PredictMed: A Machine Learning Model for Identifying Risk Factors of Neuromuscular Hip Dysplasia: A Multicenter Descriptive Study

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Abstract

Neuromuscular hip dysplasia (NHD) is a common and severe problem in patients with cerebral palsy (CP). Previous studies have so far identified only spasticity (SP) and high levels of Gross Motor Function Classification System as factors associated with NHD. The aim of this study is to develop a machine learning model to identify additional risk factors of NHD. This was a cross-sectional multicenter descriptive study of 102 teenagers with CP (60 males, 42 females; 60 inpatients, 42 outpatients; mean age 16.5 $\pm$ 1.2 years, range 12–18 years). Data on etiology, diagnosis, SP, epilepsy (E), clinical history, and functional assessments were collected between 2007 and 2017. Hip dysplasia was defined as femoral head lateral migration percentage $>$ 33% on pelvic radiogram. A logistic regression-prediction model named PredictMed was developed to identify risk factors of NHD. Twenty-eight (27%) teenagers with CP had NHD, of which 18 (67%) had dislocated hips. Logistic regression model identified poor walking abilities ($p < 0.001$; odds ratio [OR] infinity; 95% confidence interval [CI] infinity), scoliosis ($p = 0.01$; OR 3.22; 95% CI 1.30–7.92), trunk muscles' tone disorder ($p = 0.002$; OR 4.81; 95% CI 1.75–13.25), SP ($p = 0.006$; OR 6.6; 95% CI 1.46–30.23), poor motor function ($p = 0.02$; OR 5.5; 95% CI 1.2–25.2), and E ($p = 0.03$; OR 2.6; standard error 0.44) as risk factors of NHD. The accuracy of the model was 77%. PredictMed identified trunk muscles' tone disorder, severe scoliosis, E, and SP as risk factors of NHD in teenagers with CP.

Keywords
- machine learning
- prediction model
- cerebral palsy
- neuromuscular hip dysplasia

Introduction

Cerebral palsy (CP) is a term used for a group of nonprogressive motor and postural control and postural disorders resultant from damages during early stages of brain development.[1] Hip dysplasia and dislocation are a common and severe problem[2,3] in patients with CP; the risk of neuromuscular hip dysplasia (NHD) is highest in patients with the most severe forms of CP, especially in nonwalking patients.[4] Hip displacement occurs in more than one-third of children with CP, and it is typically progressive. Hip dislocation can result in pain and difficulty with sitting and perineal care.[5]

Higher internal rotation than external is common in this population, resulting in internal rotation gait in walking

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patients. Factors thought to contribute include hip flexor tightness, imbalance of hip rotators and hamstring muscles, flexor and adductor tightness, spasticity (SP), and femoral anteversion.[6] Scoliosis with pelvic obliquity is strongly associated with NHP.[7,8]

The reported incidence of hip displacement and the risk factors identified vary. Knowledge regarding the overall incidence of NHD and associated risk factors in children with CP can facilitate diagnosis and treatment.[3] Dedicated screening programs are effective in identifying risk of NHD and in preventing dislocation.[9] However, high-quality evidence on NHD risk factor identification in children/teenagers with CP is lacking.[10–13]

Machine learning (ML) is a contemporary branch of artificial intelligence for analysis of complex data using algorithms to find data patterns that are not apparent to humans. Regression and logistic regression are among the first ML supervised algorithms used to implement predictive models in health care.[11,12]

ML algorithms are defined as supervised if the output classes are known (e.g., NHD, yes/no). Supervised ML prediction models can thus help identify risks factors of NHD. Prediction models can help in estimating the probability (Prob) that a condition (e.g., NHD) is present or likely to occur.[13–15] In supervised ML algorithms, the output of some inputs (training examples) are given. By training examples, the program learns a function (e.g., logistic regression) that will be used for prediction on new incoming patients with unknown status. The procedure[16] followed by a supervised learning algorithm is:

1. Collecting data on a training set and on a testing set;
2. Choosing a function to be learned (i.e., a logistic regression);
3. Running the learning algorithm on the training set;
4. Fine-tuning the function parameters (e.g., regression coefficients);
5. Evaluating the accuracy of the learned function on the testing set.

Typically, each subject/patient is described by a feature vector, which contains multiple variables. The number of variables should not be too large but should contain enough information to predict the outcome. Logistic regression is used in the supervised ML algorithm following the steps described. It calculates the Prob of a patient to have an outcome (i.e., hip dysplasia).

Hip displacement surveillance programs are recommended for children with CP because it is a common condition in this population and because early stage of hip displacements can be overlooked.[5] Treatment is more successful when hip displacement in children with CP is identified early.[3] Early identification and intervention with conservative or less invasive measures (abduction posture, botulinum toxin injection, and/or abductor muscles tenotomy) instead of osteotomy is important to help manage NHD in children with CP.[17] In previous studies, a supervised ML model named "PredictMed" was developed[18] and validated to predict neuromuscular scoliosis (NS),[8] gastrostomy placement,[19] and identifying factors associated with intellectual disabilities[20] in patients with CP. The aim of our study is to identify risk factors of NHD in teenagers with CP using the supervised ML model, PredictMed.

Methods

Study Design

Ethical approval: The study was designed, conducted, and monitored in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization guidelines, and relevant national and local laws. The study protocols were approved by the relevant independent ethics committees/Institutional Review Boards, and all patients provided written informed consent. Ethics committee approval and informed consent was registered with number "2017728 v 0-MR003 (reference method 003)."

This was a longitudinal descriptive multicenter study conducted between June 2007 and June 2017. Assessments and data collection for the implementation of the model were conducted in the last 6 months of 2014, and data analysis began in June 2015 and lasted 24 months.

Subjects

Of 486 children with CP in Nice region (France), 102 subjects, 60 from the Lenval University Pediatric Hospital and 42 from the Day Hospital of Nice (60 males, 42 females, age 16.5 ± 1.2 years) met the following inclusion criteria: age between 12 and 18 years at last follow-up, being spastic, dystonic, having mixed spastic/dystonic or hypotonic CP classified using the Surveillance of Cerebral Palsy in Europe system,[21] and having at least 3 years of follow-up (6.4 ± 1.2 years, range 3–12) (►**Table 1**). The exclusion criteria were progressive encephalopathy or spinal cord neuropathology. We had no missing data.

Measurements

All data were collected from the medical records by the senior author, who coded the narrative notes and filled the database "PredictMed"[8,18,19] based on the medical notes that were written by a multidisciplinary team, including pediatricians, pediatric neurologists, orthopaedic surgeons, physiotherapists, and epidemiologists (►**Table 1**).

Data on etiology (ET), diagnosis, functional assessments, type of SP, epilepsy (E), hip radiology, and clinical history were collected in anonymous form between 2005 and 2017.

The guidelines of the "Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis" (TRIPOD) statement were followed (Supplementary Material S1; available online only).[14]

ET of CP was classified as antenatal (genetic, cerebral malformation, infection, or vascular), perinatal (anoxic, ischemic, or infectious), or postnatal (cranial trauma, infectious, E, or pos-natal anoxic/ischemic injury).[8,18] Motor function was assessed using the Manual Ability Classification System (MACS)[8] and the Gross Motor Function Classification System (GMFCS),[5,17] both have a five-point classification system with higher scores indicating worse motor functioning. Trunk muscles' tone was assessed with the Trunk Impairment Scale (TIS)[22] including static and dynamic sitting balance scores and classifying muscle tone as hypotonic, spastic, or normal.

Table 1 Clinical presentation according to the presence or absence of neuromuscular hip dysplasias

Patients profile	Neuromuscular hip dysplasia		
	Yes (%)	No (%)	Total (%)
Patients *n* (%)	28 (27)	74 (73)	102 (100)
Male	17 (28)	43 (72)	60 (100)
Female	11 (26)	31 (74)	42 (100)
Average age (mean, SD)	16.4 (1.87)	16.8 (1.87)	16.6 (1.87)
Spasticity, *n* (%)	26 (34)	49 (66)	75 (100)
Hemiplegia	2 (22)	7 (78)	9 (100)
Diplegia	1 (7)	13 (93)	14 (100)
Tri/quadriplegia	23 (44)	29 (56)	52 (100)
Dystonia, *n* (%)	3 (21)	11 (79)	14 (100)
Well-controlled epilepsy, *n* (%)	17 (34)	33 (66)	50 (100)
Intractable epilepsy	5 (23)	17 (77)	22 (100)
No epilepsy, *n* (%)	6 (20)	24 (80)	30 (100)
Severe scoliosis (%)	17 (44)	22 (56)	39 (100)
Standing ability (%)	4 (9)	41 (91)	45 (100)
Truncal tone disorder (%)	22 (41)	32 (59)	54 (100)
Antenatal causes	15 (25)	46 (75)	61 (100)
Perinatal causes	10 (37)	17 (63)	27 (100)
Postnatal causes	3 (21)	11 (79)	14 (100)

Abbreviation: SD, standard deviation.

Functional abilities were assessed with the Functional Mobility Scale (FMS),[23] the Lower Extremity Functional Scale (LEFS),[24] and the Posture and Postural Ability Scale (PPAS).[25] The FMS measures functional mobility and walking capacity (W) using a six-level classification system with higher scores indicating better motor functioning. The LEFS measures of lower extremity function using an 80-point scale with higher scores indicating better function. The PPAS measures posture in sitting using a seven-level classification system with higher scores indicating better postural control.

Scoliosis was determined by the presence of a Cobb angle >10 degrees on spinal radiograph, and it was labeled as "severe" scoliosis when the Cobb angle was >40 degrees[8,18,26] (►**Table 1**). Neurologic status was classified according to the anatomy of the spastic disorder (hemiplegia, diplegia, tri/quadriplegia), the presence of hypertonia in the upper or lower limbs, the presence of dystonia (D), and the severity of E. SP was quantified using the Bohannon and Smith's modified Ashworth Scale and the Modified Tardieu Scale.[8,18] Severity of E was determined by the pediatric neurologists and identified as "well controlled" or "intractable"[27] accordingly with the International League Against Epilepsy, which defines intractable E/continued seizures despite attempted treatment with at least two antiepileptic medications[28,29] (►**Table 1**).

Clinical Hip Assessment Focused on Internal Rotation and Hip Abduction

Hip function, gait, and pain were assessed using the modified Harris Hip Score (MHHS).[30] All patients had at least one pelvic X-ray assessed by a pediatric orthopaedic surgeon. In case of multiple X-rays, the most recent was assessed except for patients who were operated on; for these, we assessed the preoperative X-ray.

Hip morphology was classified using the Melbourne Cerebral Palsy Hip Classification Scale (MCPHCS).[31] It uses a seven-level classification system with higher scores indicating more displacement.

The dysplasia was assessed based on the Perkins' line: when the lateral margin of the femoral head was medial to Perkins' line and the migration percentage (MP) was negative, it was given a value of 0%. When the whole femoral head was lateral to the Perkins' line, the MP was registered as 100%. Depending on the MP, the hips were classified as normal (MP under 33%), subluxation (MP = 33 up to 89%), or dislocation (MP $\geq$ 90%).[4]

The type of ET, SP, truncal tone (TT), presence of D, sex (SE), GMFCS, MACS, W, and E were assessed at first control; NS was assessed at last control.

Statistical Analysis

We created contingency tables and performed Fisher's exact tests to identify confidence intervals (CIs) and distribution frequencies of risk factors of hip dysplasia.[32] Then, we calculated the odds ratios, 95% CIs, and the z statistics (►**Table 2**) using the OpenEpi software, a web-based epidemiologic calculator[33] and the MedCalc statistical software.[34] The common threshold for selection of relevant variables (with p-value <0.2)[35,36] were used as independent input variables in a bespoke multiple logistic regression model to predict each patient's Prob of having NHD using the glm() function of open source software R.[37] The dependent binary variable was the presence of hip dysplasia (MP $>$ 33%, yes/no). The independent variables were type of ET, SP, TT, presence of D, E, NS, SE, GMFCS, MACS, W.

In accordance with the statistical learning theory described by Vapnik,[16] we split the patients' data in a "training set" and a "test set."[33] We trained the logistic regression algorithm on a "training set" of 80 patients (then excluded from the test set) to predict the Prob of NHD development for a new patient (belonging to a "test set" of 22 patients) by using the values of the best selected independent variables W + SP + E + NS + TT disorder + GMFCS score (►**Table 3**). To minimize the dependency from the compositions of training and test sets, we used cross-validation by randomly generating 20 different couples of training and test sets, that is, the training and test set compositions were randomly changed in 20 rounds of cross-validation. We calculated the accuracy, sensitivity, and specificity of the predictions for each couple and calculated the average.[34]

Sensitivity, specificity, and accuracy of the predictions were described as usual in terms of true positive (TP), true negative (TN), false negative (FN), and false positive (FP). Sensitivity was defined as the proportion of actual positives which were identified as such. Specificity was defined as the proportion

Table 2 Contingency table comparing the two groups (with and without neuromuscular hip dysplasia) using the Fisher's exact test and contingency tables with significant *p*-value

Independent variables		Neuromuscular hip dysplasia		Fisher's exact test *p*-Value equals	Odds ratio estimate	95% confidence intervals
		Yes	No			
Walking independently	Yes	0	42	0.0001	Infinity	Infinity
	No	28	32			
Standing position	Yes	4	41	0.0003	7.45	2.35–23.63
	No	24	33			
Truncal tone disorder	Yes	22	32	0.0017	4.81	1.75–13.25
	No	6	42			
Presence of spasticity	Yes	26	49	0.0057	6.63	1.46–30.23
	No	2	25			
MACS 3 vs. MACS 4/5	Yes	26	51	0.0109	5.86	1.28–26.81
	No	2	23			
Neuromuscular scoliosis	Yes	17	24	0.0128	3.22	1.30–7.92
	No	11	50			
GMFCS 3 vs. GMFCS 4/5	Yes	26	52	0.0182	5.5	1.2–25.2
	No	2	22			

Abbreviations: GMFCS, Gross Motor Function Classification System; MACS, Manual Ability Classification System.

Table 3 List of the logistic regressions coefficient (independent variables) associated with the presence of neuromuscular hip dysplasia

Independent variables	Logistic regression				
	Odds ratio estimate		Standard error	Z ratio	Prob (>|z|)
	Logarithm	Linear			
1. Intercept	3.4773	32.3721	3.1441	1.106	0.26874
W	−2.798	0.0614	1.0216	−2.739	0.00615
SP	0.7168	2.0478	0.3177	2.256	0.02405
E	0.9720	2.6432	0.4439	−2.190	0.02854
NS	1.1917	3.2926	0.5805	2.053	0.04009
2. Intercept	−4.5266	0.0108	1.5709	−2.881	0.00396
TT disorder	1.0692	2.9130	0.4996	2.140	0.03233
GMFCS score	0.7801	2.1816	0.3753	2.078	0.03767

Abbreviations: E, epilepsy; GMFCS, Gross Motor Function Classification System; NS, neuromuscular scoliosis; Prob, probability; SP, spasticity; TT, truncal tone; W, walking capacity.
Notes: *1. Logistic Regression*: The increasing of SP, E, NS (positive values) and decreasing of W (negative values) are predictive factors with the presence of neuromuscular hip dysplasia (in the "Estimate" column). As an example, this means that for every unit increase in NS, the log odds = ln ($p/1-p$) increases 1.1917 times (where p = probability to develop neuromuscular hip dysplasia), while for every unit decrease in W, the log odds = ln ($p/1-p$) decreases −2.798 times for W. *2. Logistic Regression*: The increasing of TT disorder and GMFCS score (positive values) are predictive factors of neuromuscular hip dysplasia (in the "Estimate" column). More precisely, this means that for every unit increase in TT disorder, the log odds = ln ($p/1-p$) increases 1.0692 times (where p = probability to develop neuromuscular hip dysplasia), while for every unit increase in GMFCS, the log odds = ln ($p/1-p$) increases 0.7801 times. The "Prob (>|z|)" column at the far right in the table indicates the significance strength of the respective parameter in terms of *p*-value as neuromuscular hip dysplasia predictor. This means that the significance of W, SP, E, NS, TT disorder, and GMFCS score in predicting neuromuscular hip dysplasia is very probable, with a p-value < 0.05.

of actual negatives which were correctly identified as such. Accuracy was defined as the precision of the measurement system, related to reproducibility and repeatability[34] and it was calculated as $(TP+TN)/(TP+TN+FP+FN)$.[37] We assessed the predictive ability of the model on a new test set through the predict glm() R-function (a). For each patient of the test set, it outputted a Prob of having NHD in the form of Prob (NHD = yes | glm [W +SP + E + NS + TT + GMFCS]), having by definition $0 < \text{Prob} < 1$. We fixed the decision boundary threshold. Thus, if Prob (NHD = yes | glm [W

+SP + E + NS + TT + GMFCS]) > threshold, then we predicted the presence of NHD. We checked thresholds from 0.1 to 0.8 and compared the accuracy, sensitivity, and specificity of the results.[34] For example, if choosing 0.3 this means that if we predict the Prob of developing NHD predicted by the logistic regression model for a given subject is > 0.3, then we classify that subject as a potential developer of (or having) NHD. If the patient (belonging to the test set) is really affected by NHD, then he is classified as TP, as opposed to an FP. In a similar way, we classified patients as either TN or FN.[34] Once this was done for each patient of the "test set," we compared the predictions with the known status of the patient (e.g., if he/she has NHD or not) to calculate the accuracy, sensitivity, and specificity of the logistic regression predictive algorithm. The logistic regression algorithm flowchart is shown in ►**Fig. 1**.

Results

The clinical presentation according to the presence of NHD is shown in ►**Table 1**. At last follow-up (6.4 ± 1.2 years, range 3–12), 28 subjects (27%) had hip displacement, of which 18 (67%) had dislocated hips with a mean age of 5 years at first hip displacement.

Motor skills, hip dislocation, functional, and postural abilities are summarized in ►**Fig. 2**. In relation to motor function, 76% ($n = 78$) had GMFCS ≥4 (mean 4.3 ± 1.2) and MACS ≥4 (mean 4.3 ± standard deviation 1.4). In relation to trunk movement capacities, 59% ($n = 60$) had only static sitting balance, 37% ($n = 38$) had dynamic sitting balance, only 4% ($n = 4$) had good postural balance, and nobody reached the maximum TIS score of 23 points. Trunk muscles' tone disorders was found in 53% ($n = 54$, 5 hypotonic, 49 spastic). In relation to functional mobility, half of the subjects could not walk, 47% ($n = 48$) were able to walk with aids, and only 2% ($n = 2$) could walk independently. In relation to lower extremity function, 49% ($n = 48$) had extreme difficulty; 35% ($n = 36$) had strong difficulty; 18% ($n = 18$) had moderate difficulty; and nobody had little or no difficulty. In relation to postural ability, 59% ($n = 60$) could not sit or needed support to be in aligned sitting posture, 29% ($n = 30$) were able to maintain sitting but cannot move, while only 12% ($n = 12$) were able to transfer weight laterally and move out of sitting position.

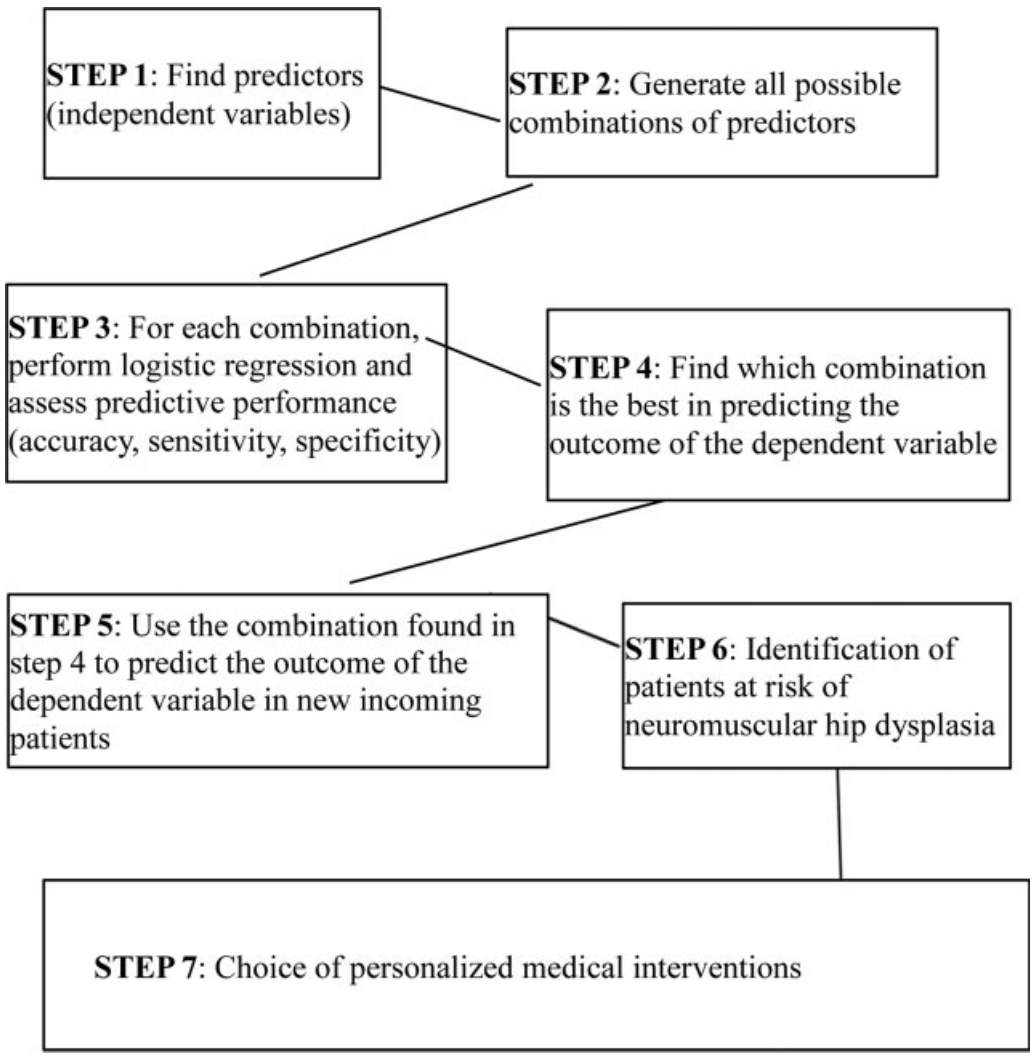
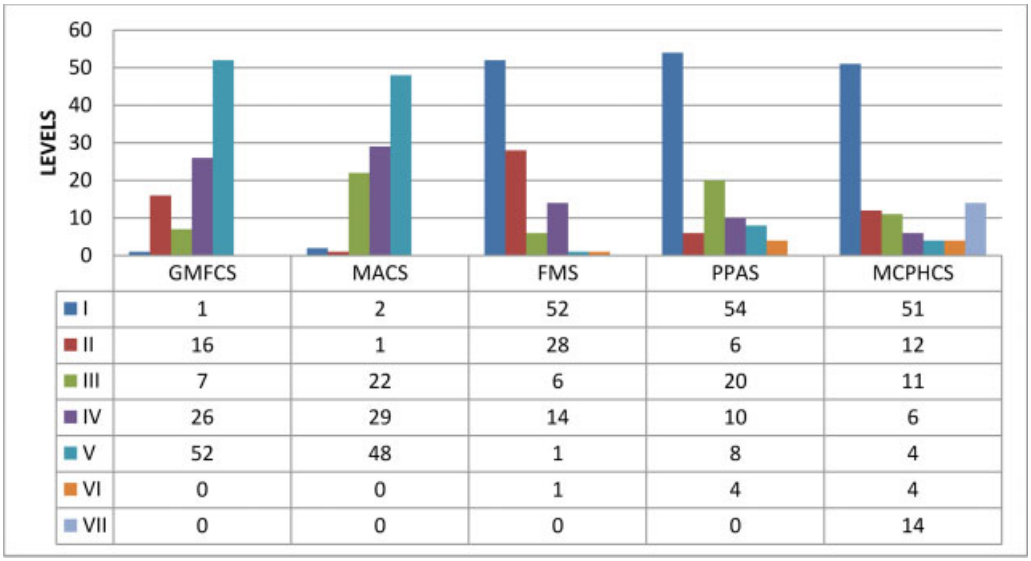


Fig. 1 Logistic regression algorithm flowchart.



	GMFCS	MACS	FMS	PPAS	MCPHCS
I	1	2	52	54	51
II	16	1	28	6	12
III	7	22	6	20	11
IV	26	29	14	10	6
V	52	48	1	8	4
VI	0	0	1	4	4
VII	0	0	0	0	14

Fig. 2 Distribution of patients according to the Gross Motor Function Classification System (GMFCS), Manual Ability Classification System (MACS), Functional Mobility Scale (FMS), Posture and Postural Ability Scale (PPAS), and Melbourne Cerebral Palsy Hip Classification Scale (MCPHCS).

The neurological status concerning SP, D, E, and NS is shown in ►**Table 1**.

Concerning hip range of motion, uni- or bilateral internal rotation was >40 degrees in 27% ($n = 27$) of the patients; 56% ($n = 57$) presented limited hip abduction <20 degrees.

Radiological hip morphology showed that 61% ($n = 62$) had normal or near normal hips, 11% ($n = 11$) had dysplastic hips, 6% ($n = 6$) had dysplasia with mild subluxation, 4% ($n = 4$) had moderate to severe subluxation, and 4% ($n = 4$) had dislocated hips (►**Fig. 2**).

Seven per cent of the subjects ($n = 6$) had a MHHS >72/91, 41% ($n = 42$) scored between 41 and 72, 22% ($n = 23$) scored between 16 and 40, and 30% ($n = 31$) scored 15 or less. Twenty-eight patients had hip dislocation; of these, 22 underwent a femoral osteotomy (7 cases of proximal femoral resection), and 11 of these also had a pelvic osteotomy. Five patients underwent a bilateral procedure. Multiple tenotomies concerned 25 patients. Botulinum toxin was injected in the adductor's muscles of 17 patients, and 2 of these also had the hip flexors injected.

The following variables were associated with NHD in the univariate analysis: walking ($p = < 0.001$) and standing capacities ($p = < 0.001$), truncal muscles tone disorder ($p = 0.002$), presence of SP ($p = 0.006$), NS ($p = 0.01$), manual ($p = 0.01$), and gross motor abilities ($p = 0.02$) (►**Table 2**). Multivariate regressions indicated that the factors most associated with NHD were W ($p = 0.006$), presence of SP ($p = 0.\ 02$), E ($p = 0.03$), TT disorders ($p = 0.03$), gross motor function ($p = 0.03$), and NS ($p = 0.04$). The best multivariate model had 77% accuracy, 43% sensitivity, and 98% specificity (►**Table 3**).

Discussion

In this study, we developed and tested a ML model to identify risk factors of NHD in teenagers with CP.

First in literature, the present study identified a link between trunk muscles' tone disorder, severe scoliosis, E, and the presence of NHD. Teenagers with CP with TT disorders and NS were four times more likely to develop NHD compared with those without these conditions. The presence of E was also a predictor of NHD. In line with the literature,[2,6,25] 27% (►**Table 1**) of the patients had at least one hip displacement of more than 33 degrees.

Previous studies[2,4,25,31,38] have so far identified only SP and high levels of GMFCS as factors associated with NHD.

As previously reported,[2,4] we found that the risk of hip displacement varied according to CP subtype: 7% for spastic hemiplegia, 4% for diplegia, 79% for tri/quadriplegia, and 10% for D. Similarly, to recent studies,[3,39] we also found that the GMFCS level has a strong impact on subluxation risk and that the risk continues to the end of growth. However, since this is a retrospective study, GMFCS and W could also be consequences rather than risk factors for NHD.

As indicated by Hägglund et al,[2] the risk of displacement was related to the level of gross motor function: from 7% in children with GMFCS level ≤III to 93% in in children with GMFCS level ≥IV. Furthermore, we also found a strong relationship between GMFCS and final MCPHCS.[31] Therefore, for GMFCS ≥IV, we also recommend an annual radiograph if migration percentage (MP) <30% or every 6 months if MP >30% between ages 2 and 8 years, followed by radiograph every 2 years until the age of 18 years.[37]

There is a pronounced trend toward NHD in nonambulant children.[4,9,25] In our cohort, 42% of the nonstanding teenagers developed hip dysplasia. Postural management and daily standing programs could reduce the risk of hip subluxation and increase function in children with CP.[17] Standing capacities, SP, manual, and gross motor abilities were strong predictors of NHD.

Accurate information is important when assessing the risk of hip displacement for teenagers with CP, for counseling

parents, and in the design of screening programs and resource allocation.[3] The model created had an NHD prediction accuracy of 77%, which is adequate for clinical use.[8]

Main clinical implications of our findings include the following:

- In presence of one or multiple predictors, frequent clinical assessment is suggested with special focus on abduction, internal rotation, and pain. The frequency of pelvic X-ray should also increase, especially if there is a clinical deterioration.
- Increased conservative measures as night and daily abduction posture and exercises should also be proposed. In case of SP and limited abduction, botulinum toxin injections should be prescribed at an early age.
- Concerning surgery, abductor muscle tenotomy and obturator nerve neurotomy are less invasive treatments that are potentially useful to prevent dislocation in case of abductor retraction and mild dysplasia. The exact cause of internal rotation (i.e., muscular and/or anteverted femur) must be defined before contemplating surgery.[4] In case of muscular imbalance, a tenotomy should be proposed. In case of persistent femoral antetorsion, a derotation femoral osteotomy is recommended.

Limitations

Limitations of this study include the retrospective analysis and the limited number of patients. This allowed obtaining a very high specificity, a good accuracy, and a moderate sensitivity.

A possible issue is to study the predictive performance of the algorithm if considerably increasing the number of patients while maintaining the same number of independent variables (< 15). At present, we have a limited number of patients to study (hundreds) and we plan to study and fine-tune the model on a quite greater number of them (thousands) to verify and eventually improve the predictive performance of the model itself. At this stage, we plan to calibrate on a much larger base of data of the model and to evaluate its potential overfitting (e.g., by studying a receiver operating characteristic curve) due to the limited numbers of patients available at present with respect to the high number of independent variables (e.g., features).

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Conflict of Interest
None declared.

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