Gait phenotype in Batten disease: A marker of disease progression

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Background: Gait impairment and its etiologic correlate has not previously been subject of special attention in Batten disease.

Methods: In the present review, the clinical picture of gait phenotype during Batten disease course accompanied by descriptions of the known concomitant patho-anatomical changes is presented.

Results: In CLN1 a non-rhythmic gait is seen around 1-1½ years of age. Shortly after, postural hypotonia and exaggerated tendon reflexes develop. The disease reaches a burnt-out stage during the third year of age and subsequently the children are almost without voluntary movements. The existing literature indicates that gait phenotype in CLN1 is caused by early involvement of the spinal interneurons followed by impact of the cortex and the cortico-spinal tracts. The earliest walking abnormality in children with CLN2 is a clumsy, ataxic, and spastic gait, which is in accordance with the existing imaging and histologic studies showing early involvement of the cerebellum and the cortico-spinal pathways. In CLN3, a reduction in walking speed is present at the age of 7–8 years. It occurs simultaneously with a reduction in the white matter microstructure and brain connectivity networks. Functional impairment of the basal ganglia contributing to a parkinsonian gait phenotype occurs in the mid-teens. In the late teens and early twenties involvement of the peripheral nerves, neurogenic musculoskeletal atrophy, loss of tendon reflexes and postural control are seen.

Conclusion: The progressively impaired gait function in Batten disease is related to timing of damage of distinct areas of the nervous system depending on subtype and is a powerful marker of disease progression.

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1. Introduction

The neuronal ceroid lipofuscinoses, also known as the CLN diseases or Batten disease, are a group of monogenic inherited neurodegenerative disorders that mostly present in the first decade of life [1]. They share a broadly similar clinical presentation characterized by visual failure, seizures, and a progressive decline in cognitive and motor abilities. The disorders also show variation, most notably in the age of onset and rate of disease progression, and it has been suggested that they actually are distinct disorders with separate underlying molecular causes with a similar pathological endpoint of pronounced neuron loss and autofluorescent storage material accumulation [2]. The disease-causing mutations are devastating, not only upon the brain, but extends to other components of the nervous system, including the peripheral and autonomic nervous systems and also to different somatic tissues [3–8].

Motor disability relative to voluntary movement is an early sign in all types of CLN disease. Generally, motor disability correspond to patho-anatomical findings localized in the brain, spinal cord, peripheral nerves or muscles, and concerning CLN1, CLN2 and CLN3 these progressive structural changes are well described. With regard to CLN3 it is thus well documented that the gait at some point becomes parkinsonian and that thalamic, nigrostriatal and striatal dysfunction partly contribute to this manifestation [9,10]. Interestingly, parkinsonian gait has not been described in connection with neither CLN1 nor CLN2; here is hypotonia and ataxic gait present [11,12], suggesting an early cerebellar involvement.

Gait phenotype and its etiologic correlate has not previously been subject of any special attention in Batten disease. The purpose of the current study is to describe the present knowledge of neural control of walking and gait phenotype during the course of Batten disease with focus on CLN1, CLN2, and CLN 3 in their classical forms [1].

1.1. Search strategy and selection criteria


2. Neurological aspects of walking

At a basic level, walking movements emerge from the activity of motor neurons in the spinal cord that innervate peripheral muscles causing them to contract. Yet, motor neurons are just the final actors that control movement. Their activity is directed by a huge network of neurons that are capable of generating patterned motor output that ensures coordinated spatiotemporal muscle contractions, while integrating sensory input (visual, somatosensory and vestibular) and supra-spinal information arriving directly or indirectly from the cortical, basal ganglia, brainstem, and cerebellar systems [13].

The prefrontal, premotor, and primary motor cortex is critical for planning, initiation, and execution of intended locomotion. The motor and premotor regions send extensive projections to the spinal cord via the cortico-spinal tract. However, only about ten percent of projections make monosynaptic connections to spinal motor neurons, the majority of terminations are on to interneurons in the spinal cord [14,15]. As movements initiated by motor cortical demands must be coupled with postural and locomotor controllers to ensure that postural changes generated by the movements are corrected for, motor and premotor cortical areas have direct projections to the vestibular nuclei, mesencephalic locomotor region (MLR) and to neurons in the pontomedullary reticular formation (PMRF) and to interneurons of the spinal cord [14,16].

The motor circuit of the basal ganglia is considered to be important for the selection and suppression of movements [17], the execution of automatic action [18], and scaling of motor output [19]. The basal ganglia do not project directly to the spinal cord and any influence the basal ganglia has on posture and locomotion is mediated indirectly by modulating the activity of thalamocortical pathways or locomotor and muscle tone circuits through the internal segment of the globus pallidus and substantia nigra reticulata [20].

The cerebellum is considered to be critical for the detection and correction of motor errors and the subsequent refinement of motor output [21]. Accordingly, the cerebellum is the recipient of multisensory, cortical and subcortical input. Like the basal ganglia, the cerebellar output does not project directly to the spinal cord, but is mediated indirectly through cortical and subcortical targets. In general, a syndrome of hypotonia, ataxia and postural instability is the motor hallmark of cerebellar lesions.

MLR receives input from motor regions of the cortex, basal ganglia and cerebellum. Motor regions of the frontal cortex have both indirect (via basal ganglia and cerebellum) and direct input to locomotor generating regions of MLR [22]. This provides supraspinal control of locomotor mode and intensity. PMRF receives direct input from the vestibular nuclei, the motor and premotor cortex and cerebellum, and indirect input from the basal ganglia. A subset of reticulo-spinal neurons makes monosynaptic connections to the motor neurons, while the majority terminates on premotor spinal interneurons.

Human walking requires a fine coordination between the two legs during which flexors or extensors on one side of the body are silent whilst those on the other side are active. In addition, when we walk, arms and legs may move in synchrony or in opposition indicating that human bipedal locomotion also relies on neural interactions between cervical and lumbar segments of the spinal cord. As described above, only a minority of terminations from the motor and premotor regions, the basal ganglia, cerebellum and brainstem are direct on to the motor neurons in the ventral horn. The majority end in an indirect manner at a network of interneurons in the spinal cord that are collectively called central pattern generating (CPG) network. CPG can be divided into independently rhythm-generating and pattern-forming spinal interneuron networks allowing left-right coordination, balanced left-right activation and the flexor-extensor alternations during locomotion [23,24]. CPG thus controls locomotor rhythm and pattern of muscle activity including specific functional aspects of locomotion like speed and termination of ongoing movement [25,26].

Muscle tone is defined as the resistance to passive movement, either of the extremities, called phasic tone or of the axial muscles, called postural tone [27]. Ataxia, defined as impaired coordination of voluntary muscle movement, is usually caused by cerebellar dysfunction or impaired vestibular or proprioceptive afferent input to the cerebellum [28]. Although not totally identical, the expressions muscle stretch reflex and deep tendons reflex are commonly used synonymously [29]. Attenuated deep tendons reflexes suggest lower motor neuron problems, most frequently of the spinal nerve roots, and exaggerated tendon reflexes are seen when the descending motor tracts from the cerebral cortex and/or brain stem are affected. In Table 1 is listed a summary of the neurological and physiological framework of walking.
3. CLN1 disease

CLN1 disease or infantile NCL is caused by mutations in the CLN1 gene that encodes the lysosomal enzyme Palmitoyl Protein Thioesterase-1 (PPT1) [1,30]. There is currently no effective therapy for CLN1 disease, and all cases are fatal, usually between 7 and 12 years of age [11,31,32]. In their publication from 1973, Santavuori and coworkers [11] provide a very detailed description of the course of the disease, including how locomotion develops during the condition. The developmental milestones are normal until the age of 8–10 months. First symptom is mental stagnation starting around one year of age. Slightly later, motor development ceases. Thereafter muscular hypotonia, truncal and limb ataxia, and in the half of children who, prior to recognized disease onset, have demonstrated a very early onset of spinal pathology including a significantly earlier affection of spinal interneurons than of neurons in CNS and of the motor unit in the spinal cord. Spinal interneurons are precisely the neurons that are critical for controlling the speed and coordination of locomotion, and as the demonstrated pathologic deviations in the spinal cord were accompanied by an early and significantly altered gait phenotype as regard speed and coordination compared to control wild-type mice and fully consistent of early motor deterioration in a patient with a well-known CLN1 mutation [39], it was suggested that spinal interneuron pathology significantly contributes to the early gait phenotype in CLN1 (Fig. 1a).

Magnetic resonance imaging (MRI) during disease course and post-mortem studies [33–38] all demonstrate a generalized and increasing atrophy of all brain components. Atrophy begins earliest and proceeds fastest in the cerebellum (about 1 year of age), with the thalamus lagging slightly behind, whereas atrophy is seen later in the cerebellum (about 2-2½ years of age) and the brainstem (3 years of age). Post mortal histological studies [33,34] show an almost complete loss of cortical neurons and secondary loss of axons and myelin sheaths in the white matter. The pontine nuclei are almost completely destroyed [33]. Throughout the brain stem and spinal cord, degeneration of the pyramidal tracts is seen, whereas the primary motor nuclei of the brain stem, the posterior columns, spino-cerebellar tracts, the anterior motor horn cells of the spinal cord and the peripheral nerves appear well preserved [34].

### 3.1. Gait phenotype

Truncal and limb ataxia occurs very early, e.g. 1-1½ years of age. As cerebellum, from a patho-anatomical perspective, is affected late in the disease course, cerebellum is hardly responsible. At the same age (1-1½ years), postural hypotonia with preserved or even exaggerated tendon reflexes is seen, which non-forcibly can be explained by the proven early damage of the supra-spinal areas. As previously noted only a minority of terminations from the motor and premotor cortex are direct on to the motor neurons. The vast majority end in an indirect manner at a network of interneurons in the spinal cord. Recently, Neubajal and coworkers [39] in setting of a comprehensive evaluation of the nature and timing of early CLN1 disease pathology of Ppt1-deficient (Ppt1−/−) mice, have demonstrated a very early onset of spinal pathology including a significantly earlier affection of spinal interneurons than of neurons in CNS and of the motor unit in the spinal cord. Spinal interneurons are precisely the neurons that are critical for controlling the speed and coordination of locomotion, and as the demonstrated pathologic deviations in the spinal cord were accompanied by an early and significantly altered gait phenotype as regard speed and coordination compared to control wild-type mice and fully consistent of early motor deterioration in a patient with a well-known CLN1 mutation [39], it was suggested that spinal interneuron pathology significantly contributes to the early gait phenotype in CLN1 (Fig. 1a).

### 4. CLN2 disease

CLN2 disease is caused by a mutation in the gene encoding the soluble lysosomal enzyme tripeptidyl peptidase 1 (TPP1) [1,30]. Affected children are functionally normal until the age of 2–4 years and subsequently have seizures and delayed language acquisition followed by a rapid decline in motor, language, cognitive, and visual function. By the age of 6, the children are usually unable to walk and sit unsupported. The only detailed description of motor deterioration in CLN2 is included in the Weill Cornell rating scale study from 2007 [40] in which both a “Gait scale” and “Motor scale” were used. The reported onset of motor dysfunction was 3.5 years of age (range 1.9–5.9 years of age). Muscle strength in upper and lower extremities was decreased in all children evaluated at an age older than 4 years, and the muscle stretch reflexes were increased and the plantar response was “up-going”. The gait abnormality of those children who were still ambulatory, were of the spastic and ataxic type. Since 2017, Cerliponase alfa (Brineura; BioMarin Pharmaceutical Inc, Novato, CA) has been an approved treatment for CLN2, and trials have shown a significant reduction in the rate of decline of motor and language functions in comparison with a natural

### Table 1

<table>
<thead>
<tr>
<th>Part of CNS</th>
<th>Part of gait function</th>
<th>Efferent projections to</th>
<th>Afferent projections from</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal region of the cortex</td>
<td>Planning, initiation and execution of locomotion</td>
<td>Via cortico-spinal tract:</td>
<td>Motor regions of cortex Mesencephalic locomotor region of the brainstem</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>Important for selection and suppression of movement. Execution of automatic actions, and scaling of motor output</td>
<td>Polysynaptic modulating activity of thalamocortical pathways, pendunculopontine nucleus, and through globus pallidus and substantia nigra reticulate.</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Critical for detection, correction and refinement of motor output</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brainstem (mesencephalic locomotor region)</td>
<td>Provide supraspinal control of locomotor mode and intensity</td>
<td>The majority projections terminate on interneurons in the spinal cord. A subset of projections have monosynaptic connections to the motor neurons in the spinal cord</td>
<td>Directly from motor regions of the cortex, cerebellum, and vestibular nuclei, and indirect input from the basal ganglia.</td>
</tr>
<tr>
<td>Interneurons in the spinal cord</td>
<td>Control locomotor rhythm and the pattern of muscle activity that govern bipedal gait and termination of ongoing movement</td>
<td>To motor neurons in spinal cord, directly or via other spinal interneurons, securing left-right coordination and balance, and flexor-extensor alternations during locomotion</td>
<td></td>
</tr>
</tbody>
</table>
We still lack results of long-term follow-up, and we do not yet know the effect when treatment is initiated early or even before symptoms have started.

Key MRI features of CLN2\(^{[42–45]}\) include progression of gray matter atrophy most prominent in vermis and the cerebellar hemispheres, which virtually is present in all patients at 3–4 years of age. At that time cerebral atrophy is seen in around 50–75% of the described cases, and linear hyperintensity of the central white matter is seen in 70–80%. The white matter changes are noted with a gradient from more severely affected posterior structures to mild affected anterior structures\(^{[42–45]}\). There are very few autopsy studies of patients with CLN2 and they primarily focus on electron microscopic and/or immunohistochemistry changes\(^{[46,47]}\). However, in one histological study\(^{[47]}\), where 2 siblings with the classic form of late infantile NCL (i.e. CLN2 disease) are described, the most severe neuronal loss was, in accordance with the imaging studies, observed in the cerebellum. Neurons of the spinal cord seems be comparatively preserved\(^{[47]}\).

4.1. Gait phenotype

The early walking abnormality of children with CLN2 is in form of a clumsy, tumbling, ataxic and spastic gait. In conjunction with the increased muscle stretch reflexes and the “up-going” plantar response, this points to a combination of an early cerebellar affection, especially of the vermis, in combination with a lesion of the cortico-spinal pathways (Fig. 1b).

5. CLN3 disease

CLN3, also called the juvenile form of neuronal ceroid lipofuscinosis (JNCL), is the most prevalent CLN disease. Clinically, it begins with progressive visual loss between 4 and 8 years of age, followed by seizures, loss of motor performance and dementia. Patients are usually bedridden at 20 years of age, and death occurs in the third decade of life\(^{[1,48]}\). It is due to mutations of the CLN3 gene that encodes a ubiquitously expressed protein localized to the lysosomal membrane.

5.1. Gait phenotype

Until recently, it has been the common belief that gait function is not affected during the initial years of disease\(^{[48]}\). This view has been challenged by a recently published study from the Netherlands\(^{[49]}\), where motor function, assessed by a 6-Minute-Walk-Test (6MWT)\(^{[50]}\) was evaluated repeatedly in children with...
CLN3 and compared to one control cohort with isolated visual impairment and a second cohort where visual impairment occurred in combination with neurologic impairment not related to CLN diseases. For data analysis, distance walked in meters and age was used. In CLN3 disease, 6MWT scores were already significantly impaired when the children were 7–8 years of age. Subsequently, 6MWT scores continuously declined, initially and including the 13 year of age in a linear fashion, then more rapidly. In contrast, an upward trend of 6MWT scores with age, similar to healthy sighted children, was observed in the control cohort having isolated visual impairment. The control cohort with additional neurologic impairment displayed a non-significant decreased 6MWT walking distance independent of age. The latter controls at all ages outperformed patients with CLN3, even those tested early in the disease course. Of note is the described linear decline of the walking speed until and including 13 years of age followed by a more pronounced aggravation resulting in a non-linear multilevel model [49]. A very interesting observation because it is precisely around the age of 13–14 years that patients with CLN3 develop extrapyramidal symptoms similar to what is characteristic for Parkinson’s disease, i.e. bradykinesia, impaired balance and shuffling gait with a flexed posture [51–53]. Unlike in Parkinson’s disease, tremor is uncommon, and extrapyramidal signs are subtle and occur in a severe functional, of spontaneous movement and in the late teens the use of a wheelchair becomes obligatory [52,54]. After mobility has completely disappeared, patients with CLN3 continue to exhibit parkinsonian-like motor patterns in the form of rigidity of the extremities, and when placed in a wheelchair they often sit with lateral flexion of the trunk (e.g. Pisa-syndrome) which is another hallmark of Parkinson’s disease [55,56]. In a study from 2013, Nielsen and Ostergaard [54] described the disease course among 35 Danish CLN3 patients, who during a period of 20 years all had been seen regularly at the Center for Rare Diseases, Aarhus University Hospital, Denmark and examined 1–2 times annually. A review of all available hospital records containing a continuously maintained history of the clinical course and including precise indication of time moments for different events, for example age at first seizure, age at gastric feeding tube placement, age of death, etc. showed, in accordance with the Rochester outcome study from 2012 [57], that females with CLN3 have a more precipitous decline than males, and die at an earlier age [54,57]. This more precipitous outcome also comes to a time of total loss of the patella-tendon reflex, which among females in the Danish CLN3 population [54] occurred four years earlier than in males (20.3 years (± 1.4) and 24.6 years (±4.2) (mean age ± SD, respectively; data not previously published). Accordingly, motor conduction velocity of the deep peroneal nerve shows a pronounced slowing in older and more severe and bedridden CLN3 cases [58].

Conventional magnetic resonance imaging (MRI) of patients with CLN3 reveals progressive cerebral, cerebellar, and hippocampal atrophy, decreased gray matter volume in the drosomedial part of the thalamus, and decreased white matter volume in the corona radiate [59–61]. Cerebral atrophy is not found until the age of 9 years and occurs mainly beyond the age of 14 years of age, and then initially in the occipital cortex [59]. Cerebellar atrophy is seen even later [59]. Diffusion-weighted imaging enables investigation of the white matter microstructure [62,63]. Using this technique in CLN3 patients, significant impairment in the white matter microstructure and brain connectivity networks has been demonstrated before the age of 10 years, thus present substantial earlier than can be demonstrated using conventional MRI [64,65]. Using functional studies, both thalamic, nigrostriatal and striatal dysfunction has been reported in CLN3 [67,68], but as the impairments only showed a modest correlation with the extrapyramidal symptoms, it has been suggested that degenerative changes of other CNS areas may also be contributory to the parkinsonian phenotype seen in CLN3 [66,67].

Postmortem investigations have shown a diffuse symmetric atrophy of the cerebral hemispheres, cerebellum, and brain stem and a diffusely enlarged ventricular system [68]. The changes are diffusely distributed throughout the layers in all gyri of the cortex, in the cerebellum, the brain stem, and in the spinal cord. Peripheral nerves show loss of axons and myelin sheaths [68], and in the skeletal muscles, neurogenic atrophy is seen [68].

It may be difficult to retrieve a single cause for the gradual decrease in walking speed early in the disease course. It might reflect a subclinical parkinsonian trait but as it occurs in parallel with onset of the cognitive decline [69,70], reduction in attention span, executive dysfunction or other neuropsychological difficulties are also reasonable to consider. In summary, the existing literature thus indicates that in CLN3 early gait phenotype predominantly reflects an early involvement of the white matter microstructure and brain connectivity networks, which in early adolescence is accompanied with degenerative changes of the basal ganglia and thalamus. By the late teens, loss of posture control is followed by peripheral nerve involvement and loss of the muscle stretch reflex (Fig. 1c).

6. CLN4–CLN14 disease

In the 1960s, the CLN diseases were divided into four groups based on age of onset: an infantile, late infantile, juvenile, and adult form. Improvements in technology have allowed identification of several CLN disease genes and today 13 genetically distinct types of CLN have been identified; CLN1–CLN8 and CLN10–14 [71]. Variant forms of the late-infantile subtype, CLN5 (CLN5), CLN6 (CLN6), CLN7 (MFS8), and CLN8 (CLN8) occur rarely, although, in different countries, rather regularly. Research of their motor impairment is less extensive as in the classical late-infantile subtype (CLN2). Generally, the debut of symptoms is slightly later than in CLN2 and the rate of progression somewhat slower, but similar to CLN2, the initial motor impairment is in form of a clumsy, tumbling, ataxic and spastic gait [72–74]. Correspondingly, early cerebellar atrophy is recorded on MRI [72–74] CLN10–CLN14 is seen only occasionally; some are present only in few families. Research of their motor impairments, imaging and post mortem findings in these subtypes are nowhere near as extensive as for CLN1, CLN2, or CLN3 disease, why a description of their gait phenotype is outside the scope of this study.

7. Discussion

The motor cortex along with the cerebellum, basal ganglia and brainstem are involved in decision making, planning and execution of movement. The quality of movement however, relies heavily on the translation of descending inputs and feedback from the periphery on to the spinal neurons and interneurons which in their body, dendrites, and axons have encoded information needed for recognition, regulation and transformation of sensory afferent feedback, and integration of descending input [27].

Although the CLN diseases share a broadly similar clinical presentation, the motor loss that relentlessly accompanies all CLN diseases manifests itself in different ways depending on the subtype. In CLN1, gait abnormality starts between 1 and 1½ years of age as an uncoordinated and non-rhythmic gait most probably related to an early impact of spinal interneurons, followed by postural hypotonia and exaggerated tendon reflexes. In CLN2, a clumsy, ataxic, and spastic gait related to impairment of cerebellum and an upper motor neuron involvement is seen, whereas in CLN3 impairment of the basal ganglia contributing to a parkinsonian gait
phenotype is seen in the mid-teens followed by loss of postural tone and the muscle stretch reflex in the early twenties. The current study has limitations. It suggests from the premise that the majority of the pathological and histological studies of human tissue are 40–50 years old, i.e. from a period when a specific diagnosis was not genetically verified. However, the clinical symptoms used today to describe the classical and genetically verified CLN1-CLN3 subtypes are completely identical to the clinical descriptions as they appear in the earlier pathological and histological case series of the infantile, late infantile and juvenile forms of NCLs from the 1970s and 1980s. Another point of criticism might be the children’s life expectancy. It was shorter then than today, which means that there may have been some later changes in the brain and/or the peripheral nervous system which had not managed to arise due to early death. This applies especially for the post-mortem examinations, but is of minor importance in relation to the imaging studies that mainly assess the early stages of the disease and are of more recent date.

In Batten disease, new treatment regimens are emerging [75], including enzyme replacement therapy, stem-cell therapy, gene therapy, and pharmacological drugs. While these new modalities of treatment show up, the need for biomarkers that could serve as a consecutive metric for therapeutic response is increasing. The present study demonstrates that there is a great difference in motor disability progression and gait dysfunction in the different forms of Batten disease, not only in relation to speed, but also which parts of the central nervous system are affected first and/or worst. This is of great importance in relation to monitor treatment results during disease course most appropriately, but it also has consequences for which route of administration to choose, as clearly shown in a recent treatment trial of the CLN1 mouse model, Ppt1-deficient (Ppt1−/−) mice [3]. Targeting the spinal cord via intrathecal administration of an adeno-associated virus (AAV) gene transfer vector in combination with forebrain-directed gene therapy showed a dramatic and synergistic improvement in motor function with an unprecedented increase in life span when compared to mice in which the same gene therapy was administered at only one of the two sites [3]. These findings highlight the need for further investigations of spinal cord pathology across both animal model studies and human tissue to further understand the basis of the vulnerability of the spinal cord, not only in CLN1, as it also raises the important question of whether, how and when the spinal cord, especially the spinal interneurons, may be affected in other subtypes of the CLN diseases, and consequently also may require different approaches of treatment.

8. Conclusion

Gait impairment and the underlying anatomical correlate during the disease courses of Batten disease manifest itself in different ways depending on subtype. In CLN1 truncal ataxia and a non-rhythmic gait is seen between 1 and 1½ years of age. Impairment of the cerebellum has an early impact on locomotion in CLN2, while in CLN3 the initial motor symptom is slowing of walking speed. Later extrapyramidal symptoms and loss of postural control are seen. Changes in gait phenotype may be a powerful and distinct marker for CLN disease progression. Further studies on the impact of spinal interneurons are desirable.

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Declaration of competing interest

The author has no conflict of interest to declare.

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