INTRODUCTION

Cerebral palsy (CP) is a term for a group of conditions where the common element is a permanent but non-progressive disorder of movement or posture originating from an injury to the immature brain.\(^1\) CP affects approximately 1-2/1000 newborn infants, and European\(^2\) and Australian data\(^3-4\) show an overall decrease in the prevalence over the late 1990s and 2000s. CP is an umbrella term. It encompasses a wide range of severities, comorbidities and aetiological pathways where the role of certain genetic mutations becomes increasingly evident as well.\(^5\) The causative brain abnormalities can be detected in more than
80% of cases with MRI and involve a broad spectrum of different disorders affecting various structures of the brain. In order to investigate and understand the connections between brain anomalies and other factors in children with CP, the MRI results need to be classified.

The Surveillance of Cerebral Palsy in Europe (SCPE) research group has created a survey for registration of children with CP and a classification system for their MRI findings. The SCPE group collects data from registers in more than 20 European countries, including the CP Register of Southwest Hungary.

Our aims were to investigate perinatal and clinical factors associated with available MRI results. The distribution of MRI patterns based on the magnetic resonance imaging classification system (MRICS) and associations between perinatal and clinical characteristics and MRI patterns were studied.

We intended to assess the usefulness of MRICS. The detailed evaluations of brain MRI scans of children with CP help not only to reveal the aetiology of CP but also to establish the prognosis if performed early.

2 | PATIENTS AND METHODS

We have conducted an observational, population-based cohort study that was carried out in the Department of Paediatrics of the University of Pécs.

2.1 | The study cohort

Children with CP born between the year of 1990-2015, who lived at the age of four in the Southwest Hungary area including Baranya, Somogy and Tolna counties, were involved in the study. The CP definition given by the SCPE research group was used throughout this study. We focused only on those children with CP who had available MRI results.

2.2 | SCPE and the CP Register of Southwest Hungary

The Hungarian register is part of the SCPE group. Therefore, the register follows SCPE guidelines regarding the definition (see below), inclusion/exclusion criteria, upper age limit for registration and minimum age for children who died. The SCPE working group was established in 1998 to disseminate knowledge about CP through epidemiological data, to develop best practice in monitoring trends in CP, to raise standards of care for individuals with CP, to inform for service planning and to provide a framework for collaborative research. The CP Register of Southwest Hungary joined to the group in 2010. Our register covers Baranya, Tolna and Somogy counties, which belong to the area of the University Hospital of Pécs and district hospitals of Kaposvár and Szekszárd. The data of the CP

Key notes

- We studied the role of magnetic resonance imaging (MRI) classification system in clarifying the aetiology of cerebral palsy (CP).
- MRI results were conclusive in 86.4% of children, in pre-term infants white matter injuries, in term babies maldevelopments and grey matter anomalies were the most common anomalies.
- It is highly encouraged to perform cranial MRI in every patient with CP because it helps not only to reveal the aetiology but allows to establish the prognosis.

patients were obtained not only from the databases of these three hospitals, but other sources were used as well in the covered area including early intervention centres, rehabilitation centres, advocacy groups and special homes for disabled children. We collected not only the clinical data of children with CP but the population-based denominator data as well.

Registers affiliated with SCPE use a definition for CP that includes five key elements: CP is a group of disorders, that is it is an umbrella term; it is permanent but not unchanging; it involves a disorder of movement and/or posture and of motor function; it is due to a non-progressive interference/lesion/abnormality; this interference/lesion/abnormality is in the developing/immature brain. All children diagnosed with CP who were born in Southwest Hungary and lived there at the age of four years were included in our database. Children were excluded if they had progressive disease, hypotonia as the sole clinical feature or isolated spinal neural tube defect. Patients with postneonatally acquired CP were not excluded.

The data entered into our local register were collected from paper-based and electronic medical records of the above-mentioned institutes. The official data form of JRC-SCPE register was applied, but in this study, we used the data of our local CP register. Completed surveys were organised and digitalised at the Department of Paediatrics of the University of Pécs. Collaboration agreement was done between the Joint Research Centre-SCPE and the University of Pécs. We send regularly and annually the desired data to the JRC-SCPE register from 2010. Approvals for data collection, for the study and for the register, were obtained from the regional ethics committee of our University.

Although five years is the optimal age for the confirmation of CP diagnosis, cases can be considered for inclusion in the SCPE database if they fulfil the clinical criteria after their fourth birthday. According to the SCPE guidelines, children in whom the diagnosis of CP is made after the age of two years, but have died before a confirmed diagnosis (between the age of two and five), should also be entered into the database. Children lost to follow-up at the age of five but with unambiguous diagnosis of CP after the age of three years old should also be submitted to SCPE database.
2.3 | The collected data

In this study, the following data were collected from medical records: sex, birth weight, gestational age (prematurity was defined as birth before the 37th gestational week), method of birth, multiple birth, Apgar score measured at 5 minutes, convulsions within the first 72 hours, CP subtypes (bilateral spastic, unilateral spastic, dyskinetic or ataxic; for mixed forms subtypes, the dominant clinical feature was considered), levels of Gross Motor Function (GMF) Classification System\textsuperscript{11} and Bimanual Fine Motor Function,\textsuperscript{12} presence of epilepsy and brain MRI results. Intellectual status of the children was examined by psychologists with MAWGYI-R test, the Hungarian paediatric adaptation of Wechsler intelligence test (normal IQ ≥ 70, mild impairment IQ 50–69, moderate-severe impairment IQ ≤ 49) or by clinical impression. Clinical impression was used only in those children whose intellectual impairment was definitely very severe (IQ < 20).

Brain MRI results were classified into five groups based on MRICS.\textsuperscript{7} MRI scans were evaluated first by experienced neuroradiologists. We classified the MRI results in every case, and finally, all MRI classifications were re-evaluated with the help of our co-author (ZH) who is a specialist in paediatric neuroradiology. The groups were the followings: maldevelopment, predominant white matter injury, predominant grey matter injury, miscellaneous changes and normal. In case we found several patterns, we classified the predominant pattern that was believed most likely to have led to the CP. When more MRI scans became available, the findings of the latest scan were considered.

2.4 | Statistical analysis

SPSS Statistics 24 (IBM Corp, New York, USA) and RStudio (R.RStudio, Inc, Boston, MA) were used for statistical analysis. Different prognostic factors were assessed by chi-square independence test or Fisher’s exact test to reveal differences between the CP groups with different MRI patterns. The level of significance was defined as .05.

3 | RESULTS

We identified 418 children with CP who were born in the investigated birth years. Out of these, 257 (61.5%) had available MRI.

3.1 | MRI patterns in relation to perinatal and clinical variables

MRIs were performed at the age of two years or later in 65.4% of the cases. White matter injuries were the most frequent abnormalities in 35.4% of patients. Occurrence of maldevelopments and grey matter injuries were similar, and they occurred in 18.7% and 19.8% of the cases, respectively. Furthermore, 12.5% of patients were classified into the miscellaneous group. No abnormality was revealed by MRI in 13.6% of patients.

3.1.1 | Perinatal data

Perinatal data are summarised in Table 1. Important differences were revealed in the distribution of MRI patterns across categories of birth weight, birth gestation and plurality.

Considering birth weight, 59.4% of babies born under 2500 g had white matter injury and 79.2% of those babies whose birth weight was below 1500 g had MRI evidence of white matter injury. Maldevelopments and grey matter injuries mainly affected children born with normal birth weight. Patients with normal MRI had normal birth weight in 78.1% of cases.

The distribution of gestational age categories correlated well with those of birth weight categories. Extreme preterm birth (<28 weeks) was strongly associated with white matter injury (21/24 cases, 87.5%) compared to 37/69 (53.6%) cases born 28–36 weeks and 26/145 (17.9%) cases born at 37 weeks and older. Compared to all MRI patterns, grey matter injury was particularly associated with term birth (80% vs 60.9%) and birthweight higher than 2500 g (77.1% vs 59.8%), a 5-minute Apgar score below seven (19.5% vs 12.9%) and neonatal seizures (31.8% vs 18.8%).

Children from multiple births had white matter injury in 75.0% (15/20).

We found no significant difference in the distribution of sexes and Apgar score categories, methods of delivery and neonatal seizures in relation to MRI subcategories.

It is interesting that males were over-represented in white matter injury (61.5%), miscellaneous findings (62.5%) and normal MRI (68.6%) but not in maldevelopments and grey matter injury.

Considering the delivery method, 39.8% of all CP children were born by caesarean section with a range from 28% of those with maldevelopments to 50% of those with white matter injury. A 5-minute Apgar score less than seven might be expected, as seen commonly in children with grey matter injury (19.5%), but a score less than four is unexpectedly common in children with normal imaging (7.1%).

Of 39/169 (1%) cases with neonatal seizures, 13 (33.3%) had white matter injury and 14 (35.9%) had a grey matter injury pattern. The remaining 30.8% cases were spread between maldevelopments, miscellaneous and normal patterns. Another somewhat unexpected finding was that neonatal seizures were seen least often in those children with maldevelopments (8.8%).

3.1.2 | Clinical data

Clinical data are summarised in Table 2. White matter injuries were found in 39.6% of children with bilateral spastic CP. Those children had grey matter injury, 64.7% had unilateral spastic CP. These patients constituted 38.8% (33/85) of all patients with unilateral
We found normal MRI in 35 patients, 16 of them had bilateral spastic CP and 13 of them had unilateral spastic CP. GMF Classification System and Bimanual Fine Motor Function scores were the most favourable in the groups with normal MRI and with grey matter injury; in every category, the rate of scores I-II was more than 60%. The patients with maldevelopments and those with miscellaneous findings scored worse; more than 65% of patients received scores III-V.

Intellectual impairment was the most severe in patients with maldevelopments; 74.4% of them had IQ ≤ 49. The rate of normal intellectual ability was the highest in the group with grey matter injury and with normal MRI (56.8% and 41.9%, respectively).

The prevalence of epilepsy was above 60% in every group with abnormal MRI. The highest rate was observed in the miscellaneous group.

### Discussion

In our study, we examined patients with CP from our CP register which covers the population of Southwest Hungary. As far as we know, this is the first research investigating a Hungarian population with all types of CP. Previously, Hollódy and Szőts have conducted a study with Hungarian CP patients, but only on individuals with bilateral spastic CP born between 1975 and 1986.

The rate (61.5%) of our patients who had at least one MRI correlated well with the Australian data. They involved patients born between 1999 and 2006 and were able to classify 67% of their patients based on MRI results.

Generally, the recommended time for MRI depends very much on the type of expected injury. At least one MRI examination is usually recommended in patients with CP after the age of two when the myelinisation of the brain is almost complete. The MRI findings may help to understand the aetiology of CP. Several classification systems exist considering the MRI findings of CP patients; the harmonisation of these systems is however challenging.

In 86.4% of our patients, abnormalities were found on MRI scans. Korzeniewski et al reviewed 20 studies and found that 80.1% (55.1%-100%) of patients demonstrated image abnormalities. Reid et al found normal MRI in almost the same proportion (13% vs 13.6%) of their patients compared with our results. In their

### Table 1

|                     | Maldevelopment | WMI | GMI | Miscellaneous | Normal | Total |
|---------------------|----------------|-----|-----|---------------|--------|-------|
| N                   | 48 (18.7%)     | 91 (35.4%) | 51 (19.8%) | 32 (12.5%) | 35 (13.6%) | 257 (100%) |
| %                   | 25 52.1        | 27 29.8    | 38 42.3    | 12 37.5    | 11 31.4    | 108 42.0   |

**Abbreviations:** BW, birthweight; GMI, grey matter injury; WMI, white matter injury.
In our study, the rate of white matter injury (45%) seemed to be higher, and the rate of maldevelopment (10%) was lower compared to our results. In Benini’s research, the rate of normal MRI was much higher (29%). The great discrepancy between Benini’s results and our findings can probably be explained with the fact that in their study, patients underwent 1.5 T MRI between 1999 and 2002, while our patients were examined by 1.5 and 3 T MRI until 2015. Another explanation is the difference in definition regarding the umbrella term of CP. Very mild cases are less likely to show abnormalities on MRI.

### 4.1 Evaluation of perinatal data in relation to MRI results

In our study, white matter injury was found mainly in the prematurity/low birth weight category while term newborn infants/newborn infants with normal birth weight were more often affected by grey matter injury or maldevelopment. In Reid’s study, the rate of prematurity was lower among patients with white matter injury (55.3%). However, those patients with brain malformation and grey matter injury were mainly born after 37 gestational weeks, similarly to our population (77.2% and 88.9%). Most of the patients with normal MRI were born with normal birth weight and at term.

### 4.2 Clinical data and MRI patterns

Unilateral spastic CP type was mostly associated with grey matter injury (33/85 of patients). In these cases, the one-sided occlusion of the arteria cerebri media was the most common MRI finding. Bilateral spastic CP was most frequently caused by white matter injury (57/144), where bilateral periventricular leukomalacia seemed to be the most common aetiology.

Interestingly, not only the patients with normal MRI seemed to have better GMF Classification System, Bimanual Fine Motor Function and IQ scores, but also those with grey matter injury. Numata et al. investigated 86 patients born at term with spastic diplegia. Surprisingly, they revealed no differences in the frequency of intellectual impairment between groups with normal and abnormal MRI findings and over 50% of their patients with normal MRI had intellectual disability. This is the reason why they labelled negative MRI results as ‘undetected abnormalities’.

It should be highlighted that our study found a high prevalence rate of epilepsy. More than 60% of patients were affected by epilepsy in every group with abnormal MRI. The high prevalence can be explained by the fact that in our survey, we investigated whether the children had epilepsy in their childhood, while the other studies investigated the epileptic status of their patients in a limited time period.
4.3 | Strengths and limitations

Our data were population-based and covered the CP population of one definite region. A relatively large number of patients were enrolled and evaluated in the study, and two-thirds of the patients had one or more MRI scans. All children were examined by experienced neuropaediatricians with the same approach. MRI scans were evaluated first by experienced neuroradiologists, and finally, all MRI were re-evaluated by our co-author (ZH) who is a specialist in paediatric neuroradiology. The same SCPE survey was used. MRI scans were not performed at a specific age. If the pathology was clear before the age of two, the MRI scan was not repeated in every case.

5 | CONCLUSIONS

The characteristics of the Hungarian CP population correlate well with international data considering the male predominance, the birthweight, the prematurity and caesarean section rate, the Apgar scores and the rate of spastic CP. A higher prevalence of epilepsy was observed in our population possibly due to the longer observation period. A total of 13.6% of our patients with CP had normal MRI. Prematurity was associated mainly with white matter injuries, while mature infants most frequently had maldevelopments and grey matter injuries. Scores of fine and gross motor function and IQ were more favourable in patients with grey matter injuries or with a normal MRI scan. Epilepsy is a very common co-morbidity in CP.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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