicators of genetic CP. Presence of intellectual disability, no preterm birth, and no unilateral distribution of symptoms were classified as moderate genetic indicators.

Conclusions: Genetic causes of CP are increasingly identified. The clinical characteristics associated with genetic CP can aid clinicians regarding to which individual with CP to offer genetic testing. The identified potential genetic indicators need to be validated in large CP cohorts but can provide the first step toward a diagnostic algorithm for genetic CP.

Introduction

Cerebral palsy (CP) is the number 1 cause of motor disability in children with a prevalence of around 1.6 per 1000 live births.[1] The term CP has origins tracing back centuries and has evolved over time, carrying a substantial amount of historical baggage. Currently, CP is defined by Rosenbaum et al.[2] as a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain. The motor symptoms of CP are often accompanied by disturbances of sensation, cognition, communication, perception, and behavior; by epilepsy; and by secondary musculoskeletal problems. As the definition suggests, the population of individuals with CP is heterogeneous. Therefore, individuals are clinically categorized

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Meaning of the abbreviations of the various genes can be found in OMIM (Online Mendelian Inheritance in Man) databank.

Data availability statement: Data and templates used in this article can be retrieved by contacting h.eggink@umcg.nl.

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based on the dominant motor symptom as spastic, dyskinetic, or ataxic CP.[3]

CP is a clinical descriptive term based on history and physical examination. The onset of symptoms in CP is before age two years as a result of a nonprogressive cause.[4,5] Despite this static condition, symptoms can change over time due to maturation of the central nervous system. In addition to an accurate history and examination, neuroimaging is recommended in the diagnosis. Magnetic resonance imaging (MRI) scans are abnormal in up to 80% and can identify signs of CP-causing events, such as hypoxic-ischemic lesions and/or cortical malformations.[6-8]

The pathways leading to CP are multifactorial and not completely understood. CP was historically considered an acquired disorder attributable to events occurring in the ante-, peri-, or postnatal period as was first described by W. Little, although not using the term "CP."[8] Perinatal asphyxia was considered the most prevalent cause but is nowadays estimated to cause only a minority of CP cases.[5,9] In addition, the availability of new, rapid, and cost-effective genetic sequencing techniques, collectively known as next-generation sequencing, has led to the identification of an increasing number of genetic disorders that can give rise to the clinical picture of CP.[10-12] The estimated frequency of genetic causes in CP ranges from 14%[13] to 31.1% also depending on living in a higher- versus lower-income country.[14] This increase in genetic etiologies is thereby shifting the paradigm of what is actually considered to be CP.[15] Although some suggest that genetic CP should be rather referred to as CP mimic, the current CP definition is a clinical description independent of etiology and therewith comprising both genetic and acquired causes.[16]

Identifying a genetic cause is of utmost importance for optimizing treatment and genetic counseling regarding recurrence risk and prognosis. Furthermore, an unknown cause may result in lifelong senses of guilt for the parents, particularly mothers, which may impact the quality of their lives significantly.[17] Unfortunately, it is challenging for clinicians to identify which characteristics might be suggestive of a genetic cause and therewith in which patients genetic testing should be considered.

To increase the existing knowledge regarding the genetic causes of CP, this study has two objectives: first, to get an up-to-date overview of the currently known genetic causes of CP published in the literature and second, to identify clinical and diagnostic characteristics suggestive of these genetic causes. The identification of characteristics of a genetic cause of CP provides the first step toward a diagnostic algorithm to help clinicians identifying genetic CP.

Methods

This study was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42020190213/July 24, 2020).

Search strategy

The systematic literature review was conducted between June 2020 and April 2023. The PubMed database was searched to identify genetic studies of CP. All synonyms and field tags for the relevant keywords "cerebral palsy" and "genetic(s)" were established to construct our comprehensive search strategy (Appendix A). The search strategy included articles published between 1990 and April 2023 because of very limited number of publications on genetic causes of CP before 1990. Reported individuals with CP with nonprogressive symptoms manifesting before age two years and a specified genetic cause were included. In addition, useful clinical and diagnostic data were included.

Screening of the articles was performed using the format of workbooks designed specifically for systematic reviews.[18] The screening process was performed by one reviewer (A.M.J.). The screening of titles and abstracts resulted in potentially relevant articles, which were consequently screened by reading the full text. Before screening, a Cohen kappa test was performed to check whether the second reviewer (H.E.) reached consensus in selecting relevant articles. Disagreements were resolved by judgment after adding a third reviewer (T.J.D.K.).

Identification of CP genes and candidate CP genes

The identified genes were categorized into CP genes (reported in at least two individuals) and candidate CP genes (described in one individual). The genes were inserted in the Online Mendelian Inheritance in Man (OMIM) database to identify the generally accepted term of the matching phenotype. Only the CP genes were used for further analysis. The candidate CP genes were put aside as their significance is unclear now. Future reports may, however, establish that these are indeed clinically relevant CP genes when more cases are identified.

Determination of genetic indicators

Genetic CP population

The individuals with the included CP genes were grouped together as the *genetic CP population*. Relevant diagnostic (i.e., neuroimaging findings) and clinical (history, neurological symptoms, additional symptoms) characteristics reported of these individuals were extracted from the papers. Neuroimaging findings were categorized into five groups based on Korzeniewski et al.[8]: congenital malformations, gray matter damage, white matter damage, ventriculomegaly/atrophy/cerebrospinal fluid space abnormalities, and miscellaneous abnormalities not included in any of the categories above.

The prevalence per characteristic was calculated by dividing the number of individuals by the total number of individuals in which the specific characteristic was reported.

Reference CP population

The prevalence of clinical and diagnostic characteristics in individuals with genetic CP was compared with the reported prevalence in the CP population, by using recent and widely used systematic reviews including over 1000 CP cases. In the absence of a complete overview, several reviews were included.[5,8,19-23] As these populations were reported as representative for the total CP population, these comprise both acquired and genetic etiologies and are referred to as the *reference CP population*.

Criteria for genetic indicators

Only when the presence or absence of a characteristic was reported in $\geq$50% of the included cases in the *genetic CP population*, prevalence was compared with the *reference CP population*. In case of a documented presence or absence of the characteristic in <50%, it could only be reported as *possible* genetic indicator (+/−).

Genetic indicators could be *positive* (in presence of this characteristic a genetic origin is more likely) or *negative* (in absence of this characteristic a genetic origin is more likely). Genetic indicators were defined as *strong* (++ or −−) if the difference in prevalence within the *genetic CP population* compared with that of the *reference CP population* was >30%. A difference of 20% to 30% was considered as a *moderate* (+ or −) genetic indicator.

In addition, the chi-square test was applied to statistically determine the differences in the genetic and reference populations.

The critical *P* value was calculated by applying the Bonferroni correction.

Results

A total of 1930 studies were retrieved from the search in PubMed (Appendix B). After initial screening, 134 articles were included for data extraction and analysis based on full-text review.[24-44,45-65,66-81,82-111,112-131,132-146,147-157] These articles were most often case reports or cohort studies.

The CP genes and candidate CP genes

The 134 studies described clinical data of 885 individuals, whose patient characteristics and clinical data were extracted. In 272 of 885 individuals, reported in 78 articles, the inclusion criteria were met (diagnostic criteria of CP, age of presentation less than two years, and a genetic cause reported in two or more individuals). A total of 55 genes were identified in these 272 cases and included in the *genetic CP population* and summarized with descriptives in Appendix C.

Mutations were found in single nuclear genes, larger copy number variations (CNVs, e.g., 6q25.3 deletion), or as mutations in mitochondrial DNA. The most frequently CP-associated genes were *PLP1* (21 cases), *ARG1* (17 cases), *CTNNB1* (13 cases), *ATL1* (12 cases), and *SLC6A3* (11 cases) (Table 1).

Genetic defects described in only one case were labeled as candidate CP genes, consisting of 79 genes reported in 29 articles (Appendix D). As mentioned before, these genes were excluded in the search for the genetic indicators.

Prevalence of clinical and diagnostic characteristics

Clinical characteristics of the 272 cases with genetic CP were retrieved from the publications and compared with characteristics of the selected reference CP population (Appendix E).

No difference in gender frequencies was present. In genetic CP, a lower prevalence was found in perinatal risk factors (18% vs 55%) and preterm birth defined as a gestational age <37 weeks (6% vs 34%).[21]

With regard to the motor phenotype, predominant spasticity was less frequent in the genetic population (55% vs 85% to 90%), dyskinesia was higher (39% vs 7%), and ataxia was within the same range (6% vs 4%).[5] In 8% of the individuals with genetic CP unilateral symptoms were described, which was lower than in the reference group (18% to 36%).[19]

Additional (non-)neurological features were gathered too, although not all of them were reported in >50% in the genetic CP population. Intellectual disability (ID) had a higher prevalence (80%) in the genetic CP population, predominantly reported as moderate to severe ID, when compared with 50% in the reference group. Prevalence of epilepsy and/or seizures was similar to the reference group (64% vs 35% to 62%). Visual impairment (86% vs 30% to 50%) and microcephaly (78% vs 2% to 6%) were more prevalent in individuals with genetic CP.[20,22,23]

In 201 of 272 of the individuals in the genetic CP population, MRI findings of the brain were reported. Abnormal findings were seen with a similar percentage (74%) as in the reference group (80%). White matter damage was the most frequently described abnormality in the genetic CP population (53%).

Identification of genetic indicators

The following characteristics were identified as strong positive indicators of genetic CP (>30% difference in prevalence): dyskinesia and the absence of spasticity. Moderate genetic indicators included (20% to 30% difference in prevalence) ID, the absence of preterm birth, and no unilateral symptoms. These were all found to be statistically significant (see Appendix E).

Unfortunate, well-known indicators of a possible genetic disorder such as positive family history or consanguinity were not reported in CP literature, so prevalence could not be calculated for these indicators. These were added as strong genetic indicators based on their identification as a "red flag" for genetic CP in previous research.[15,158]

The absence of perinatal risk factors, visual impairment, and microcephaly were reported in <50% of genetic CP cases and therefore identified as possible genetic indicators (Table 2). An abnormal MRI was not associated with a genetic origin. Other characteristics were not discriminating between the genetic CP population and the reference CP population.

TABLE 1.
Most Frequently Identified Genes Associated With Cerebral Palsy Phenotype

Gene	Number of Cases Described (n > 4)
PLP1	21
ARG1	17
CTNNB1	13
ATL1	12
SLC6A3	11
ADCY5	11
KANK1	10
GNAO1	10
BCAP31	9
SPTBN2	8
AFG2B	8
DDC	7
F5	7
NSRP1	6
SLC16A2	6
GCDH	6
SPR	5
ARX	5
SPAST	5
PRUNE1	5
ATP1A3	5

For a complete overview of all identified genes, see Appendix C.

Discussion

Here we provide a comprehensive overview of all genes causing a CP phenotype and their specific characteristics based on a systematic review of the literature. A total of 885 individuals were reported to have a CP phenotype associated with a monogenic disorder or structural DNA abnormality. From these cases, we identified 55 CP genes (reported in two or more individuals) and another 78 candidate genes (reported in one individual). We gathered clinical and diagnostic characteristics in all reported individuals fulfilling the diagnostic criteria for CP and one of the 55 CP genes (n = 272). The prevalence of characteristics in these 272 individuals was compared with the prevalence in published reference CP populations. This comparison led to the identification of genetic indicators, which were categorized into strong (dyskinesia, absence of spasticity) and moderate (ID, no unilateral symptoms). Parental consanguinity and a positive family history were added as they are widely accepted as genetic indicators, despite being poorly documented in the existing CP literature.

Genes associated with CP—the tip of the iceberg?

This study is the first systematic review both identifying genes associated with a CP phenotype and describing clinical

TABLE 2.
Overview of Indicators for Genetic Cerebral Palsy

Strong	Moderate	Possible
1.Dyskinesia	1. Intellectual disability	1. Absence of perinatal risk factors
2.Absence of spasticity	2. Absence of preterm birth	2. Visual impairment
3.Consanguinity*	3. No unilateral symptoms	3. Microcephaly
4.Positive family history*		

* Well-known genetic indicator; comparison with reference population was not possible because it was not reported in cerebral palsy literature.

characteristics. We identified 55 CP genes, consistent with previous overview studies.[15,159] In accordance with earlier research, these involved both monogenic mutations and CNVs. Although CNVs where less frequent, it is good to realize that CNVs will not be detected by exome sequencing.[10]

The identified genes are heterogeneous, with respect to their underlying molecular pathways. The genes may have a direct effect on the development of the brain, or as with thrombophilias might also target other tissues (platelets) that are therewith more vulnerable. These indirect mechanisms may lead to a higher risk of perinatal stress or to a higher risk of more severe brain damage such as brain infarction, ultimately leading to the clinical phenotype of CP. Our findings support the widespread possible etiologies that lead to CP. After all, the diagnosis of CP remains a clinical diagnosis.

Zooming in, the most frequently reported genes were mainly associated with hypomyelinating leukodystrophies such as Pelizaeus-Merzbacher disease (*PLP1*) and metabolic disorders, for example, argininemia (*ARG1*). In addition, genes associated with thrombophilias (e.g., *F5*, *PROC*), hereditary spastic paraplegias (*HSP*, e.g., *ATL1, SPAST*), and neurotransmitter synthesis disorders such as sepiapterin reductase deficiency (*SPR*) were identified.

Pelizaeus-Merzbacher disease is known to be associated with CP phenotype since its presentation mainly consists of spasticity with other neurological features.[15] Although it usually has a progressive course contrary to CP, this was not (yet) the case in the included case reports in this review. Metabolic disorders underlying the CP phenotype were found in earlier review studies as well.[160] The identification of such metabolic disorders in individuals with CP is of utmost importance, because these are potentially treatable disorders and disease-specific treatments can ameliorate or minimize symptoms.[161] The advantages of identifying such an etiologic diagnosis not only includes disease-specific treatment strategies but also leads to avoidance of unnecessary additional investigations, less uncertainty for the parents, better family counseling, and benefits from appropriate support groups.

Disease-causing mutations in 78 genes were described in only one individual each and marked as candidate CP genes. Future publications might reveal more individuals with these potential genes and increase their clinical relevance. Since more and more research focuses on genetic causes of CP, our expectations are that the list of genes identified in this study is only a fraction of the CP-associated genes to be described in the upcoming years. The list we provide may be the starting point of developing CP-specific gene panels.

Although some clinicians might not consider a possible genetic cause in CP yet, a recent systematic review and meta-analysis found out that the diagnostic yield of genetic testing in CP of 31.1% is high enough to recommend exome sequencing as standard care for diagnostic evaluation of individuals with CP.[14] It is good to acknowledge the fact that availability of exome sequencing and budgets for genetic testing are limited in many countries, making it impossible to test all children with CP. The genetic indicators identified in our study provide tools to identify those individuals who might benefit from a genetic test.

Indicators for genetic cerebral palsy

We identified clinical and diagnostic characteristics that are more prevalent in individuals with CP with a genetic cause, and based on this we identified several strong indicators of genetic CP. The possible strong genetic indicator is the type of motor phenotype: both dyskinesia and the absence of spasticity as predominant symptom possibly point toward a genetic origin. It is interesting that although the absence of spasticity is a possible genetic indicator, genes causing spastic paraplegia such as *HSP* genes have been found to be associated with a genetic origin. Not only the type of motor symptom but also the distribution should be taken into account, as spastic paraplegia is more prone to be genetic in contrast to the tetraplegic spasticity that is thought to be associated with the classic form of acquired CP; this underscores that our genetic indicators are more a rough guideline than a strict checklist of criteria for genetic CP and should be tested in a cohort study to identify their indicative strength in more detail.

Ataxia was not identified as an indicator for genetic CP in our population; however, it was in previous literature.[15,159] As ataxia is the prominent phenotype in a minority of individuals, it may be difficult to find a significant difference between the genetic population and the reference group. However, this does not rule out that ataxia might be a genetic indicator. The absence of spasticity has not been directly flagged as a genetic indicator before; however, the presence of ataxia has been and that might suggest the absence of spasticity indirectly.

Parental consanguinity and a positive family history could not be identified as indicators for genetic CP due to the absence of the prevalence in the reference group to compare with. However, we suggest them to be included as indicators for genetic CP because a positive family history, a pattern of disease inheritance in the family tree, or consanguinity is self-evidently known as a “red flag” for genetic causes.[24] A positive family history has been strongly associated before with a genetic etiology in CP.[15,159] The prevalence of parental consanguinity (30%) and a positive family history (68%) in the 272 individuals published with a genetic cause for CP are already quite high but may become even higher since there were a large number of missing values in the published case reports.

Regarding the moderate indicators, we identified ID, no preterm birth, and no unilateral symptoms as moderate genetic clues. ID was not mentioned before as a red flag for genetic CP, which might be explained by exclusion of individuals with ID in other CP studies, in combination with the varying definition of ID across studies.[25-27] The presence of unilateral symptoms was identified as a negative genetic predictor, meaning that unilateral symptoms are more associated with a nongenetic CP. Genetic diseases are most commonly associated with more generalized symptoms instead of unilateral symptoms, which are associated with a unilateral lesion.

More data are necessary to draw conclusions on features such as perinatal risk factors, micocephaly, and visual impairment. Since less than 50% of the 272 individuals in our genetic CP dataset reported on these features, these were considered possible genetic indicators. The absence of perinatal risk factors was highlighted before as argument for genetic evaluation, and the difference in the

reported percentage between the genetic and reference population (18% vs 55%) does point toward this direction but could not be definitely supported.[15,159] The prevalence of microcephaly was high (78%) in the genetic population. Microcephaly thus was considered a possible genetic indicator meaning that more data are necessary to support our outcome. The timing of microcephaly occurrence is important to take into account because the presence of microcephaly can indicate both a variety of longer-existing problems, such as disturbances in fetal development (possibly genetic), and an event happening at the end of the pregnancy (possibly acquired). The high prevalence might also be associated or go hand in hand with the low number of preterm births in our genetic dataset. In a systematic review concerning microcephaly in individuals with CP, the proportion of congenital anomalies was higher in children born at term than preterm.[23] Regarding pregnancy duration, only 6% of the in our review identified individuals with genetic CP were born prematurely. The higher rate of preterm birth in the reference group (34%) is probably associated with acquired events since preterm birth has a high risk of hypoxic-ischemic complications.

In the previous literature, a normal MRI was associated with a higher risk of a genetic cause of CP.[159] We did, however, find that the majority of the individuals with genetic CP (74%) had MRI abnormalities. There are specific brain MRI findings for genetic causes of CP identified before in the literature.[15] Once identified, those specific MRI findings can lead directly to a more focused diagnostic genetic evaluation. Unfortunately, a detailed description of MRI abnormalities was missing in an important part of the cases included in our systematic review, which prevents us from drawing more specific conclusions. These findings do, however, show that the presence of MRI abnormalities does not exclude a genetic cause and further more detailed descriptions of genetic MRI abnormalities are needed.

What's in the name?

The genetic causes of CP comprise a large variety of genotypes and phenotypes, consistent with the heterogeneity of CP as a group of disorders; this leads to a gray area in terminology and an increasing complexity in diagnosing CP.[162] Currently, researchers are divided into two camps. On the one hand, there is the view that a disorder with an underlying genetic etiology presenting with a CP phenotype should not be included in the CP definition, but should be referred to as "CP mimic."[15,159] According to this standpoint genetic subtypes of CP are misdiagnoses.

On the other hand, there is the belief that genetic causes are not necessarily excluded in the CP definition if one considers CP a clinical syndrome rather than an etiologic diagnosis. Genetic CP cases should therewith be considered as more of an "atypical" presentation.[25] For the purpose of our study, we chose to follow this concept and include genetic subtypes in CP definition. During our literature search, we encountered disagreement in age of presentation necessary for CP diagnosis as well, varying from age less than one year to less than two years.

Our suggestion is to remain open-minded concerning definitions and to have a patient-centered approach in children with neurogenetic disorders. In addition, as an earlier diagnosis of CP is increasingly encouraged it may be that slowly progressive courses are included as well.[4] We are aware of the fact that this open-minded vision leads to the inclusion of genes that are associated with "progressive" disorders as well, such as MECP2, although CP is described as "nonprogressive." However, since every mutation can lead to a wide spectrum of phenotypes including progressive, slowly progressive, and static disorders, we chose to include these genes as well, provided that the concerning case report met our criteria and described a nonprogressive case.

Strengths and limitations

This is the first review systematically looking at characteristics of genetic CP. Owing to our broad search terms, we collected information on a large number of individuals. Case inclusion and gathering of characteristics was fully dependent on the information given in the included case reports and series. Despite the broad search, a significant number of possibly interesting cases could not be included due to an unknown age of presentation. The CP genes found included all individuals clinically labeled as CP by the publishing authors and fulfilled our inclusion criteria of a description of a nonprogressive disorder with a manifestation before age two years. Some of the reported genes are classically associated with progressive diseases; among these genes are the most reported genes PLP1 and ARG1. In these cases, it is possible a slowly progressive course of the disease might be missed. However, with the increasing number of genetic tests of the past decade(s) it also has become more and more clear that a single gene does not respond with a single clinical phenotype but can lead to a spectrum in terms of course, severity, and even symptoms present (pleiotropy). Therefore, a slow progressive or even static course is possible and suits with the goal of this review to keep a broad view on the CP population. Future prospective studies are needed to clear out the point entirely, as this broad approach coincides with a wide variation in studies and therewith reported characteristics with the presence of missing values.

A complete overview of characteristics of the total CP population as a reference group is currently lacking. We tried to solve this by comparing our findings with recently published large cohort studies and meta-analysis concerning the total CP population, including acquired and genetic causes. As these studies are frequently used to describe the prevalence of characteristics, this was the most reliable option.

Last, awareness should be raised about the lack of availability of genetic tests due to lack of resources in low- and middle-income countries or due to insufficient insurance coverage, even though CP has a higher prevalence in lower income groups. Genetic indicators identified in this review may help select cases in which there is a higher probability of a genetic cause. Therewith, they have the potential to prevent unnecessary costs and investigations. In this approach, differences between lower- and higher-income countries should be considered in terms of presentation and etiologies. Future research in line with this study should underline the importance of knowledge on underlying etiologies and can hopefully prioritize the need for availability and accessibility of genetic tests all over the world, to increase our understanding of the pathophysiology of CP.

Conclusions

This study contributes to the further understanding of CP etiology by the identification of specific characteristics as possible genetic indicators that might help to select those individuals who can benefit from a genetic test. We identified an extensive list of (candidate) genes associated with CP, possibly serving as a first step in the search for a diagnostic framework for genetic CP leading to a situation where a genetic test might become the standard procedure in all children with such a suspicion for genetic CP.

CRediT authorship contribution statement

A.M. Janzing: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **E. Eklund:** Writing – review & editing, Supervision, Methodology, Conceptualization. **T.J. De Koning:** Writing –

review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **H. Egginк:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

All authors have approved the acknowledgement of their contributions. There were no competing interests of authors.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2024.01.025.

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