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Dopaminergic polygenic scores and BDNF/TrkB neurotrophin biology as predictors of rehabilitation response in hypotonic cerebral palsy: a scoping review of the research gap

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Abstract

Hypotonic cerebral palsy (CP) represents a small minority of all CP cases and remains one of the most understudied subtypes in biomarker and rehabilitation research. While dopaminergic polygenic scores and BDNF genetics have emerged as predictors of motor learning response in spastic CP, no studies have examined these biomarkers specifically in hypotonic CP. The omission has acquired new urgency: the first phase 2 trial of a neurotrophin-based agent in CP, an intranasal formulation of recombinant human NGF, began enrolling in March 2026, but enrolment is restricted to children with spastic CP, so the trial will generate no data for the subtype in which neurotrophin biology has never been characterised. This scoping review synthesizes current evidence on neurotrophins (NGF/BDNF), TrkB receptor isoform balance and dopamine polygenic scores as potential predictors of rehabilitation response in CP, and identifies the resulting gaps for hypotonic CP. Precision rehabilitation is therefore advancing on a subtype-selective evidence base, and hypotonic CP will remain outside it until baseline biomarker data exist. Generating those data does not require a new trial infrastructure: descriptive profiling of neurotrophin and dopaminergic markers within existing CP registries and rehabilitation cohorts is feasible now, and is the necessary first step before this population can be included in biomarker-guided treatment at all.

KEYWORDS: hypotonic cerebral palsy · ataxic–hypotonic CP · BDNF · NGF · TrkB · NTRK2 · dopamine polygenic score · rehabilitation · biomarkers · neuroplasticity

1. Introduction

Hypotonic cerebral palsy (CP) is a rare and understudied subtype of CP characterized primarily by low muscle tone (hypotonia) rather than spasticity, dystonia or ataxia [1]. It is often grouped together with ataxic forms, leading to limited dedicated research on its pathophysiology and treatment response [2]. While precision rehabilitation and biomarker-guided interventions are beginning to emerge in spastic CP and other neurological conditions [3], there is almost no work specifically addressing biomarker predictors of rehabilitation response in hypotonic CP.

In this article, the term "hypotonic CP" is used in a broad sense, encompassing both pure hypotonic presentations and the ataxic–hypotonic subtype described in population-based registries [2, 4]. In European registry data, ataxic CP accounts for approximately 3.8% of all CP cases, although this proportion varies substantially between registers (0–12.9%), reflecting persistent difficulty in classifying this subtype [4].

This scoping review synthesizes current knowledge on: (i) the epidemiology and pathophysiology of hypotonic CP; (ii) the state of NGF/BDNF research in CP and related conditions; (iii) dopamine-related

polygenic scores as predictors of motor learning and rehabilitation response; (iv) emerging evidence on TrkB receptor isoform balance as a modulator of BDNF signaling; (v) reasons why hypotonic CP is particularly understudied; and (vi) key research questions needed to build a biomarker framework for personalized rehabilitation in hypotonic CP. The focus is on children and young people, but many concepts are extrapolated from broader CP and neurorehabilitation literature.

2. Methods

This scoping review followed the general principles of the PRISMA-ScR framework. Peer-reviewed articles and reviews were identified using PubMed, MEDLINE and Google Scholar, complemented by AI-assisted searches (NeuroLab AI and Perplexity Deep Research) covering 2015–2026. Search terms included combinations of "hypotonic cerebral palsy", "ataxic–hypotonic CP", "neurotrophin", "BDNF", "NGF", "NTRK2", "TrkB", "dopamine polygenic score", "motor learning", and "rehabilitation".

Titles and abstracts were screened for relevance to: (i) hypotonic/ataxic–hypotonic CP; (ii) neurotrophin biology in CP or closely related paediatric conditions; or (iii) genetic or biomarker predictors of motor learning or rehabilitation response. Case reports without mechanistic or biomarker data and non-English papers were excluded. Given the emerging nature of the field, no formal risk-of-bias assessment or quantitative synthesis was attempted.

Because the field includes an active industry-sponsored trial not indexed in the peer-reviewed literature, the search was complemented by a targeted search of ClinicalTrials.gov (conditions: cerebral palsy; interventions: cenegermin, nerve growth factor; sponsor: Dompé) and of the sponsor's corporate communications. A further attempt was made on 26 July 2026 to locate a formal registration record for that trial in CTIS, EudraCT and the Italian national clinical-trials observatory; no accession number was retrievable, and the trial is therefore cited to the sponsor's announcement. All peer-reviewed references cited in this revised version were verified against PubMed/Europe PMC records on 24 July 2026, with a second verification pass on 26 July 2026 in which each cited PMID was retrieved and its authors, title, journal and year checked against the reference entry, and in which targeted searches were run to test each statement asserting an absence of evidence; the trial information in section 4.3 derives from a sponsor press release and is identified as such. In a third revision (1 August 2026), terminology was updated to current usage ("fetal growth restriction"), the abstract was rewritten without citations, and untargeted proteomics was added to the proposed biochemical profiling; no new literature claims were introduced in that round.

3. Background on Hypotonic Cerebral Palsy

3.1 Prevalence and Clinical Phenotype

Hypotonic CP (sometimes termed atonic CP) is one of the rarest CP subtypes and is frequently classified within the broader ataxic–hypotonic category rather than separately [2]. In the largest European register-based study to date, ataxic CP represented 3.8% of all CP cases across 20 registers, with marked between-register variation (0–12.9%), underlining that diagnosis of this subtype remains a challenge [4]. In the Canadian Cerebral Palsy Registry, 35 children with ataxic–hypotonic CP were identified against 1,804 children with other CP subtypes [2].

The nosological status of hypotonic CP remains actively debated, and some authors question whether it should be retained as a discrete category at all [5]. This debate is itself part of the problem addressed here: a subtype whose existence is contested is unlikely to be recruited as a stratum in biomarker studies.

Clinically, hypotonic CP is characterized by generalized or predominantly axial hypotonia, reduced antigravity postural control, delayed motor milestones, and often a wide-based, unsteady gait when walking is achieved [1]. Deep tendon reflexes may be normal or reduced rather than hyperreflexic, and primitive reflexes are less prominent than in spastic forms. Children often show "floppy" posture, head lag and poor trunk stabilization in infancy, with later emergence of compensatory joint locking and co-contraction [1].

Notably, registry data indicate that ataxic–hypotonic CP does not impart a worse prognosis with respect to gross motor function (GMFCS distribution) or overall comorbidity burden than other CP subtypes, although communication impairment is more frequent [2].

3.2 Pathophysiology and Lesion Patterns

Hypotonic CP is associated with damage to structures responsible for tone regulation and coordination, particularly the cerebellum and its connections, rather than the classic periventricular white matter lesions of spastic diplegia. Registry studies indicate that children with ataxic–hypotonic CP more frequently have:

- normal MRI (OR 3.8, 95% CI 1.4–10.5) or cerebral malformations (OR 4.2, 95% CI 1.5–11.9) rather than the acquired injury patterns typical of spastic CP [2]; in the European cohort, neuroimaging was normal in 29% and showed brain maldevelopment in 28.5%, with brain injuries in only 19% [4]; and
- higher rates of fetal growth restriction (OR 2.6, 95% CI 1.0–6.8) and congenital malformation (OR 2.4, 95% CI 1.2–4.8), together with less frequent perinatal adversity (OR 4.3, 95% CI 1.5–11.7 in favour of other subtypes) and higher gestational age at birth (median 39.0 vs 37.0 weeks), suggesting a predominantly genetic or prenatal etiology [2]. Genetic syndromes were described in 9% of European cases [4].

These findings support the view that ataxic–hypotonic CP is a distinct nosologic entity within the CP spectrum, with its own pathogenesis and risk factors [2], often linked to genetic variants affecting cerebellar and cortical development [4, 6]. In contrast to spastic CP, where corticospinal tract (CST) injury and loss of descending inhibition are central, hypotonic CP may reflect impaired integration of cerebellar, brainstem and cortical control of muscle tone and posture, with CST involvement being variable and less well characterized.

4. Current State of NGF/BDNF Research in Cerebral Palsy

4.1 Neurotrophins and Neural Plasticity

Brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are key neurotrophins supporting neuronal survival, axonal growth and synaptic plasticity. BDNF predominantly signals via TrkB receptors and is crucial for activity-dependent synaptic modulation and long-term potentiation [7], while NGF acts primarily via TrkA receptors to support cholinergic and sensory neurons [8]. Both have been widely studied in preclinical models of stroke and traumatic brain injury (TBI), where increasing neurotrophin levels (via direct delivery, gene therapy or physical exercise) improves functional recovery, but translation into clinical practice remains limited [8].

4.2 BDNF in Children with CP

In children with severe CP (GMFCS IV–V), plasma BDNF concentration has been reported to be approximately 40% lower than in typically developing peers [9]. Importantly, this difference was not observed in children with mild CP (GMFCS I–II), suggesting that reduced peripheral BDNF may be linked to severity rather than to the CP diagnosis per se. The same cohort showed markedly lower daily physical activity and an intake of energy, n-3 fatty acids and dietary fibre of only approximately 50% of that of typically developing children [9], complicating interpretation of whether BDNF deficiency is primary or secondary.

Genetic variation in BDNF (Val66Met polymorphism) has been examined as a possible moderator of rehabilitation response. In a cohort of children with unilateral spastic CP undergoing intensive hand training, BDNF Val66Met did not significantly predict functional gains measured by the Assisting Hand Assessment, whereas a polygenic score for dopamine genes showed a strong association (see Section 5) [3]. Other work suggests Val66Met may influence motor-related sensorimotor cortical oscillations in youth with CP, consistent with a subtle effect on plasticity [10], but the functional impact is modest and inconsistent across studies. This inconsistency is consistent with a systematic review and meta-analysis in healthy humans, which found little overall effect of BDNF gene polymorphisms on motor performance and motor learning

[11]. Taken together, these data suggest that any role of BDNF genetics may be context-dependent and potentially more relevant in the injured or developing nervous system than in healthy individuals — a hypothesis that remains untested in hypotonic CP.

4.3 NGF and Neurotrophin-based Interventions in CP

Direct NGF or BDNF therapies have so far been explored mainly in acquired brain injury rather than CP. Small paediatric case series of intranasal recombinant human NGF in children with severe TBI or post-traumatic unresponsive wakefulness syndrome report functional and neurofunctional gains without major safety signals [12, 13], but these studies lack controls, involve very small numbers, and are highly heterogeneous; the current evidence base has been summarized in a recent narrative review [8].

This translational step has now been taken. In March 2026 Dompé Farmaceutici announced enrolment of the first patient, at the Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome, in a phase 2 investigational study of an intranasal formulation of recombinant human NGF (cenegermin-bkbj) in cerebral palsy [14]. The study is planned to enrol 60 children across 10 Italian centres and, alongside safety and tolerability, will assess daily functioning, quality of life, motor abilities and neurodevelopmental outcomes [14]. To the author's knowledge this is the first interventional trial of a neurotrophin-based, putatively disease-modifying agent in CP. No record of the study was retrievable from ClinicalTrials.gov at the time of writing, nor could a CTIS, EudraCT or Italian national registry accession be located; the trial was authorised by the Italian Medicines Agency and is conducted within the Italian national system, and the details above therefore rest on the sponsor's public announcement rather than on a registry record.

The intranasal route itself is no longer exploratory. A phase 3 trial of intranasal cenegermin against vehicle in 272 adults with non-arteritic anterior ischaemic optic neuropathy began recruiting in July 2026 [15], indicating that nose-to-brain delivery of recombinant human NGF has advanced to confirmatory testing in a neurological indication. All other registered cenegermin trials concern ocular surface disease (neurotrophic keratitis, dry eye disease).

The eligibility criteria of this trial are directly relevant to the present review. Enrolment is restricted to children with spastic CP, aged two to six years, at any level (I-V) of the Gross Motor Function Classification System - Expanded and Revised (GMFCS-E&R) [14, 16]. The trial is therefore inclusive across severity but exclusive across subtype: hypotonic and ataxic-hypotonic CP are not eligible. The first clinical test of neurotrophin-based therapy in CP will consequently generate no efficacy, safety or pharmacodynamic data for the subtype in which the neurotrophin rationale has never been evaluated at all. This is the research gap that motivates the present review, and it is now a gap with a concrete timeline attached: if the phase 2 result is positive, extension to other CP subtypes will require prior characterisation of neurotrophin biology in those subtypes, which at present does not exist.

Overall, NGF/BDNF research in CP is still at an early stage, with:

- observational evidence of altered peripheral BDNF levels in severe CP [9];
- mechanistic support from broader neurotrophin, exercise and paediatric brain injury literature [7, 8, 12, 13]; and
- a first phase 2 trial of intranasal NGF now under way in spastic CP [14], from which hypotonic CP is excluded.

To date, no studies have quantified NGF or BDNF levels specifically in hypotonic CP or evaluated neurotrophin-targeted interventions in this subgroup.

5. Dopamine Polygenic Scores as Predictors of Rehabilitation Response

Dopamine plays a central role in reward-based learning and motor skill acquisition. Several studies have investigated whether common polymorphisms in dopamine-related genes modulate motor learning and rehabilitation outcomes in children with CP and other neurological conditions [3, 17, 18].

5.1 Polygenic Dopamine Score in Unilateral Spastic CP

A seminal study by Diaz Heijtz et al. (2018) examined 33 children (18–60 months) with unilateral spastic CP who had participated in a training programme involving 2 hours of active training of the involved hand daily over a two-month period. Saliva samples were genotyped for polymorphisms in COMT, DAT, DRD1, DRD2, DRD3 and BDNF, and a polygenic dopamine (DA) score was calculated to reflect higher or lower predicted dopaminergic neurotransmission [3].

Key findings:

- Children with a high DA polygenic score, incorporating polymorphisms of five dopamine genes and reflecting higher endogenous dopaminergic neurotransmission, showed the greatest functional outcome gains on the Assisting Hand Assessment after training [3].
- The association between dopamine gene variation and treatment outcome was statistically significant, whereas the BDNF Val66Met polymorphism did not significantly predict outcome [3].

This study provided the first direct evidence that naturally occurring genetic variation in the dopamine system partially explains why some children with similar brain lesions and functional levels respond much more strongly to intensive rehabilitation than others. The authors concluded that a polygenic DA score "might be valid for treatment outcome prediction and for designing individually tailored interventions for children with cerebral palsy" [3].

5.2 Extended Evidence Across CP and Non-CP Cohorts

Follow-up work has explored dopamine-related gene scores in broader samples of children and young adults with and without CP performing motor sequence learning and probabilistic classification tasks under rewarded and unrewarded conditions [17]. This more recent work examined whether individual variation in dopamine-related genes modulates the benefit derived from reward during motor and probabilistic learning, extending the question beyond a single intensive upper-limb intervention [17].

Separately, genetic variation in dopamine neurotransmission has been associated with motor development in infants born extremely low birthweight — a population at elevated risk of CP — supporting the relevance of dopaminergic genotype to early psychomotor development more broadly [18].

Collectively, these findings point to dopamine polygenic scores as promising biomarker predictors of motor learning capacity and rehabilitation response in CP and related conditions. However, research has focused almost exclusively on spastic (predominantly unilateral) CP, and no data exist for hypotonic CP.

5.3 Implications for Hypotonic CP

Although existing dopamine polygenic score studies in CP have focused on unilateral spastic CP or mixed cohorts [3, 17], the underlying mechanism — modulation of reward-based motor learning — is not specific to spasticity. Children with hypotonic CP often require prolonged, highly repetitive postural and gait training, and may particularly benefit from gamified, reward-rich interventions. Extending dopamine polygenic score frameworks to hypotonic CP could therefore help identify individuals who need more intensive motivational support or adjunctive dopaminergic modulation to achieve comparable training gains.

6. TrkB Receptor Isoforms and their Relevance to BDNF Response

BDNF exerts its effects primarily through the TrkB receptor, encoded by the NTRK2 gene. TrkB exists in multiple isoforms [19]:

- Full-length TrkB (TrkB-FL), containing the complete intracellular tyrosine kinase domain; and
- Truncated TrkB (TrkB-T1), lacking the intracellular catalytic domain and capable of acting as a dominant-negative receptor that sequesters BDNF and dampens downstream signaling [19].

Mechanistic work indicates that alternative splicing of NTRK2 is tightly regulated and that the balance between TrkB-FL and TrkB-T1 is a critical determinant of how neural circuits respond to BDNF [19].

Truncated TrkB is not, however, merely inhibitory: it also has signalling roles of its own, and its net effect is context-dependent [19]. Consistent with the importance of spatial and isoform-level regulation, BDNF transcripts themselves are differentially trafficked within neurons, shaping distinct dendritic compartments [7].

Although these findings come from in vitro and animal models, they suggest that individual differences in TrkB isoform ratios could significantly influence the effectiveness of BDNF-elevating interventions such as exercise, pharmacologic agents or gene therapy. At present:

- there are no clinical studies measuring TrkB-FL/T1 ratios in children with CP;
- the role of NTRK2 variants in CP motor outcomes is unknown; and
- no rehabilitation protocols are tailored based on TrkB expression.

Nevertheless, TrkB isoform balance represents a theoretically plausible biomarker axis for future personalized neurotrophin-based rehabilitation strategies. In the context of hypotonic CP — where conventional CST-centric biomarkers may be less informative — TrkB-FL/T1 ratios could become a determinant of who actually benefits from BDNF-enhancing interventions such as intensive exercise or future neurotrophin-based pharmaceutics. This remains a hypothesis requiring direct empirical testing.

7. Why Hypotonic Cerebral Palsy Is Understudied in Biomarker Research

Several factors contribute to the paucity of biomarker research specifically focused on hypotonic CP:

1. Low Prevalence and Phenotypic Heterogeneity. with Ataxic–hypotonic CP Accounting for

under 5% of cases in most registers [4], single-centre cohorts often include too few patients to power subgroup analyses; the Canadian registry, for example, identified only 35 such children against 1,804 with other subtypes [2]. Moreover, hypotonia may be axial, appendicular, or mixed, and often coexists with ataxia or subtle spasticity, complicating classification.

2. Predominantly Genetic or Prenatal Etiologies. Registry Data Show Higher Rates of

congenital malformations and fewer perinatal risk factors in ataxic–hypotonic CP [2], with genetic syndromes identified in a substantial minority [4], suggesting diverse genetic pathways rather than a single ischemic or hemorrhagic mechanism. Exome studies in children diagnosed with ataxic CP have identified de novo point mutations in a meaningful proportion of cases [6]. This heterogeneity makes it harder to design targeted biomarker studies and clear mechanistic hypotheses.

3. Historical Focus on Spasticity and Cst Injury. the Majority of CP Research Has Focused

on spasticity, which is more prevalent and historically more disabling. Biomarker and neuroimaging work (DTI, TMS) has prioritized CST integrity and upper motor neuron signs, which are less central or more variable in hypotonic CP.

4. Diagnostic Overlap and Misclassification. Hypotonic Presentations May Be Classified Under

ataxic CP, mixed CP, or even non-CP genetic ataxias and myopathies, leading to under-recognition of hypotonic CP as a distinct phenotype. The wide between-register variation in reported prevalence (0–12.9%) directly illustrates this problem [4], and reduces the visibility of hypotonic CP in registries and clinical trials.

5. Lack of Specific Treatment Paradigms. Evidence-based Guidelines and Intervention Trials

in CP have largely been developed for spasticity and hypertonicity (e.g., botulinum toxin, selective dorsal rhizotomy, baclofen) [20], with relatively few hypotheses tailored to hypotonia. Without a strong interventional pipeline, biomarker-driven personalization has not been prioritized.

6. Absence of a Standardized Measure of Tone. There Is No Widely Implemented, Quantitative

method for measuring hypotonia in young children, and low tone continues to be judged largely by subjective clinical examination [21]. A 2026 scoping review of Prechtl's General Movements Assessment and the Motor Optimality Score-Revised in infants with developmental central hypotonia identified only 14 eligible studies across 12 diagnoses and concluded that the evidence base is limited, heterogeneous and predominantly descriptive [21]. This constrains biomarker research twice over: without a reproducible phenotype definition, cohorts cannot be assembled consistently across centres, and without an outcome measure sensitive to change in low-tone populations, any biomarker-outcome association is attenuated by measurement error. The same review found the early motor phenotype to be consistent across conditions — reduced movement variability and complexity, a below-age-expected repertoire and atypical posture — indicating that standardized early motor phenotyping is achievable even where tone itself resists quantification [21].

These factors create a feedback loop: hypotonic CP is rare and heterogeneous, so it is excluded from trials; the lack of data then perpetuates the perception that it is not a tractable research target, especially in high-cost biomarker studies.

8. Proposed Research Questions and Directions

Based on current evidence and gaps, the following research questions could guide a biomarker-driven research agenda for rehabilitation in hypotonic CP.

8.1 Descriptive Biomarker Profiling in Hypotonic CP

Research Question 1

What are the baseline profiles of neurotrophins and dopaminergic markers in hypotonic CP?

- Cross-sectional studies measuring serum/plasma BDNF, NGF, GDNF, and related growth factors (IGF-1, NT-3/4) in children with hypotonic CP compared with spastic CP and typically developing controls, stratified by GMFCS level given the severity-dependence observed in existing data [9].
- Genotyping for BDNF Val66Met, NTRK2 variants, and polygenic dopamine scores to assess distributions and associations with clinical phenotype.
- Where infants are studied before five months corrected age, the General Movements Assessment and Motor Optimality Score-Revised offer a feasible, reliable means of phenotyping that does not depend on subjective tone grading [21].

Research Question 2

How does CST and cerebellar connectivity differ in hypotonic CP vs spastic CP?

- DTI tractography of CST, cerebellothalamic and cerebellocortical pathways, combined with TMS (motor evoked potentials) to characterize structural and functional connectivity.
- Correlation of imaging markers with neurotrophin and dopamine-related genetic biomarkers.

8.2 Biomarkers as Predictors of Rehabilitation Response in Hypotonic CP

Research Question 3

Do baseline BDNF/NGF levels predict response to intensive rehabilitation in hypotonic CP?

- Prospective observational studies in which children with hypotonic CP undergo structured, intensive motor training (e.g., trunk and postural control programs) with pre/post measurement of neurotrophin levels and functional outcomes.
- Testing whether children with higher baseline BDNF or greater training-induced increases show larger gains in the Gross Motor Function Measure (GMFM) [22] and postural control, with GMFCS [16] used for stratification.

Research Question 4

Does a polygenic dopamine score predict motor learning capacity in hypotonic CP?

- Extending the DA polygenic score framework [3] from unilateral spastic CP to hypotonic CP, examining associations with motor learning tasks (sequence learning, balance tasks) and rehabilitation outcomes.
- Investigating interactions with reward-based training (e.g., gamified physiotherapy), building on evidence that reward sensitivity may itself be genotype-dependent [17].

Research Question 5

Is TrkB isoform balance (TrkB-FL vs TrkB-T1) associated with plasticity and training response?

- Exploratory studies measuring NTRK2 expression and splicing (e.g., in peripheral blood mononuclear cells as a proxy, or via induced pluripotent stem cell models) to determine whether individuals with hypotonic CP exhibit altered TrkB-FL/T1 ratios.
- Testing associations between TrkB isoform patterns, BDNF responses to exercise and the magnitude of motor gains.

8.3 Toward Personalized Rehabilitation Protocols

Research Question 6

Can biomarker-informed stratification improve the design of rehabilitation trials in hypotonic CP?

- Designing small, multi-arm pilot trials in hypotonic CP where participants are stratified by biomarker profiles (e.g., high vs low DA polygenic score, high vs low baseline BDNF) and allocated to different intensities or types of training (e.g., conventional physiotherapy vs more reward-rich, high-intensity neuromotor exercise).
- Evaluating feasibility, safety and preliminary effect sizes to inform larger adaptive trials.

Research Question 7

Are there "responder" and "non-responder" phenotypes in hypotonic CP analogous to spastic CP?

- Combining clinical (age, severity, comorbidities), imaging (CST/cerebellar integrity), genetic (DA and BDNF/NTRK2 variants) and biochemical (neurotrophins, inflammatory markers) variables in multivariate models to identify clusters of high vs low responders to specific rehabilitation modalities.
- Extending the biochemical layer beyond candidate analytes to untargeted plasma or serum proteomics, which allows responder phenotypes to be defined without an a priori hypothesis about which pathways matter, and is well suited to a subtype where the relevant biology has not yet been characterised.

Research Question 8

How can non-invasive biomarkers be integrated into routine clinical workflow?

- Developing pragmatic protocols for repeated peripheral BDNF/NGF sampling, simple motor learning tasks and wearable-sensor-based gait/posture metrics to track treatment responses in real-world settings.

9. Limitations

This scoping review has several limitations. First, it was conducted by a single author, which increases the risk of selection bias and subjective interpretation of the literature. Second, only English-language publications were included, potentially overlooking relevant data from other languages. Third, the emerging nature of the field and heterogeneity of study designs precluded formal risk-of-bias assessment and quantitative synthesis. Fourth, much of the evidence discussed is extrapolated from spastic CP, acquired brain injury or preclinical models, and its applicability to hypotonic CP is therefore hypothetical rather than demonstrated. Fifth, information on the ongoing phase 2 intranasal NGF trial derives from a sponsor press release rather than from a peer-reviewed protocol or a public trial registry record; design details, including the outcome measures and the crossover structure, should therefore be regarded as provisional until the protocol is published. Finally, AI-assisted search tools were used to identify and prioritise articles; in preparing this revised version, all cited references were re-verified individually against PubMed/Europe PMC records, and several citations present in the first version were corrected or removed as a result.

10. Conclusion

Biomarker predictors of rehabilitation response in hypotonic cerebral palsy represent a major research gap at the intersection of neurodevelopmental neurology, genetics and rehabilitation science. While dopaminergic polygenic scores [3, 17] and, to a lesser extent, BDNF genetics [10, 11] have emerged as candidate predictors of motor learning and treatment response in unilateral spastic CP, these approaches have not yet been extended to hypotonic CP. Similarly, neurotrophin biology (BDNF, NGF) and TrkB isoform balance offer a compelling mechanistic framework [7, 8, 19], but remain largely unexplored in this rare CP subtype. The launch of the first phase 2 intranasal NGF trial in spastic CP [14] makes this omission consequential rather than merely academic: without baseline characterisation of neurotrophin biology in hypotonic CP, that subtype cannot be included in any subsequent extension of the programme.

Closing this gap will require:

- dedicated cohorts of children with hypotonic CP;
- systematic biomarker profiling (genetic, biochemical, imaging) alongside standardized rehabilitation protocols; and
- early-phase trials that explicitly test biomarker-guided stratification and personalization.

Such work has the potential not only to improve outcomes for a neglected group of patients, but also to illuminate fundamental principles of motor system plasticity under conditions of low tone and cerebellar-predominant pathology.

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