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SMC1A epilepsy syndrome: clinical data from a large international cohort

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Abstract

SMC1A epilepsy syndrome or developmental and epileptic encephalopathy-85 with or without midline brain defects (DEE85, OMIM #301044) is an X-linked neurologic disorder associated with mutations of the *SMC1A* gene, which is also responsible for about 5% of patients affected by Cornelia de Lange syndrome spectrum (CdLS). Only described in female patients, *SMC1A* epilepsy syndrome is characterized by the onset of severe refractory epileptic seizures in the first year of life, global developmental delay, a variable degree of intellectual disability, and dysmorphic facial features not typical of CdLS. This was a descriptive observational study for the largest international cohort with this specific disorder. The main goal of this study was to improve the knowledge of the natural history of this phenotype with particular attention to the psychomotor development and the epilepsy data. The analyzed cohort shows normal prenatal growth with the subsequent development of postnatal microcephaly. The incidence of neonatal problems (seizures and respiratory compromise) is considerable (51.4%). There is a significant prevalence of central nervous system (20%) and cardiovascular malformations (20%). Motor skills are generally delayed. The presence of drug-resistant epilepsy is confirmed; the therapeutic role of a ketogenic diet is still uncertain. The significant regression of previously acquired skills following the onset of seizures has been observed. Facial dysmorphisms are variable and no patient shows a classic CdLS phenotype. To sum up, *SMC1A* variants caused drug-resistant epilepsy in these patients, more than two-thirds of whom were shown to progress to developmental and epileptic encephalopathy. The *SMC1A* gene variants are all different from each other (apart from a couple of monozygotic twins), demonstrating the absence of a mutational hotspot in the *SMC1A* gene. Owing to the absence of phenotypic specificity, whole-exome sequencing is currently the diagnostic gold standard.

KEYWORDS
cohesinopathy, Cornelia de Lange syndrome spectrum, developmental disability, drug-resistant epilepsy, *SMC1A* gene

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1 | INTRODUCTION

The *SMC1A* gene (*SMC1L1*, MIM #300040) encodes one of the proteins of the cohesin-core complex that tethers sister chromatids together to ensure correct chromosome segregation in both cellular mitosis and meiosis. In addition, as a part of the cohesin ring, the SMC1A protein is involved in gene transcription regulation and genome organization and plays a pivotal role in the DNA Damage Repair pathway. *SMC1A* maps to Xp11.22 in a region that escapes X inactivation (Sultana et al., 1995).

In mammals, *SMC1A* was first identified during the screening of a cDNA library deriving from human lymphocytes (Lafreniere et al., 1991) and its role as a disease-causing gene emerged in 2006, when pathogenetic variants of *SMC1A* were identified in patients affected by the Cornelia de Lange Syndrome (CdLS, OMIM #300590) (Musio et al., 2006).

CdLS is a rare developmental malformative syndrome characterized by small stature, limb abnormalities, characteristic facial features, developmental delay, and behavioral issues. Congenital heart disease is found in 25% of individuals, renal abnormalities in 10%, cleft palate in 20%, cryptorchidism in 80% of men, and bicornuate uterus in 19% of women. Structural brain abnormalities can occur especially in individuals with *NIPBL* variants and seizures occur in about 20% of individuals (Kline et al., 2018). At present, mutations (mainly missense or in frame in/del outside the HINGE domain) in the *SMC1A* gene are thought to be responsible for 5% of cases of CdLS, while mutations involving the *NIPBL* gene are retrieved in up to 70% of patients. Finally, pathogenic mutations in *RAD21*, *SMC3*, *HDAC8*, *ANKRD11*, and *BRD4* genes have been reported in a minority of CdLS cases (Kline et al., 2018).

Huisman et al. (2017), within a collaborative international study, focused on CdLS patients with *SMC1A* mutations, reported cases of female children with truncating variants of the gene and displaying clinical features different from those generally retrieved in CdLS. This phenotype resembles Rett syndrome, with epileptic encephalopathy, profound intellectual disability, and stereotypic movements. In the following years, other authors described a clinical phenotype characterized by the co-occurrence of drug-resistant epilepsy and psychomotor delay in female patients with *SMC1A* variants (Barañano et al., 2022; Bozarth et al., 2023; Chinen et al., 2019; Goldstein et al., 2015; Hansen et al., 2013; Jansen et al., 2016; Kruszka et al., 2019; Lebrun et al., 2015; Naik & Shah, 2021; Oguni et al., 2019; Symonds et al., 2017; Wenger et al., 2017).

The name of this new phenotype has not been standardized yet. Indeed, it is variably referred to as *SMC1A* epilepsy syndrome, *SMC1A* loss of function (LoF) epilepsy, *SMC1A*-related developmental and epileptic encephalopathy, or developmental and epileptic encephalopathy-85 with or without midline brain defects (DEE85, OMIM #301044). The term "*SMC1A* epilepsy syndrome" will be used from here on for simplicity.

Despite the lack of a standardized nomenclature, heterogeneous clinical information on approximately 44 patients with *SMC1A* epilepsy syndrome has been published to date. Case reports of girls with pharmacoresistant epilepsy and *SMC1A* variants were initially reported (Goldstein et al., 2015; Jansen et al., 2016). Symonds et al. (2017) realized the first case series in which the phenotype of 10 girls were analyzed simultaneously, and Barañano et al. (2022) described a series of 13 female patients from the United States with *SMC1A* variants and intractable epilepsy. Finally, recently other 3 patients were reported and, in attempt to characterize common and patient-specific features, a summary of the 41 previously described patients was also provided (Bozarth et al., 2023).

We hereby report a detailed clinical description of 35 individuals with pathogenic or likely pathogenic *SMC1A* variants and epilepsy through a systematic collection of data. Our main goal was to provide clinicians with improved awareness about the natural history of this phenotype, with particular focus on psychomotor developmental and epileptic data. Second, we analyzed the clinical features of the patients enrolled in order to establish whether it fell within the phenotypic spectrum of the CdLS as defined by the 2018 International Consensus Statement (Kline et al., 2018).

2 | METHODS

Patients were recruited in collaboration with the European *SMC1A* Foundation. Patients' caregivers were contacted by the Foundation; collected data were reviewed by the referring pediatricians or geneticists. Written informed consent was obtained for all patients.

Patients were eligible if they had a documented *SMC1A* variant and epilepsy.

The internal review board of the Department of Paediatrics, University of Milano-Bicocca (Monza) approved the study.

Data were collected through a wide ad hoc questionnaire (available from authors on request) that focused on demographic data, physical phenotype, prenatal development and pregnancy, major malformations, postnatal growth, psychomotor development, behavioral abnormalities, epilepsy, feeding abnormalities and gastrointestinal disorders, other medical complications, type of genetic tests performed (conventional karyotype, comparative genomic hybridisation (CGH) array, specific panel for cohesin genes or epilepsy-associated genes, and whole-exome sequencing [WES]). Growth was evaluated with reference to the World Health Organization (WHO) percentile ranges/standard deviation scores (SDS).

For the purpose of this study, the degree of activity of baseline epileptic disorder was categorized into three classes: "good seizure control" if seizures occurred less than once per month; "partial seizure control" if seizures were recorded, as an average, between once a month and once per week; and "poor seizure control" if seizures occurred more frequently than once a week.

The history of the clinical diagnosis of CdLS has also been evaluated. Questionnaires were filled out by patients' caregivers between October 2020 and March 2021, either under the guidance of referring pediatricians/geneticists or independently. We also collected the reports of brain magnetic resonance imaging (MRI), electroencephalogram (EEG), and genetic tests.

Finally, we collected patients' photographs, along with dedicated parental consent, in order to perform an internal revision of facial dysmorphisms. This assessment was performed by the authors AS and MM according to the criteria of the 2018 International Consensus Statement on CdLS (the presence of cardinal features and/or suggestive features). These criteria have been used to assess whether patients presented a phenotype consistent with classical CdLS, non-classical CdLS, or at least an indication to perform a molecular test for CdLS.

Statistical analysis was performed using SPSS software package version 26. Quantitative variables were reported as mean, median, and standard deviation (SD). Categorical variables were described by means of frequencies/percentages and were compared using the chi-square test. The significance threshold was set at $p < 0.05$.

3 | RESULTS

We collected data from 35 individuals. Participants originated from the USA (11), UK (7), Italy (4), France (2), Germany (2), the Netherlands (2), Poland (2), Spain (1), Finland (1), Turkey (1), Canada (1), and Brazil (1).

All patients were women. Median age upon enrollment was 9.5 years (range: 6 months–34 years). Twenty-nine of 35 patients (82.9%) had siblings (average number of siblings: 1.49) and none of them had been diagnosed with the same clinical condition. No case of consanguinity between parents had been reported.

3.1 | Pregnancy

All pregnancies were spontaneous. One was a monozygotic twin pregnancy. Two of 34 mothers (5.9%) developed preeclampsia. Two patients (5.7%) showed ultrasound evidence of intrauterine growth restriction (IUGR) at the beginning of the third trimester. In five cases (14.3%) fetal malformations were detected upon ultrasound evaluation: holoprosencephaly (two), arachnoid cyst (one), aortic coarctation (one), interatrial septal defect (one).

3.2 | Perinatal history

Twenty-two patients were born in a vaginal delivery (62.9%), seven by planned caesarean sections (20%), and four by emergency caesarean sections (11.4%). No information about the delivery was available for two (5.7%) patients. The mean gestational age (ga) at delivery was 39 weeks.

The average birth weight of the patients was 3074 g. The average length at birth was 48.9 cm, while the average head circumference at birth was 33.5 cm.

Birth weight, length, and head circumference showed the following distribution, with reference to the WHO growth charts:

1. weight was normal (between 3rd and 97th percentile, corresponding to −1.9 SDS and +1.9 SDS for general population) in 29 patients (82.9%), <3rd percentile (<−1.9 SDS) in 4 patients (11.4%), and >97th percentile (>+1.9 SDS) in no patient (0%). Birth weight data were not available for two patients (5.7%).
2. length was normal (between −1.9 SDS and +1.9 SDS) in 21 patients (60%), <−1.9 SDS in 4 patients (11.4%), and >+1.9 SDS in 1 patient (2.9%). Birth length data were not available for nine patients (25.7%).
3. head circumference was within normal limits (between −1.9 SDS and +1.9 SDS) in 18 patients (51.4%), <−1.9 SDS in 3 patients (8.6%), and >+1.9 SDS in no patient (0%). Birth head circumference data were not available for 14 patients (40%).

Apgar score values at the first minute were available for 19 patients. The mean value was 8.9.

Apgar score values at the fifth minute were collected for 18 patients. The mean value was 9.6.

Neonatal problems have been described in 18 of 35 patients (51.4%; see Table 1 for details).

Admission to the neonatal intensive care unit (NICU) was necessary for 12 patients (34.3%), with an average stay of 14.7 days.

3.3 | Major malformations

Major malformations have been detected in 14 of 35 patients (40%), with the following distribution by apparatus: limbs: 2 patients (5.7%); lips/palate: 1 patient (2.9%); cardiovascular system-heart: 7 patients (20%); urinary tract: 2 patients (5.7%); genitals: 2 patients (5.7%); and central nervous system (CNS): 7 patients (20%; Table 1).

Thirty-two of 35 patients (91.4%) performed at least one cerebral MRI during their lifetime. Two performed more than one brain MRI during their lifetime (mean number of MRIs performed: 1).

3.4 | Postnatal growth

Postnatal weight was normal (between −1.9 SDS and +1.9 SDS for the general population) in 16 patients (45.7%), <−1.9 SDS in 15 patients (42.8%), and >+1.9 SDS in 1 patient (2.9%). Postnatal weight data were not available for three patients (8.6%).

Postnatal length was normal (between −1.9 SDS and +1.9 SDS) in 20 patients (57.1%) and <−1.9 SDS in 12 patients (34.3%). Postnatal length data were not available for three patients (8.6%).

In nine patients (25.7%) both postnatal weight and length were <−1.9 SDS.

Postnatal head circumference was within normal limits (between −1.9 SDS and +1.9 SDS) in 16 patients (45.7%), <−1.9 SDS in 15 patients (42.8%), and >+1.9 SDS in 1 patient (2.9%). Postnatal head circumference data were not available for three patients (8.6%).

At the last clinical evaluation, the data on weight and length growth were as follows (percentages related to available data):

TABLE 1 Prevalence of neonatal complications, CNS and CHD malformations, and medical issues.

	Number of cases	%
Neonatal complication		
Truncal hypotonia	9	25.7
Neonatal seizures	8	22.9
Breathing difficulties	11	31.4
Inadequate nutrition	8	22.9
CNS malformation		
Holoprosencephaly	2	5.7
Cortical atrophy	2	5.7
Corpum callosum atrophy	1	2.9
Hippocampal malrotation	1	2.9
Cerebellar cyst	1	2.9
Subarachnoid cyst	1	2.9
Sinus pericranii	1	2.9
CHD		
Interatrial septal defect	4	11.4
Interventricular septal defect	2	5.7
Pulmonary valve atresia	1	2.9
Aortic coarctation	1	2.9
Medical issue		
Visual anomalies	9	25.7
Auditory anomalies	2	5.7
Spine abnormalities	10	28.5
Other orthopedic problems	13	37.1
Recurrent infections	10	28.5
Autoimmune diseases	3	8.6
Others	13	37.1

Abbreviations: CHD, congenital heart disease; CNS, central nervous system.

1. weight (data available for 21 patients): normal in 14 patients (66.6%), <−1.9 SDS in 6 patients (28.6%), and >+1.9 SDS in 1 patient (4.8%);
2. length (data available for 18 patients): normal in 12 patients (66.7%) and <−1.9 SDS in 6 patients (33.3%);
3. head circumference (data available for 11 patients): normal in 3 patients (27.3%), <−1.9 SDS in 6 patients (54.5%), and >+1.9 SDS in 2 patients (18.2%).

3.5 | Neurodevelopment and milestones

Of 34 girls aged >8 months, expected to be able to maintain a sitting position (Marcdante, 2019), this milestone was achieved by 28 girls (28 of 34, 82.4%) at an average age of 14.5 months. This finding was statistically significant ($p < 0.05$). The remaining six girls (17.6%) did not achieve a sitting position at an average age of 5 years.

Of 33 girls aged >15 months, expected to be able to start walking (Marcdante, 2019), first steps have been achieved by 19 girls (19 of 33, 57.6%), with a statistically significant delay ($p < 0.05$). The average walking age was 28.5 months. The remaining 14 girls (42.4%) did not manage to walk at an average age of 8.5 years.

Of 30 patients aged >24 months, normally able to pronounce their first words (Marcdante, 2019), 17 patients (17 of 30, 56.7%) acquired this competence at an average age of 26.9 months; this finding was not statistically significant ($p = 0{,}845$). The remaining 13 girls (43.3%) did not pronounce any words. The average age of these nonverbal girls was 10.5 years.

Of 28 girls aged >36 months, normally able to speak in short sentences (Marcdante, 2019), just 8 girls (8 of 28, 28.6%) acquired this competence with delay, although not statistically significant ($p = 0.051$), at an average age of 59.2 months. The remaining 20 girls (71.4%) did not pronounce any sentences. The average age of this group of girls was 10.9 years.

Overall, gross motor skills as well as speech and language development are generally delayed in individuals with *SMC1A* epilepsy syndrome (see Table 2 for details).

Nonverbal forms of communication as well as Augmentative Alternative Communication (AAC) were used by 21 of 35 (60.0%) and 10 of 35 girls (28.6%), respectively.

Any degree of developmental regression of previously acquired skills has been reported in 18 of 35 girls (51.4%). Regressed skills included: head control (1 patient), rolling (1), sitting (6), crawling (2), walking (6), language (words and sentences) (7), social skills (1), chewing (2), swallowing (1), and suctioning (1).

The mean age upon the first detection of developmental regression was 35.3 months (data available for 14 girls).

We did not collect accurate data on functional assessment based on the compilation of functional scales and autism scales so we cannot report this aspect precisely.

3.6 | Behavioral phenotype

Behavioral abnormalities have been described in 13 of 35 girls (37.1%). We found five cases of hyperactivity, seven of autism spectrum disorder (ASD), three of self-harming behavior, and one of hetero-aggressiveness. Some girls showed a co-occurrence of two behavioral issues: self-harming and aggressivity (one), autism and self-harming (two), hyperactivity, and autism (one).

3.7 | Epilepsy

The average age on the onset of seizures was 11.8 months. With reference to epilepsy classification, the following data are available: 17 (48.6%) cases of generalized epilepsy including one case with absence seizures and another with drop attacks, and 6 (17.1%) cases with focal epilepsy.

Seventeen of 35 girls (48.6%) showed at least 1 episode of convulsive status epilepticus, 24 (68.6%) had seizures in wakefulness, and 25 (71.4%) had seizures during sleep.

TABLE 2 Developmental milestones for motor and speech/language in participants.

Milestone	Patients who have acquired the competence, *N* (%)	Average age of skill acquisition (months) − SD	Delay of skill acquisition[a] (months)	*p* value[b]
Sitting position	28 (80)	14.5 − 9.9	+6.4	0.004
Walking	19 (54.2)	28.5 − 16.9	+13.5	0.005
First words	17 (48.6)	26.9 − 25.5	+2.9	0.845
First sentences	8 (22.9)	59.2 − 30.2	+23.2	0.051

Abbreviations: *N*, number; SD, standard deviation.
[a]This delay results from the difference between the average age of skill acquisition in our cohort and the age referred as normal by Marcdante (2019).
[b]Based on one sample *t*-test.

Of 30 patients for whom this information was available, the frequency of seizures was as follows: 14 (40%) experienced seizures daily, 7 (20%) presented seizures weekly, 8 (22.9%) experienced seizures monthly, and 1 (2.9%) had seizures with an annual frequency.

Data on seizure triggers were available for 31 patients. Specific seizures' triggers have been described for 14 patients (40%). Loud noises and infections/concurrent illness were the most frequent triggers of seizures (Table 3).

Data about ongoing treatment with anticonvulsants were available for 33 patients. At the time of data collection, 31 of 33 girls (93.9%) were on a combination treatment with 2 (10 of 31, 32.3%), 3 (10 of 31, 32.3%), 4 (6 of 31, 19.3%) or even 5 (3 of 31, 9.7%) concomitant antiepileptic medications. For the remaining 2 patients (2 of 31, 6.4%) treated with multiple anticonvulsants, the number of medications was not available. Cannabidiol is used by 5 girls (5 of 33, 15.1%).

Overall, the patients enrolled were on 23 different medications, that could be classified into the following antiepileptic categories: antifocal drugs, broad-spectrum drugs, drugs for absence seizures, benzodiazepines, others (rufinamide, stiripentol, and cannabidiol).

A good control of seizures was described in 12 patients (34.2%); epilepsy is uncontrolled in 17 patients (48.6%), and partially controlled in 3 patients (8.6%). Data regarding pharmacological seizure control were not available for three patients (8.6%).

For patients reporting a good control of seizures, information is available for 10 patients. In detail, these patients use the following drugs (in different combinations): stirpentol, clobazam, brivaracetam, sodium valproate, lamotrigine, lacosamide, zosinamide, levetiracetam, oxcarbazepine, topiramate, phenobarbital, and cannabidiol. The average number of antiepileptic drugs taken by these patients was 2.6, while for patients presenting partially controlled seizures the average number of antiepileptic drugs taken was 3. For patients presenting uncontrolled seizures, drug treatment information was available for 15 patients. The average number of antiepileptic drugs taken by these patients was 3.3.

Overall, *SMC1A* variants mostly caused drug-resistant generalized or focal epilepsy in the patients, more than two-thirds of whom were shown to progress to developmental and epileptic encephalopathy.

Seven of 35 girls (20.0%) were on a ketogenic diet. The average duration of a ketogenic diet was 51 months (4.2 years) (information available for six patients). The reported outcome of a ketogenic diet on seizure control was as follows: reduction in seizures <50% for 3 patients, <75% for 1 patient, >50% for 1 patient, and >75% for 1 patient. Twelve girls had attempted a ketogenic diet in the past, with the average duration of treatment being 20.6 months (1.7 years). Reasons for the discontinuation of a ketogenic diet included ineffectiveness of seizure control (nine patients), ineffectiveness/refusal (one), and hypertriglyceridemia (one).

TABLE 3 Specific seizures triggers described in SMC1A epilepsy patients and relative frequencies (in the first column is reported the number of patients who presented that specific trigger, while in the second one the same data is reported as percentage of the total number of analyzed SMC1A epilepsy patients).

Trigger	*N*	%
Loud noises	4	11.4
Sight of rapid movements	1	2.9
Sudden movements	2	5.7
Sleep deprivation	2	5.7
Tiredness	2	5.7
Overstimulation	1	2.9
Infections/current illnesses	4	11.4
Menstruation	3	8.6
Discontinuation of contraceptive pills	1	2.9
Defecation	2	5.7
Constipation	2	5.7
Urination	1	2.9
Pain	1	2.9
Warm environment/hot–cold transition	1	2.9
Sunlight	1	2.9
Crowded places	1	2.9

Abbreviations: *N*, number; WES, whole-exome sequencing.

Thirty-three patients (94.3%) underwent at least one EEG during their lifetime.

3.8 | Gastrointestinal and nutritional data

Abnormalities in food intake have been reported in 22 of 35 patients (62.9%). Information about the type of diet followed by the child is available for 30 patients: 12 (40%) were on a liquid diet (mean age: 9.2 years), 5 (16.7%) were on a blenderized only diet (mean

age: 6.7 years), and 13 (43.3%) were on a mixed diet (mean age: 11.3 years).

The use of nasogastric tube feeding was described for 13 of 35 patients (37.1%), for an average time of 166 days. The mean age of tube placement was 28.1 months. The placement of a gastrostomy was necessary for eight patients (22.9%, with an average age of placement of 4 years). All eight girls currently continue to require enteral nutrition.

The two main gastrointestinal issues found in these patients are gastroesophageal reflux disease (GERD) and constipation. Ten of 35 patients had GERD/esophagitis (28.6%). In three cases, the diagnosis of GERD was clinical, while four girls received an endoscopic diagnosis. The mean age upon the onset of symptoms related to GERD was 27.9 months. From a treatment perspective, 6 of 10 patients (60.0%) were on a pharmacological treatment with a proton pump inhibitor, with reported benefits. Only one patient underwent reflux surgery at the age of 9 years.

Constipation was reported in 26 of 35 patients (74.3%). Among them, 5 only received dietary indications (19.2%), while 21 were started on pharmacological treatment (80.8%). The medications used to treat constipation included polyethylene glycol (15), probiotics (1), senna (plant laxative) (2), bisacodyl (1), and lactulose (1).

3.9 | Additional medical issues

Other medical issues have been described in 24 of 35 patients (68.6%). See Table 1 for details and the prevalence of different medical comorbidities.

3.10 | Dysmorphisms

Facial dysmorphisms were reported in 14 patients (40%).

A centralized reassessment of dysmorphisms was performed by skilled geneticists in 11 patients, for whom one or more photographs were available. In detail, the criteria from the 2018 International Consensus Statement on CdLS (the presence of cardinal features and/or suggestive features) have been used to assess whether patients presented a phenotype consistent with classical CdLS, nonclassical CdLS or at least an indication to perform a molecular test for CdLS.

Of 11 patients reassessed, none presented with a clinical phenotype consistent with either classical or nonclassical CdLS upon the centralized expert-revision. Only in one patient a molecular test for suspected CdLS was indicated.

3.11 | Genetic tests

Conventional karyotyping was performed in 13 of 35 patients (37.1%). They were all normal except for one case (chromosomal anomaly not specified in the questionnaire). Array-CGH has been performed in 12 patients (34.3%), resulting normal in 11 cases and abnormal in 1 case showing a Xp11.22 microdeletion involving *SMC1A* gene. A genome-wide panel for cohesin genes or epilepsy-associated genes has been performed in five patients (14.3%), resulting normal in two cases and abnormal in three cases.

WES has been performed in 31 patients (88.6%) and in all these cases represented the diagnostic test for the condition.

SMC1A gene variants identified through WES or panels for cohesin genes/epilepsy-associated genes are shown in Table 4. It was possible to collect information about the mutation (nucleotide change and/or amino-acid change) for 28 patients, while for the other 7 just the presence of an LoF mutation was reported in the questionnaire without any specification of nucleotide change and/or amino-acid change. According to the data collected relating to the 28 patients mentioned above, an LoF mutation (frameshift, missense or not specified) has been found in 23 cases (82.1%), a missense mutation in 5 cases (17.9%).

4 | DISCUSSION

Heterogeneous clinical information for approximately 44 patients with *SMC1A* epilepsy syndrome is available within the current medical literature (Barañano et al., 2022; Bozarth et al., 2023; Chinen et al., 2019; Goldstein et al., 2015; Hansen et al., 2013; Jansen et al., 2016; Kruszka et al., 2019; Lebrun et al., 2015; Naik & Shah, 2021; Oguni et al., 2019; Symonds et al., 2017; Wenger et al., 2017).

In addition, the largest cohort of affected patients reported to date includes 13 girls (Barañano et al., 2022). Through collaboration with the European representative of the SMC1A Foundation, we collected homogeneous clinical information on 35 patients, thus reporting the largest international cohort of patients affected by this condition ever previously described. Only Bozarth et al. (2023) collected data from previous studies to provide a description of the 41 cases described in the literature.

By analyzing the large amount of data collected, we managed to shed light on several emerging features of the disease.

In terms of fetal development, we reported mostly normal intrauterine growth, with variable detection of prenatal major malformations. In detail, we found a remarkable occurrence of abnormalities, greater than the one reported in physiological pregnancies (14.3% vs. 3–5%). In addition, our data highlighted a high incidence of holoprosencephaly (5.7% compared to 1:8000–1:10,000 estimated incidence in liveborn). To note, this aspect has been previously reported also by Kruszka and colleagues (PMID: 31334757) showing that SMC1A and cohesin complex might be fundamental for median forebrain development.

A detailed collection of birth parameters led us to conclude that birth weight and length are normal in most affected children (82.9% and 60.0%, respectively), while microcephaly was reported in 8.6% of cases. In addition, despite a good neonatal adaptation to extrauterine life with a good Apgar score, a significant proportion (51.4%) of newborns developed early-onset clinical issues due to neurological, respiratory, and nutritional complications, leading to NICU admission in a

TABLE 4 *SMC1A* gene variants identified in patients with SMC1A epilepsy analyzed in our study (details of nucleotide change, amino-acid change, and type of mutation).

Patient	1	2	3	4	5	6	7	8[a]	9
Nucleotide change	c.3103C>T	NS	c.1342_1348del	c.967C>T	c.2368del	NS	c.866del	c.2853_2856del	Deletion of 3428 pb (exons 2–7)
Amino-acid change	p.(Arg1035Ter)	NS	p.(Ser448LysfsTer6)	p.(Gln323Ter)	p.(Arg790GlyfsTer8)	p.(Arg377GlyfsTer2)	p.(Ser289Ter)	p.(Ser951ArgfsTer12)	NS
Transcript/Type	Nonsense/Truncating	LoF	Frameshift/truncating	Nonsense/truncating	Frameshift/truncating	LoF	Nonsense/truncating	Frameshift/truncating	LoF

Patient	10	11	12	13[b]	14	15	16[c]	17[c]	18
Nucleotide change	c.2110C>T	c.3557T>C	c.358del	c.2420G>A	NS	c.72del	c.2477del	c.2477del	NS
Amino-acid change	p.(Gln704Ter)	p.(Val1186Ala)	p.(Glu120AsnfsTer2)	p.(Arg807His)	p.(Ast1109AlafsTer102)	p.(Gln25ArgfsTer25)	p.(Asn826ThrfsTer3)	p.(Asn826ThrfsTer3)	NS
Transcript/ type	Nonsense/truncating	Missense	Frameshift/truncating	Missense	Frameshift/truncating	Frameshift/truncating	Frameshift/truncating	Frameshift/truncating	LoF

Patient	19	20	21	22	23[d]	24[c]	25	26[d]	27
Nucleotide change	c.3165dup	c.353dup	NS	c.3037C>T	c.2394dup	c.511C>T	c.2314G>T	c.1609del	c.2948A>G
Amino-acid change	p.(Lys1056InfsTer13)	p.(Ser118ArgfsTer2)	NS	p.(Gln1013Ter)	p.(Arg799ThrfsTer4)	p.(Arg171Ter)	p.(Val772Leu)	p.Val537PhefsTer42	p.(Tyr983Cys)
Transcript/ type	Frameshift/truncating	Frameshift/truncating	LoF	Nonsense/truncating	Frameshift/truncating	Nonsense/truncating	Missense	Frameshift/truncating	Missense

Patient	28	29	30[d]	31	32	33[d]	34	35
Nucleotide change	Deletion of exon 1	c.95G>A	c.3046_3048delGTGinsG	c.2607_2608del	c.547C>T	c.3549_3552dupGGCC	NS	NS
Amino-acid change	NS	p.(Gly326Glu)	p.(Val016AlafsTer28)	p.(Gln869HisfsTer17)	p.(Gln183Ter)	p.Ile1185GlyfsTer23	NS	NS
Transcript/ type	LoF	Missense	Frameshift/truncating	Frameshift/truncating	Nonsense/truncating	Frameshift/truncating	LoF	LoF

Abbreviations: LoF, loss of function; NS, not specified.
[a]Patients already reported in Goldstein et al. (2015).
[b]Variant already reported in Yuan et al. (2019).
[c]Patients already reported in Symonds et al. (2017).
[d]Patients already reported in Barañano et al. (2022).

remarkable share of patients (34.3%). The occurrence of seizures in 22.9% of the analyzed patients in the neonatal period confirms that early-onset epilepsy is a distinctive feature of this disease, as already described by different authors (Barañano et al., 2022; Bozarth et al., 2023; Hansen et al., 2013; Huisman et al., 2017; Jansen et al., 2016; Kruszka et al., 2019; Lebrun et al., 2015; Symonds et al., 2017; Wenger et al., 2017).

Despite the lack of organ-specific involvement, we retrieved a high prevalence of malformations (40%). While associations with CNS malformations had already been widely described (Barañano et al., 2022; Bozarth et al., 2023; Goldstein et al., 2015; Jansen et al., 2016; Kruszka et al., 2019; Lebrun et al., 2015; Oguni et al., 2019; Symonds et al., 2017), our data show for the first time a remarkable incidence of cardiovascular malformations among affected patients (20%), prompting the need for a systematic echocardiographic evaluation for all the patients diagnosed with *SMC1A*-related epilepsy.

In terms of postnatal growth patterns, 45.7% of the girls described presented low weight, 34.3% showed short length and 42.8% had microcephaly.

We also provided information about the average ages upon pivotal psychomotor milestones attainment. Sitting position and first steps were found to be achieved with a significant delay compared with the general population; language and speech with a delay not statistically significant. A remarkable percentage of patients did not acquire these milestones (sitting position: 17.6%; first steps: 42.8%; first words: 56.7%; short sentences: 71.4%). Most patients (60%) used nonverbal communication, about one-third AAC.

Although precise neurological data gathering was limited by the nature of the parental report, a developmental regression seems to be a quite common feature of this condition, as already described by other authors (Barañano et al., 2022; Bozarth et al., 2023; Goldstein et al., 2015; Huisman et al., 2017; Jansen et al., 2016; Symonds et al., 2017). Accordingly, we reported psychomotor regression in 51.4% of the analyzed patients, consistently with the 60% incidence reported by Barañano et al., 2022. The skills involved in this progressive neurodevelopmental impairment are rather variable. The average age of regression was available for a minority of patients and in these cases was 35.3 months.

The finding of behavioral abnormality was reported in 37.1% of patients. While an association with mild self-harming behavior had already been described by Barañano et al., we also highlighted a relevant incidence of ASD (present in 20%) (Barañano et al., 2022).

Epilepsy was a constant issue among enrolled girls, with an average age of 11.8 months upon the onset of seizures. These findings are consistent with published data, reporting seizures onset in the first 1–2 years of life (Barañano et al., 2022; Bozarth et al., 2023; Symonds et al., 2017).

Forty percent of patients experienced daily seizures; specific triggers of seizures have been identified for 40% of them. These features confirm the literature data on the high recurrence of seizures in these patients (Barañano et al., 2022; Bozarth et al., 2023; Symonds et al., 2017). Noteworthy, family members are able to recognize the specific trigger of a seizure in most cases.

From a therapeutic perspective, more than 90% of patients were on multiple antiepileptic drugs. The treatment was extremely heterogeneous, and patients analyzed in the study use 23 different active substances overall. This confirms that to date no medication has showed a remarkable efficacy in controlling the frequency of seizures in affected girls alone, although even a combination approach led to an overall limited reduction in the frequency of seizures (seizures reported as controlled by therapy in only 34.2% of patients studied).

Finally, this heterogeneity of treatments could also be related to the different management guidelines in different Countries (Barañano et al., 2022; Symonds et al., 2017).

Some patients (20%) experienced a ketogenic diet with variable results. The introduction of a ketogenic diet in babies affected by this condition has already been described (Barañano et al., 2022; Bozarth et al., 2023; Goldstein et al., 2015; Jansen et al., 2016). On the basis of our data and given the nature of the present analysis, noncertain conclusions can be drawn about the therapeutic role of ketogenic diet in these girls and its role needs to be systematically assessed.

No data were available to identify a common EEG pattern for the condition, which is still not described in the literature.

A significant number of patients were reported to present an abnormal food intake (62.9%). Only 13 patients followed a normal diet. A consistent number of patients required enteral nutrition (60%), either by nasogastric tube (37.1%) or gastrostomy (22.9%). These data are consistent with available published literature (Barañano et al., 2022).

As frequently reported among individuals with intellectual disability, a remarkable share of patients with *SMC1A* epilepsy syndrome experienced constipation (74.3%) and GERD (28.6%), requiring pharmacological treatment in most cases. While the association with GERD had already been described (Lebrun et al., 2015), the significant occurrence of constipation had not been reported before.

Additional clinical issues included orthopedic problems, recurrent infections, and visual anomalies. Though the former had already been described by different authors (Hansen et al., 2013; Jansen et al., 2016; Kruszka et al., 2019; Lebrun et al., 2015; Symonds et al., 2017; Wenger et al., 2017), infectious and visual disorders represent a novelty.

No patient in this study was recognized as presenting with a clinical phenotype related to CdLS, in accordance with the defined criteria of International Consensus (Kline et al., 2018), prompting us to conclude that the phenotype of SMC1A epilepsy syndrome is clearly distinct from CdLS (Barañano et al., 2022; Bozarth et al., 2023). Accordingly, WES was the genetic testing that led to the diagnosis of 88.6% of the patients enrolled.

Regarding mutations of the *SMC1A* gene, most of the *SMC1A* variants described in this cohort are LoF mutation (85.7%). However, even among these patients, a missense mutation of *SMC1A* is reported for 5 cases. As already mentioned, these variants can also lead to the development of the disease, although in lower percentage than an LoF mutation (Barañano et al., 2022; Bozarth et al., 2023; Huisman et al., 2017; Kruszka et al., 2019; Oguni et al., 2019). Therefore, our results are consistent with known data from the literature, and corroborate their strength due to the size of the cohort.

It is still unclear how different *SMC1A* variants cause CdLS or *SMC1A* epilepsy syndrome. Bozarth and colleagues hypothesize that the *SMC1A* gene may play a role in early brain function and development. Furthermore, these authors speculate about the fact that *SMC1A* epilepsy syndrome may be associated with both LoF and non-LoF *SMC1A* variants. Accordingly, the non-LoF variants associated with *SMC1A* epilepsy syndrome described in the literature are specifically located in the N/C-terminal ATPase head or the central hinge domain of SMC1A protein, which are predicted to influence cohesin assembly, thus mimicking an LoF effect (Bozarth et al., 2023). In our study, the non-LoF variants described do not fall in the hinge nor in the N/C-terminal head domain of SMC1A protein. We also verified that the amino-acid change did not affect a residual site of a known posttranslational modification. In this sense, we believe that congenital genetic disorders caused by variants in genes coding for components of the epigenetic machinery attract increasing interest as they pose puzzling questions on genotype/phenotype correlation. Indeed, more functional studies are needed for untangling the underlying pathogenetic mechanism of this condition.

In addition, all but seven *SMC1A* mutations described in our patients are different from those previously reported in the literature—see Table 4 for details (Barañano et al., 2022; Goldstein et al., 2015; Symonds et al., 2017; Yuan et al., 2019).

The most relevant limitation of the present study was the fact that it was conducted based on the collection of information through questionnaires filled out by the patients' parents, who were assisted by the referring pediatrician or geneticist only occasionally. This methodological feature implies a nonnegligible margin of imprecision regarding both the accuracy of the data collected and their completeness. Nevertheless, given the rarity of the condition and the varied geographic origin of the affected patients, the collection of information through questionnaires represented the most effective way to dispose a large amount of data in a relatively short time interval and to be able to make an initial assessment of the phenotype of these girls at the time the study was carried out. Since this is an extremely rare condition, this opportunity was already an important step forward in improving current knowledge about the condition and the genotype–phenotype relationship. The method of data collection can be improved in future studies through strategies that ensure a greater reliability (such as could be the completion of the questionnaire exclusively by the referring pediatrician or geneticist).

5 | CONCLUSIONS

We can state that this condition broadens the phenotypic spectrum of diseases related to *SMC1A* gene variants, constituting itself as a different disease from CdLS, without even falling within the specific phenotypic spectrum as defined by the 2018 International Consensus (Kline et al., 2018).

Our report suggests that this condition must be taken into consideration among the possible differential diagnoses in case of a clinical picture of a female patient with global developmental delay, severe epilepsy, and possible postnatal microcephaly.

Owing to the current absence of a univocal phenotypic and epileptological characterization of the disease, we can state that the diagnostic gold standard of this condition is currently represented by WES. The fact that all *SMC1A* variants identified are different from each other suggests that there is no mutational hotspot in the *SMC1A* gene.

Our work proposes to look for possible cardiovascular abnormalities at the time of diagnosis by performing an echocardiographic analysis of these patients, in addition to a brain MRI to identify CNS abnormalities.

Finally, we shed light on the importance of frequently assessing potential nutritional issues and constipation.

From a treatment perspective, our work suggests promptly identifying potential seizure triggers to effectively avoid them, making an attempt to introduce a ketogenic diet, and using a multiple antiepileptic treatment that includes one broad-spectrum drug.

In conclusion, we reiterate the need and the importance of the multidisciplinary care of these patients that includes strategies aimed at improving relational aspects, such as the use of AAC, already tested by some girls in the study.

AUTHOR CONTRIBUTIONS

Elisabetta Gibellato, Sylvia Huisman, and Robert Śmigiel collected data. Elisabetta Gibellato and Paola Cianci wrote the manuscript with support from Milena Mariani, Barbara Parma, Andrea Biondi, Valentina Massa, Cristina Gervasini, Alex Moretti, and Alessandro Cattoni. Angelo Selicorni supervised the whole project. All authors discussed the results and contributed to the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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