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CASE REPORT

Further clinical delineation of microcephaly-capillary malformation syndrome

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Abstract

Microcephaly-Capillary Malformation syndrome (MIC-CAP) is a rare genetic disorder reported in 18 individuals to date. The clinical features typically include microcephaly, multiple cutaneous capillary malformations, seizures, neurologic impairment, and global developmental delay. Currently, there is little published information about the natural history and long-term outcomes for individuals with MIC-CAP. In this report, we provide follow up on two previously published patients and describe four new patients. The included patients highlight increased variability in the clinical spectrum and provide novel information regarding medical complications and recurrent variants.

KEYWORDS
clinical spectrum, MIC-CAP, microcephaly-capillary malformation syndrome, recurrent variants, *STAMBP*

1 | INTRODUCTION

Microcephaly-Capillary Malformation syndrome (MIC-CAP) is a rare autosomal recessive genetic disorder resulting from biallelic variants in *STAMBP*. It was first described by Carter et al. (2011) and the genetic cause was subsequently identified by McDonell et al. (2013). *STAMBP* is a deubiquitinating enzyme that functions to regulate endosomal sorting complexes required for transport that mediate sorting of ubiquitinated proteins. Lack of *STAMBP* function is associated with an accumulation of ubiquitinated proteins in vitro, which leads to enhanced apoptosis that is proposed to contribute to the development of microcephaly in MIC-CAP (McDonell et al., 2013). Additionally, reduced activation of both the RAS-MAPK and PI3K-AKT–mTOR pathway has been demonstrated, which together may contribute to the capillary malformations seen in MIC-CAP (McDonell et al., 2013).

The core clinical features of MIC-CAP include congenital microcephaly (head circumference >2 *SD* below the mean at birth), cutaneous capillary malformations, infantile onset epilepsy, global developmental delay, and additional neurologic impairment. Other frequently reported features include hypoplastic distal phalanges and nails, abnormal hair growth patterns (with temporal sparseness), movement disorders, and facial dysmorphisms (including hypertelorism, epicanthal folds, sloping forehead, and micrognathia; Carter et al., 2021). Imaging findings include a simplified gyral pattern, increased extra-axial spaces, variable degrees of reduced cortical myelination, hippocampal hypoplasia, thinning of the corpus callosum, and optic nerve/chiasm hypoplasia (Carter et al., 2021). Most reported children have profound developmental delays and spastic quadriparesis; however, there was one previously reported patient from Isidor et al. (2011) who learned to walk

independently and had some speech, indicating variability in the severity of the condition.

MIC-CAP has been reported in 18 individuals from 16 families to date (Carter et al., 2011; Demikova et al., 2018; Faqeih et al., 2015; Hori et al., 2018; Isidor et al., 2011; McDonell et al., 2013; Mirzaa et al., 2011; Naseer et al., 2016; Pavlović et al., 2014; Schugareva & Shumeeva, 2019; Wu et al., 2019). There is no literature describing the natural history or long-term outcomes of these patients. Here, we provide follow up on select previously published patients and report on several patients that have not been previously published, including one adult and another individual with the ability to walk independently, highlighting the variable clinical spectrum.

2 | METHODS

This study received ethics approval through the Children's Hospital of Eastern Ontario Research Ethics Board. Informed consent was obtained from participants at the time of recruitment, including consent for re-contact by the study facilitators. Consent for release of medical records and inclusion of patient photographs in publication was requested after initial participation.

Legal guardians of individuals with MIC-CAP were recruited to the study through social media and the rare disease medical community. A private Facebook group was identified that exists to support families of children with MIC-CAP, and a recruitment poster for participation in research was shared through this platform with permission from the creator. This directed families to a detailed survey through a secure online institutional database (RedCap). Other participants were identified through genetics professionals internationally, who then provided access to this survey to their patients.

Follow up information was subsequently received through email and phone conversations with caregivers. Medical records were requested through the patients' physicians and treating institutions and genetic testing confirming biallelic *STAMBP* variants was received for each patient.

3 | CASE DESCRIPTIONS

A summary of the clinical details is found in Table 1.

3.1 | Patient 1

Patient 1 was a male of European descent who was previously described by Carter et al. (2011) (Patient 1) and McDonell et al. (2013) (Patient 3.1). The pregnancy was uncomplicated, and mom was a gravida 1 who reported the use of cigarettes during the pregnancy, but no other teratogenic exposures. He was born at 36 weeks' gestation, weighing 2523 g (10th percentile on the Fenton curve), with a length of 45.7 cm (10th–50th percentile) and a head circumference of 32 cm (−2.3 *SD* on WHO Infant Head Circumference for Age chart). At birth, dysmorphic features and multiple capillary malformations were noted. Neuroimaging at 2 years old showed severe diffuse bilateral and symmetric supratentorial atrophy, thin corpus callosum, severe delay in myelination, thin optic nerves and chiasma, and thin pituitary gland. At 12 months of age, his head circumference was 40 cm (−5 *SD* on WHO Infant Head Circumference for Age chart).

Generalized seizures began at 7 weeks of life and were initially refractory to medication, but reasonable control was subsequently achieved on a combination of Phenobarbital and Clonazepam, though he continued to have up to 15 tonic brief tonic seizures at the time of his death. A ketogenic diet was trialed, which did not affect seizure frequency.

He had ~27 red, blanchable, oval macules scattered over the scalp, trunk, arms, back, buttocks, scrotum, and legs, in keeping with capillary malformations. These were reported to grow in proportion with his body but did not become substantially larger with age. He had puffy dorsal surfaces of the feet, with hypoplastic third and fourth digits and distally set fifth digits. He was noted to have brachydactyly, with hypoplastic nails on the second, third, and fourth digits, and fifth digit clinodactyly (Figure 2a). He had sparseness to his hair growth in the temporal regions. Dysmorphic features included a round face, hypertelorism, long palpebral fissures, epicanthal folds, low set, posteriorly rotated ears, downturned corners of the mouth, a high arched palate, small testes, a hypoplastic scrotum, and a smooth philtrum (Figure 1a,b).

His development was significantly delayed. He did not develop head control or purposeful movement, and never learned to roll over or sit independently. He had central hypotonia with peripheral spasticity and facial diplegia. He initially was fed orally and was able to suck from a bottle and take purees from a spoon but required nasogastric feeds during his first year of life and had a gastrostomy tube placed for feeding at age 13 months.

Medical issues included increased secretions and frequent infections, often requiring antibiotics and hospital admission, and he did not attend school due to parental concerns of infection risk. He had vision loss due to optic nerve hypoplasia and did not appear to see. A small secundum atrial septal defect was diagnosed on echocardiogram during infancy, which did not require intervention. He had frequent constipation requiring large doses of laxatives. Scoliosis was present later in life.

Due to the severity of his frequent infections and recurrent hospital admissions, he was followed by a palliative care service at the local children's hospital. At age 8, he developed an upper respiratory tract infection with significant hypoxia at home. Comfort measures were initiated, and he was admitted to hospice, where he died of respiratory failure.

3.2 | Patient 2

Patient 2 was a female of European descent. She was born at 38 weeks' gestation after an uncomplicated pregnancy. At birth, she weighed 2977 g (29th percentile) and head size was reportedly

TABLE 1 Summary of patients with MIC-CAP reported herein

Patient	1	2	3	4	5	6
Demographics						
Sex	M	F	F	F	M	F
Age	Deceased age 8	Deceased age 9	Living age 12	Living age 18	Living age 10	Living age 2
Gestational Age (weeks)	36	38	39	37 + 2	Unknown	Unknown
Ethnicity	European	European	European	European	Arabic	Arabic
Genetic testing						
Diagnostic method	Research Exome	Exome	DDD Research study	Targeted sequencing	Exome	Exome
STAMBP variants[a]	p.Phe100Tyr (c.299T>A) and p.Arg424* (c.1270C>T)	p.His77Arg (c.230A>G) homozygous	p.Arg38Cys (c.112C>T) and p.His77Arg (c.230A>G)	p.Arg38Cys (c.112C>T) and c.203+5G>A	c.1119-6T>G homozygous	c.1119-6T>G homozygous
Clinical features						
Microcephaly	+	+	+	+	+	+
Small for gestational age	+	−	−	−	Unknown	Unknown
Capillary malformations	+	+	−	+	+	+
Infantile onset epilepsy	+	+	+	+	+	+
Digital anomalies	+	−	−	+	−	−
Abnormal hair pattern	+	+	−	+	−	−
GDD	+	+	+	+	+	+
Optic nerve hypoplasia	+	+	−	+	−	+
Abnormal brain imaging[b]	+	Unknown	−	+	Unknown	Unknown
Hearing impairment	−	−	−	−	+	+
Abnormal sleep patterns	+	+	+	+	+	+
Gastrostomy tube feeding	+	+	−	+	−	−
Recurrent constipation	+	+	+	+	+	+
Frequent infections	+	+	−	−	−	−
Family history						
Consanguinity	−	−	−	−	+	−
Family history of MIC-CAP	−	−	−	−	+	−
Published	+[c,d]	−	−	+[d]	−	−

Abbreviations: GDD, global developmental delay; F, female; M, male.
[a]Relative to NM_006463.4 for patients 1–4 and NM_201647.3 for patients 5 and 6.
[b]See clinical descriptions for details.
[c]Carter et al., 2011.
[d]McDonell et al., 2013.

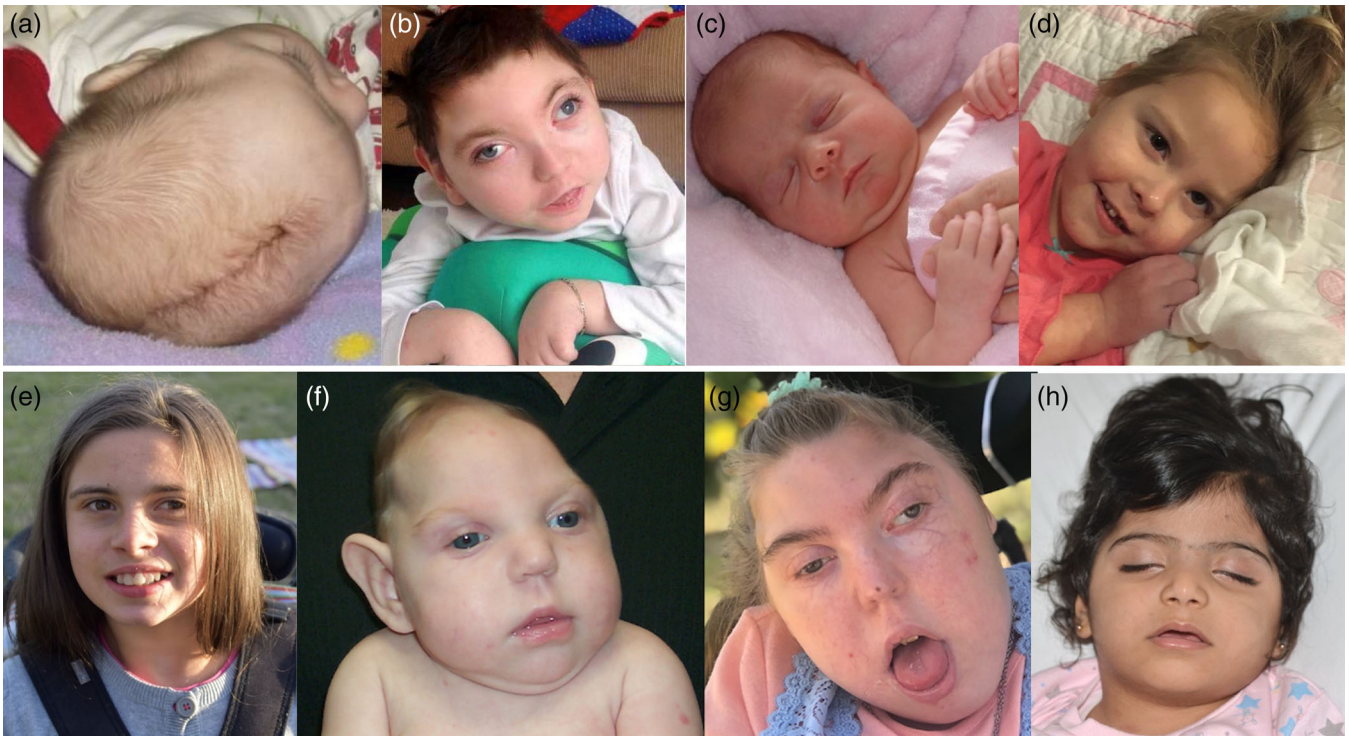

FIGURE 1 Facial appearance of patients with MIC-CAP syndrome. (a) Patient 1 as an infant, showing hair growth pattern with lateral hair whorl and longer hair growth over the sagittal suture. (b) Patient 1 at 8 years of age, with hypertelorism, upslanted palpebral fissures, thin upper lip vermillion, and short chin. (c) Patient 2 as an infant and (d) at 8 years of age. (e) Patient 3 at 12 years of age. (f) Patient 4 as an infant and (g) at 18 years of age, showing severe microcephaly with overriding sutures, hypertelorism, upslanted palpebral fissures, short nose with broad tip and hypoplastic alae nasae, and short chin. (h) Patient 6 at 2 years of age, showing synophrys, mild hypertelorism and short chin

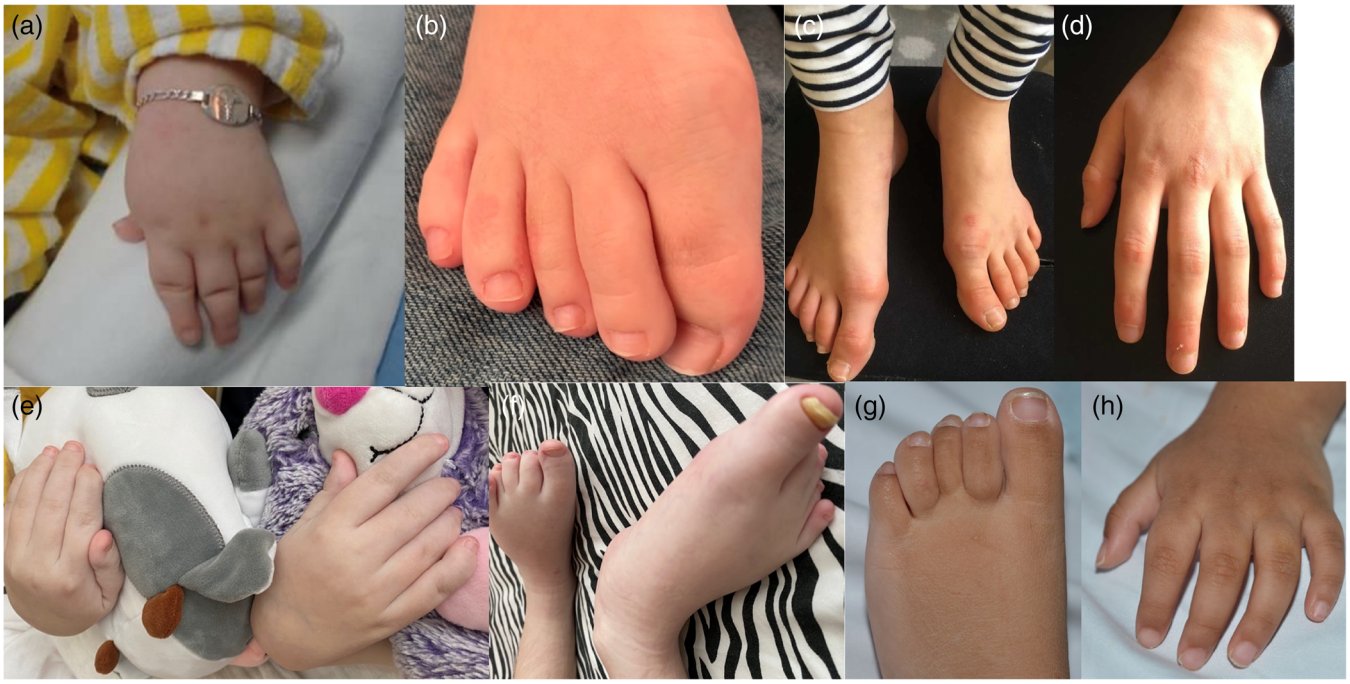

FIGURE 2 Extremities of patients with MIC-CAP syndrome. Hypoplastic nails are not universally present. (a) Patient 1 showing short, tapered fingers with hypoplastic nails. (b) Toes of Patient 2. (c,d) Feet and hand of Patient 3. (e,f) Hands and feet of Patient 4. (g,h) Toes and hand of Patient 6

normal. Microcephaly was first noted at age 5 months. Capillary malformations numbered ~20 at birth and were reported to increase in number and grow in size with age.

Developmental delay was noted in the first 3 months of life. It was reported that she could intermittently roll over, but this skill was not consistent. At the time of her death, she did not have purposeful movement and had never developed head control. She was fed fully by gastrostomy tube.

Seizures first occurred at 7 months and included infantile spasms as well as generalized tonic–clonic and partial seizures. Her seizures were reasonably controlled with medication, and her reported seizure frequency during optimum control was approximately once per week. She had been trialed on multiple antiepileptics and at the time of her death was stable on topiramate and perampanel. A ketogenic diet did provide some improved seizure control, but was discontinued due to issues with obtaining sufficient calories. Around age 7, she also developed severe episodic dystonia with autonomic instability, which was difficult to control. Around the same time, she was noted to have precocious puberty, with breast bud and body odor development. She was started on leuprolide acetate, which seemed to improve the dystonia significantly, and she later had an oophorectomy as long-term therapy with leuprolide acetate was not desirable due to pre-existing osteopenia.

Medical issues included significant problems with constipation, vomiting, and delayed gastric emptying. During the last few years of her life, she had severe gastrointestinal dysmotility and was hospitalized multiple times for recurrent ileus. As a result of these hospitalizations and placement of a central line for parenteral nutrition, she had multiple episodes of sepsis requiring intensive care. She died in hospice at the age of 9 years and 4 months.

3.3 | Patient 3

Patient 3 is a 12-year-old female of European descent. She was born at 39 weeks after an uncomplicated pregnancy, with a birth weight of 3040 g (33rd percentile), length of 48 cm (27th percentile), and head circumference of 32 cm (−1.6 *SD* on WHO Infant Head Circumference for Age chart). Her head circumference at age 9 years was 51.3 cm (second to ninth percentile). She does not have any capillary malformations. Neuroimaging at 22 months old was normal.

Her seizures began at ~10 months and have included both generalized tonic–clonic and partial seizures. Her seizures are generally well controlled on lamotrigine with or without clobazam. She is reported to sometimes have several partial seizures in a month but can go up to several months without having a generalized seizure. Seizures appear to be triggered by illness. Hand flapping movements and abnormal movements of the legs have also been noted, which appear to be involuntary.

Early developmental milestones were delayed; however, she learned to walk independently by 6 years old, and currently uses a wheelchair for ease of mobility. She did not develop speech but uses a wide variety of sounds and vocalizations to communicate. She had regression in specific motor and social skills, including previously being able to climb onto furniture, and waving "goodbye." She has sensory processing difficulties and demonstrates self-stimulatory behavior, including hand flapping. Some behavioral issues are described, including pinching and biting. She is fed fully by mouth but requires full care for feeding and dressing. She is not toilet trained. She attends school in a specialized program.

Medical issues include low visual acuity secondary to optic nerve hypoplasia, as well as constipation and issues with falling and staying asleep. She does not have recurrent infections. She began puberty at age 9, with breast and axillary hair development by age 10 and menarche by age 11. At that time, she developed new episodes of eyelid fluttering and eye deviation thought to be seizures; however, these episodes have not been captured on EEG.

She is nondysmorphic (Figure 1e), and she does not have nail hypoplasia or other digital malformations (Figure 2c,d). She has no visible capillary malformations on her skin.

3.4 | Patient 4

Patient 4 is an 18-year-old female of European descent previously reported by McDonell et al. (2013) (Patient 7.1). She was born at 36 weeks after a pregnancy that was complicated by threatened preterm labor earlier in the pregnancy. Ultrasound at 17 weeks reportedly revealed a head size on the lower end of normal. At birth, she weighed 2200 g (10th–50th percentile on the Fenton curve), with a head circumference of 28 cm (−5 *SD* on WHO Infant Head Circumference for Age chart). In the perinatal period, she had respiratory distress and was admitted to the NICU for ~3 weeks. During this time, she had frequent seizures, and was placed on a midazolam infusion for seizure control. At birth, she was noted to have microcephaly and multiple capillary malformations over her back, extremities, and buttocks. The capillary malformations have not changed in size over time. In childhood, she was noted to have hypertelorism, a short nose with a broad nasal bridge, micrognathia, tapered fingers, short fourth toes, small feet with hypoplastic nails (Figure 2f) and temporal sparseness to her hair growth (Figure 1f,g). Her head circumference at 6 months of age was 34.5 cm (−6 *SD* on WHO Infant Head Circumference for Age chart). Neuroimaging at 6 months and 2 years of age showed dilated ventricles and decreased number of gyri with flattened appearance, consistent with lissencephaly.

On most recent report, she continues to have ~5 seizures per day. Multiple daily antiepileptics are used, including topiramate, primidone, lacosamide, oxcarbazepine, and clonazepam. She started puberty at approximately age 8, with menarche at age 10 years 7 months. She was noted to have an increase in her seizure frequency at the onset of menstruation and was prescribed daily acetazolamide for this, which showed some effect. She recently has been started on progestin only birth control, which has not yet caused any significant change in seizure frequency.

She has severe spastic quadriplegia and currently has no head control or purposeful movement. She will cry but has no other sounds

for communication. She was reported to make some noises to communicate and smile during infancy but has lost this skill with age. She had a gastrostomy-tube placed for feeding at 18 months due to poor swallowing and recurrent aspiration pneumonia.

Medical issues include mild hypothyroidism, cortisol deficiency, and sleep issues with some day-night reversal requiring medication. She has vision loss due to optic nerve hypoplasia. She has constipation, which is treated intermittently on an outpatient basis with laxatives. At age 15 years, she developed hypokalemia requiring ongoing potassium supplementation, but it is not clear if this was due to the underlying syndrome or the concurrent use of multiple antiepileptics and a carbonic anhydrase inhibitor. She also has severe kyphosis of the spine and mild joint contractures of the hips and knees.

3.5 | Patient 5

Patient 5 is a 10-year-old male of Arabic descent born to consanguineous parents (first cousins). He was delivered vaginally and weighed 3025 kg at birth. Multiple capillary malformations were noted at birth, distributed across the neck, thighs, and abdomen. Microcephaly was noted at 2 months of age (measurement not available). Seizures also began at age 2 months, including both generalized tonic–clonic and focal with impaired awareness. Neuroimaging showed diffuse brain atrophy involving the cerebrum.

Initial development was delayed from infancy, but he was reported to walk independently for a brief period. He lost this ability at an unknown age, and now is only able to sit independently. He does not have any speech or sounds to communicate and was reported to be diagnosed with autism spectrum disorder (ASD). He eats fully by mouth, but is dependent for all care, including feeding, dressing, and toileting. Medical issues include clinical evidence of hearing loss, but vision is normal. He has frequent constipation and infection frequency is typical. Head circumference is 48 cm (about −4.5 *SD*s below mean). A few small capillary malformations are present on his trunk and legs.

His younger brother also has MIC-CAP syndrome (currently age 7 years), but no information is available about this child.

3.6 | Patient 6

Patient 6 is a 2-year-old female of Arabic descent. There is no family history of MIC-CAP and she has 9 unaffected older siblings. She was delivered by cesarean section and weighed 2.5 kg at birth. Seizures began at 5 months old, with semiology in keeping with Lennox–Gastaut syndrome. At 2 years of age, head circumference is 44.7 cm (−2.5 *SD* on WHO Infant Head Circumference for Age chart). Neuroimaging showed "mild progressive brain atrophy."

Development was delayed from birth, and she developed the ability to lift her head independently but has no other purposeful movement. She does not have speech or sounds to communicate. No developmental regression has been noted. She is fully fed by mouth and is dependent for all care.

She is reported to have both hearing and visual impairment and frequent constipation. A few small capillary malformations are present on her trunk. Hands and feet appear normal (Figure 2g,h).

Patients 5 and 6, though not known to be related to each other, are both homozygous for the same variant [STAMBP (NM_201647.3): c.1119-6 T>G]. This variant was determined to be likely pathogenic based on the ACMG variant classification criteria PS1 and PM2 (Richards et al., 2015).

4 | DISCUSSION

MIC-CAP syndrome is a rare disorder with only 18 affected individuals described to date. Here, we describe four new patients and provide an update on two previously published cases, including an 18-year-old female who is currently the oldest known individual with MIC-CAP.

Like most rare genetic conditions, MIC-CAP syndrome can be variable with respect to the presence and severity of the clinical features. All reported affected individuals to date have some degree of microcephaly, but the degree and onset (congenital vs. acquired) vary significantly. Multiple cutaneous capillary malformations have also been present in all patients reported previously, however we report the first individual (Patient 3) without this cardinal manifestation. Therefore, we expect that additional patients may be ascertained in future by exome sequencing with absence of cardinal features and/or a larger range of phenotypic variability. Seizures have been present in all reported individuals to date and are often intractable, especially in infancy, though many of the individuals that we report tend to have decrease in seizure frequency with age. There is no specific antiepileptic that has been universally effective. The hypoplastic digits and nails were commonly reported in previous cases but are present in only 2 of the 6 patients we describe in this report.

Initial descriptions of MIC-CAP suggested that developmental outcomes are universally poor, with lack of speech and purposeful movement in the majority of patients. However, one patient previously described (Isidor et al., 2011) and two new cases described herein (Patients 3 and 5) appear less severely affected. The patient from Isidor et al., 2011 was able to walk independently at 22 months and developed some speech. Patient 3 was able to walk at age 6, and Patient 5 was also reportedly able to walk although subsequently lost this skill. For those reported patients with more advanced motor skills, autistic-like behaviors appear to be common. Patient 3 is reported to have "stimming" behaviors with hand flapping, and Patient 5 is reported to have a diagnosis of ASD. Similar features with stereotyped hand flapping behaviors were described for both patients reported by Pavlović et al. (2014).

Sensory deficits have been documented in previous cases. We report two more patients with hearing impairment (Patients 5 and 6), which was previously reported by Carter et al., 2011 and Pavlović et al., 2014. Nearly, all reported patients have had total or partial

visual loss due to optic nerve hypoplasia; however, this was not present in Patient 3 (who also had a less severe presentation than other reported patients).

Endocrine anomalies may be part of the clinical spectrum of MIC-CAP. Childhood-onset hypothyroidism was previously reported in two patients by Pavlović et al. (2014) and Faqeih et al. (2015) and was also reported in Patient 4 herein. Precocious puberty has not been previously described but was identified in three female patients in our cohort (Patients 2, 3, and 4); all are reported to have started puberty between the ages of 7 and 9. This coincided with some degree of worsening of seizures or dystonic movements at the onset of puberty. Patient 4 had reportedly good effect from daily acetazolamide treatment, which has been documented to be efficacious for catamenial epilepsy (Lim et al., 2001; Navis & Harden, 2016). Interestingly, one patient had significant improvement in dystonia upon hormone suppression. While the relationship between hormonal changes of puberty and the dystonic crises in this patient is not clear, a trial of hormone suppression in females with refractory dystonia or seizures may be considered.

No definitive genotype–phenotype correlations have been established. However, several recurrent variants have now been identified, including p.His77Arg (c.230A>G) in Patients 2 and 3; p.Arg38Cys (c.112C>T) in Patients 3 and 4, as well as in a patient reported in Mirzaa et al. (2011) and an additional Patient (8.1) from McDonell et al. (2013). Among patients with the same variant(s), developmental progress is variable. This is highlighted by the more advanced gross motor skills of Patient 5, who has the same genotype as Patient 6, as well as other previously reported c.1119-6T>G homozygotes (Faqeih et al., 2015; Pavlović et al., 2014), all of whom had minimal developmental progress. The variant c.1119-6T>G is present in Patients 5 and 6, as well as in two previously reported families (Faqeih et al., 2015; Pavlović et al., 2014; Wu et al., 2019). This variant is not present in gnomAD (Karczewski et al., 2020) and has been reported in MIC-CAP patients from diverse ethnic backgrounds, suggesting it may be a variant hotspot rather than a founder variant.

Death in childhood is common for those most severely neurologically affected with MIC-CAP. Of the patients who died, the deaths appear to be related to secondary medical complications, including valproate-related pancreatitis (Carter et al., 2011), frequent upper respiratory tract infections (Patient 1), and central line sepsis secondary to parenteral nutrition requirements from GI dysmotility (Patient 3). The oldest reported living individual is 18 (Patient 4), and she is generally medically stable despite being severely neurologically impaired.

5 | CONCLUSION

Microcephaly-capillary malformation syndrome remains a very rare but recognizable disorder, reported in a small number of individuals to date. Clinical features include microcephaly, capillary malformations, intractable epilepsy, and neurodevelopmental impairment, although not all features are found in all patients. Management is primarily aimed at relief of symptoms, supportive care and early identification and treatment of secondary complications. Ongoing long-term follow up will be required to better refine the progression of disease, medical complexity, and typical lifespan for these patients.

AUTHOR CONTRIBUTIONS

Julianne K. Postma contacted and followed up with the patients' families for data collection, reviewed medical records, liaised with the contributing authors, and wrote the article. Jessica L. Zambonin provided initial contact with the patients' families, recruited them to the study, designed the survey tool, and edited the article. Fowzan Alkuraya provided medical records, clinical information, expert opinion, and commented on the manuscript. Suad Alyamani provided medical records, clinical information, expert opinion, and commented on the manuscript. John Graham provided medical records, clinical information, expert opinion, and commented on the manuscript. Ebtissal Khouj provided medical records, clinical information, expert opinion and commented on the manuscript. Stephen Kundell provided medical records, clinical information, expert opinion, and commented on the manuscript. Jeff Waugh provided medical records, clinical information, expert opinion, and commented on the manuscript. Melissa T. Carter oversaw the study and its design, liaised with patients' families and the contributing authors, provided expert opinion on clinical features, and edited the article.

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Data sharing is not applicable to this case report, as no new data were created aside from the variants listed in the report.

CONFLICT OF INTEREST

None of the contributing authors have any conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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