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Chromosome 8p Syndromes Clinical Presentation and Management Guidelines

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ABSTRACT

Rearrangements of the p-arm of Chromosome 8 can result in a spectrum of neurodevelopmental challenges, along with increased risk of epilepsy, structural brain and cardiac malformations, persisting developmental delays, and other health challenges. The majority of patients reported on in this sample are characterized by an inverted-duplication deletion rearrangement, but deletions, duplications, and mosaic ring changes in 8p result in similar phenotype. In this report, we add to the phenotypic and functional description of these patients according to their specific chromosomal rearrangement, share neuro-psychometric values, and propose surveillance care guidelines for caregivers and medical providers of patients with Chromosome 8p Syndromes. Observations from clinical experience with 24 patients seen at our 8p-dedicated Multi-Disciplinary Neurogenetics program are shared.

1 | Introduction

The p-arm of chromosome 8 is home to repeating Olfactory Receptor gene clusters known as Low Copy Repeat regions [1]. These repeating regions are associated with an increased chance of chromosome breakage during the process of cellular replication, making the 8p region a hot spot for inversion, duplication, deletion, and ring formation errors. These cytogenetic errors are sporadic (de novo) in the ovum, and thus do not recur within a family. Previous work has attempted to match the specific break points and size of the rearrangements to clinical phenotype [2–11]. By far the most common rearrangement is the Inverted-duplication with deletion (Invdupdel). People with 8p Invdupdel have an extra portion (duplication) of one segment of 8p and are missing another portion (deletion) of 8p [5, 6].

Many of the clinical features of 8p rearrangements have been previously reported from larger descriptive series [2, 3]. Universally reported are effects on cognitive and motor development as well as a range of other features. While these papers present very well characterized genotype–phenotype relationships, they do not propose clinical care guidance. Further, while some neurodevelopmental information is presented, values included are only from parent-report forms; thus, performance-based information is lacking. Spectrum of presentation is an important theme in genetic medicine, a theme that is very relevant in this condition. Individual presentations, in terms of severity of symptoms, vary considerably between patients, even with the same chromosomal rearrangement.

Due to the multidisciplinary care needs of the 8p population, individuals were included in a multidisciplinary neurogenetics clinic at our hospital. While caring for this population and listening to their family advocates, we recognized the lack of clinical guidelines. Our objectives with this project include characterizing the patients at our multidisciplinary clinic including

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clinical and functional characteristics and performance-based measures as well as offering recommendations for care based on our data and prior studies.

2 | Materials and Methods

A multi-disciplinary clinic (MDC) team at our center, including a geneticist, genetic counselor, pediatric neurologist, developmental pediatrician, pediatric physiatrist, therapists of physical, occupational, and speech medicine, neuropsychologist, social worker and a general pediatrician, evaluated patients in MDC visits. Patients were prospectively consented and enrolled into a parent natural history study run by the MDC with approval of the Colorado Multiple Institutes Review Board which this retrospective study falls under.

The data for this study was obtained retrospectively from charts of patients enrolled in our natural history study. Data was collected starting at the time of first visit in our clinic (earliest July 6th 2021) until our "data freeze" date (August 1st 2023). Inclusion criteria were all patients with 8p Syndromes seen during the data collection period that consented to the natural history study. There were no exclusion criteria. As we did not exclude patients because of or screen for prior research participation, patients presented in our study may have been presented previously in other manuscripts on Chromosome 8p Syndromes.

National Center for Biotechnology Information (NCBI) Genome Data Viewer was utilized to characterize genomic imbalances [12]. We categorized patients into groups: 8p Invdupdel, 8p Duplication, 8p Deletion, 8p/8q Unbalanced Translocation, and 8p Mosaic Ring.

Neuropsychological evaluations done as part of typical clinical care were retrospectively evaluated; they included both performance-based testing and parent-reported measures. Performance-based test selection was matched for developmental age and included the Mullen Scale of Early Learning or the Bayley Scale of Infant Development Fourth Edition, but also other age-appropriate measures including the Wechsler scales, the Developmental Assessment Scales Second Edition (DAS-2), Beery VMI, pegboard, Expressive Vocabulary Test Third Edition (EVT-3), and Peabody Picture Vocabulary Test Fifth Edition (PPVT-5). Parent report was collected from the Vineland Adaptive Behavior Scales (Vineland-3), Behavioral Assessment of Children Third Edition (BASC-3), and Social Responsiveness Scale Second Edition (SRS-2).

Statistical methods include descriptive statistics. Care guidelines proposed here are based on reviewing prior publications and analysis of our MDC population. Testing the feasibility and effectiveness of the care guidelines was not part of the scope of this study.

3 | Results

Our sample included 24 patients, median age 8 years (interquartile range 6–14, total range 1–46 years). Clinical characteristics of these patients are described further in Table 1.

3.1 | Genetic Testing

All patients had genetic test results reviewed prior to clinical evaluation. Testing methods included karyotypes of variable banding length, oligoarray, single nucleotide polymorphism array, and next generation sequencing with Copy Number Variation detection capability. Based on our genetic analysis using NCBI Genome Data Viewer, we had the following patients in each 8p category: 14 patients with 8p Invdupdel, 2 patients with 8p Duplication, 6 patients with 8p Deletion, 1 patient with 8p/8q Unbalanced Translocation, and 1 patient with 8p Mosaic Ring.

Average size of the interstitial deletion was 8.6 Mb for the deletion only group ($n = 6$). Invdupdel patients had a duplication average of 26.1 megabyte (Mb) and an average deletion of 6.9 Mb ($n = 11$; three patients did not have array characterization). Of the two patients with duplications only, only one had microarray characterization with duplication of 3.1 Mb. The single patient with a mosaic ring had a 28.3 Mb gain in 8p11.21-q13.3 and a 7.3 mosaic gain in 8q13.3-q21.12. The patient with the unbalanced translocation had a 6.1 Mb loss in 8p23.3-p23.3, 517 kb gain in 8p23.2-p23.1, 8.0 Mb gain in 8q24.23-q24.3. Incidental region of homozygosity of 41 Mb on 6p25.3-p21.1 is noted for the patient with an unbalanced translocation.

Several patients in this cohort had under characterized cytogenetic imbalances primarily due to technological limitations at the time of test performance. Updated diagnostic genetic testing, when indicated, yielded reclassification to a different chromosomal category. One patient was reclassified from 8p Duplication to 8p Invdupdel. A different patient, also with outdated genetic testing results, was found to have a separate craniofacial genetic syndrome in addition to a maternally inherited 8p change.

In our patient cohort, three (13%) of our patients were found to have a dual genetic diagnosis, with a significant finding outside of their 8p change. One individual with terminal deletion at 8p23.3-23.1 also has a 4 Mb duplication at 4p16.3, which has a wide clinical spectrum characterized by developmental delay, seizures, and distinct dysmorphic features. A second patient with 8p23.1 deletion was found on whole exome sequencing to have a pathogenic variant in the ASXL1 gene, associated with intellectual disability, developmental delay, seizures, structural brain abnormalities, and dysmorphic facial features. A third individual with 8p Invdupdel was also found to have a maternally inherited 17q12 duplication, though that is of unclear clinical significance.

3.2 | Medical Co-Morbidities

8p Syndrome patients frequently had seizures, abnormal findings on brain magnetic resonance image (MRI) and echocardiogram, as well as other co-morbidities. Seizures were reported by 25% of patients. Of the children with seizures, 3 had an active diagnosis of seizures and 3 had seizures in the past that had resolved for at least several years (not on antiepileptics). Of the other 75%, 4 children reported concern for seizures or

TABLE 1 | Activities of daily living, medical and developmental features by 8p genetic type.

Clinical findings, *n* (%)	All groups	8p Invdupdel	8p Dup	8p Del	8p/8q Unbalanced translocation	8p mosaic ring
n	24	14	2	6	1	1
Age in Years, median (IQR, if more than 2 patients)	8 (6–14)	8 (6–12)	2	12 (6–15.5)	18	3
Seizures (%)	6 (25%)	1 (7%)	0 (0%)	3 (50%)	1 (100%)	1 (100%)
Brain MRI findings (of 20 patients who had brain MRI results to review)	16 (80%)	13 (92%)	2 (100%)	2 (67%)	1 (100%)	0 (0%)
Sleep Disturbance	13 (54%)	6 (43%)	2 (100%)	3 (50%)	1 (100%)	1 (100%)
Cardiac diagnoses (of 20 patients who had ECHO results to review)	11 (55%)	7 (58%)	1 (50%)	3 (60%)	1 (100%)	0 (0%)
Toileting (of 19 patients > 5years old)	12 (63%)	5 (42%)	N/A	6 (100%)	1 (100%)	n/a
Had a gastrostomy for nutrition support (current or past)	3 (12%)	1 (7%)	1 (50%)	1 (16%), removed	0 (0%)	0 (0%)
Walking independently (of 21 patients > 2years old)	17 (81%)	10 (83%)	0 (0%)	5 (83%)	1 (100%)	1 (100%)
Adaptive equipment (of 22 patients > 1year old)	8 (36%)	6 (46%)	1 (100%)	1 (17%)	0 (0%)	0 (0%)
Primary verbal communicators	7 (29%)	0 (0%)	1 (50%)	6 (100%)	0 (0%)	0 (0%)
AAC primary communicators	18 (75%)	14 (100%)	1 (50%)	1 (17%)	1 (100%)	1 (100%)
Any mental or behavioral health diagnosis	12 (50%)	3 (21%)	2 (100%)	5 (83%)	1 (100%)	1 (100%)
Intellectual Disability if > age 5	19	12 (100%, only saw 12 for testing)	1 (50%)	5 (83%)	1 (100%)	0 (below age for diagnosis)

abnormalities on electroencephalogram (EEG) but no clinical diagnosis had been made and one patient had a history of only febrile seizures in toddler years.

Abnormal findings on echocardiogram (ECHO) were present in over half (55%) of our cohort. Cardiac findings largely did not require surgical interventions; 4 children that did require surgical interventions included a pacemaker for supraventricular tachycardia, a child requiring coiling for a patent ductus arteriosus (PDA), repair for atrial septal defect (ASD), and one child had Tetralogy of Fallot with associated surgical interventions. We also found left ventricular cardiomyopathy including one patient with this diagnosis at only 2 years of age, mitral value regurgitation, and aortic sinus dilation. Aside from the patient with Tetralogy of Fallot, there were no other patients with reported pulmonary stenosis.

Brain MRI findings also varied. The most common finding (12 patients, 50%) was hypoplasia/aplasia of the corpus callosum; 10 of these were patients with 8p Invdupdel. We also had 3 patients with ventriculomegaly. Overall, 80% of patients had brain abnormalities on MRI (92% in the Invdupdel group). In addition to changes in the corpus callosum, fewer patients also had hydrocephalus/ventriculomegaly, cerebral atrophy, and other changes. This patient cohort has three patients with ventriculomegaly on brain imaging. Cortical Visual Impairment (CVI) was diagnosed in 7 of the 24 (29%) patients. 54% had sleep problems noted by caregivers, but no one was diagnosed with sleep apnea.

3.3 | Activities of Daily Living

3.3.1 | Self-Care and Toileting

Twenty of 22 patients (older than 1 year) assisted caregivers with activities of daily living including dressing and hygiene. However, all required caregiver assistance for thoroughness, orientation, and sequencing of self-care tasks. Two patients were able to dress with only verbal cues to stay on task, but all other patients required caregiver support to complete dressing tasks. Eleven of 19 patients (over age 5) used the toilet, but 7 of the 11 patients required assistance with toilet hygiene, clothing management, or had occasional accidents requiring use of diapers for either daytime or nighttime incontinence. Four of the 19 patients were fully toileting independently including hygiene and clothing management; however, toilet training was often completed later than parent expectations. Of the 19 patients, 8 were fully dependent on diapers and caregivers for toileting. Within this group, parents frequently reported their child had difficulty consistently indicating when they needed to go or when their diaper was soiled.

3.3.2 | Feeding

Out of 24 patients, 23 ate entirely by mouth; only 1 was receiving supplemental gastrostomy tube feedings. One patient had previously had a gastrostomy but had since been removed. One patient required thickened liquids for safety with swallowing. Many patients required caregiver assistance for safety with feeding including adapting bite sizes due to decreased oral motor skills to chew and to avoid overstuffing; 5 required oral formula to meet nutritional needs. Many parents adapted eating plans on their own based on their child's skills. Of those who did not, the child often had a swallow study performed. In our sample, only 5 of 24 patients needed a formal radiographic swallow study.

3.3.3 | Mobility

Out of the 21 patients over 2 years whose motor skills were evaluated, 17 were found to ambulate independently, while the remaining 4 used mobility or caregiver aides to walk or move therapeutically. No individuals were reported to master this skill prior to 2 years of age. 36% of patients required adaptive equipment for ambulation, that is, even if independently ambulatory, they would use equipment for walking long distances. Regardless of their use of other assistive devices, most benefited from foot and/or ankle orthoses to provide support and promote optimal foot and lower extremity alignment. Stretching of the plantarflexion muscles was recommended in 41% of independent walkers, to help increase flexibility or reduce tip-toe gait pattern and improve efficiency. In addition to walkers and gait trainers, wheelchairs and adaptive strollers are recommended to promote mobility in the community. These devices were also used given behavioral or safety challenges. While some individuals with 8p developed higher-level gross motor and play skills, such as stair negotiation and hopping, these gains were less common.

3.3.4 | Sensory Processing Affecting Activities of Daily Living

In 20 patients, we had information about sensory processing difficulties. Of the 20, 15 had difficulty with processing sensory information from their environment, frequently with decreased registration of input. These difficulties often result in overstuffing during feeding, difficulty with hygiene activities, and poor body awareness during dressing. These patients also had difficulty with self-regulation during the day requiring assistance from caregivers and external strategies to support self-regulation.

3.4 | Communication

In this sample of patients with Chromosome 8p disorders, the most frequent recommendation from a licensed speech language pathologist was to trial augmented and alternative communication (AAC). AAC refers to any communication strategy to supplement spoken language. Specifically, our patients ranged from non-speaking individuals to total verbal communicators with reduced intelligibility. All patients had deviant speech features outside of typical development and would benefit from strategies to supplement their expressive communication. All 6 individuals with 8p deletion used verbal speech as their primary means of expressive communication. All 14 patients with 8p Invdupdel were recommended to, or were already using an augmented communication device given limited spoken language (e.g., single words, and vocalizations).

TABLE 2 | Mental and behavioral health symptoms or diagnoses 8p genetic type.[a]

Chromosomal change	Average Vineland adaptive behavior composite	Problematic behaviors reported	Irritability	Aggressions towards self or others	ADHD	Obsessions and/or obsessive compulsive disorder	Anxiety
8p Invdupdel ($n=7$)	47	2 (29%)	2 (29%)	1 (14%)	0	0	0
8p Duplication ($n=2$)	71	2 (100%)	2 (100%)	2 (100%)	0	1 (50%)	0
8p Deletion ($n=4$)	56.2	4 (100%)	0	0	2 (50%)	2 (50%)	1 (25%)
8p/8q Unbalanced Translocation ($n=1$)	49	1 (100%)	1 (100%)	1 (100%)	0	1 (100%)	1 (100%)
8p Mosaic Ring ($n=1$)	86	1 (100%)	1 – noted only while on Leviteracetam	0	0	0	0

[a]Data only presented for patients for whom we were able to gather both Neuropsychiatric testing and caregiver reports of behavioral health symptoms/diagnoses.

3.5 | Mental and Behavioral Health

Mental and behavioral health concerns included problematic refusals, Attention-Deficit/Hyperactivity Disorder, Obsessive Compulsive Disorder, anxiety, irritability, aggression, and Speech Apraxia. These are further described by genetic subtype in Table 2. Of note, Table 2 only includes patients for whom we were able to gather both Neuropsychiatric testing and caregiver reports of behavioral health outcomes.

3.6 | Cognitive Development

3.6.1 | 8p InvDupDel

Results in this group revealed the lowest levels of developmental attainment in both performance-based and parent reported measures (Table 3, Figure 1). All children age 5 and over ($n=12$) met criteria for Intellectual Developmental Disorder/Intellectual Disability. While 92% of scores fell in the Exceptionally Low range (Standard Score <70) on the Vineland-3, independence for one child was rated as broadly Low Average. Performance-based testing required use of a non age-appropriate measures for 92% of children (e.g., Mullen scales). Age equivalents for language ranged from 1 to 28-months with a wider range; motor abilities ranged from 8 to 28-months. Age was not a predictor of developmental attainment.

3.6.2 | 8p Deletion

There was a wide range of skills in this group ($n=5$), and again, age was not a predictor of level of cognitive development. Parent report fell in the Below Average range for two children and in the Exceptionally Low range for the remaining three. We were able to give an age-appropriate performance-based measure for one child. Interestingly, for this child, while overall intellectual development was Exceptionally Low (WPPSI-IV FSIQ = 57), language skills were Average (WPPSI-IV VAI = 97). Age equivalents across the group on performance-based measures for language skills ranged from 3 to 7-years old and were also higher on parent report compared to independence in activities of daily living.

3.6.3 | 8p Duplication

We saw only 2 children with this genetic change, and so generalizability is again, limited. Both children were young (ages 1 and 3 years), and so both completed an age-appropriate measure. Overall level of independence as rated by parents was variable as skills were rated as Average for one individual but Exceptionally Low for the other. For the 1-year old, the strongest skills on the performance-based measure were fine motor skills (age-appropriate). Both receptive and gross motor skills were only a few months behind (age-equivalent = 8-months), and expressive language was the weakest skill (5-month-old age equivalent). For the 36-month-old, again expressive language was the weakest skill (3-month-old age-equivalent) followed by fine motor skills (4-month-old age-equivalent), and receptive language (6-month-old age-equivalent). Gross motor skills were the strongest in this child (11-month-old age-equivalent).

TABLE 3 | Overall level of independence: Vineland-3 parent-reported results 8p genetic type.

Chromosomal change	Adaptive behavior composite (mean, median)[a]	Communication (mean, median)[a]	Daily living (mean, median)[a]
8p Invdupdel ($n=12$)	47, 46.5	33, 27	44, 44
8p Duplication ($n=2$)	76, 76	62, 62	100, 100
8p Deletion ($n=5$)	55, 63	59, 70	46, 51
8p/8q Unbalanced Translocation ($n=1$)	49	42	43
8p Mosaic Ring ($n=1$)	86	88	92

[a]Standard Score values: mean = 100, standard deviation = 15.

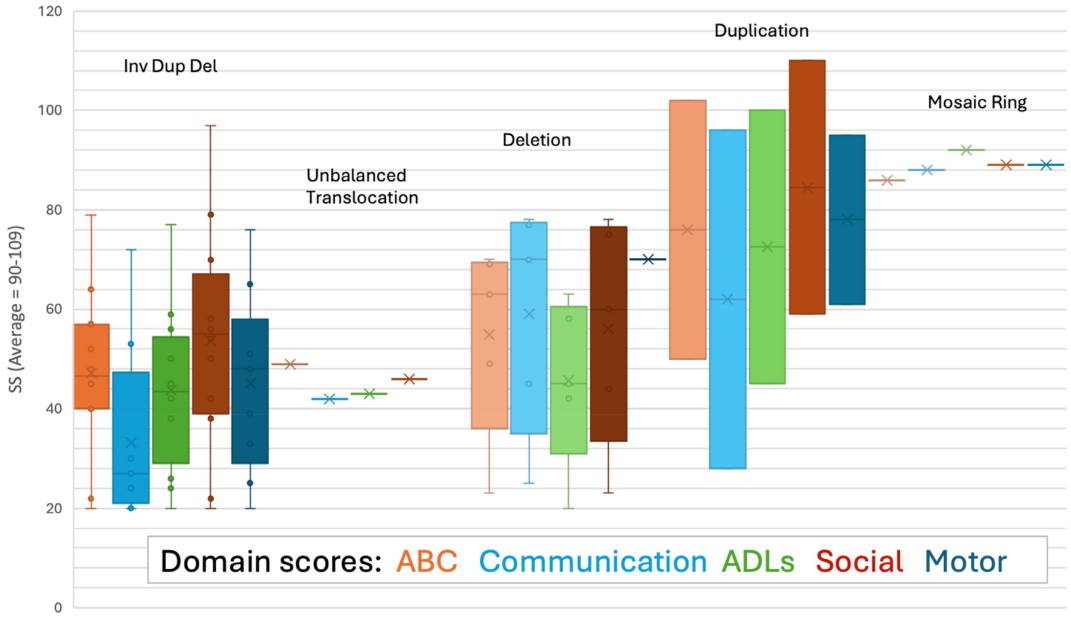

FIGURE 1 | Vineland domain level scores by 8p genetic type. *ABC = Adaptive Behavior Composite. [Colour figure can be viewed at wileyonlinelibrary.com]

3.6.4 | 8p/8q Unbalanced Translocation

We evaluated one patient (chronological age = 18 years) with this genetic change, so generalizability is limited. We were able to give an age-appropriate measure. Vineland-3 parent report revealed level of independence in the Exceptionally Low range in all domains (Adaptive Behavior Composite = 49). Estimate of IQ also fell in the Exceptionally Low range (DAS-2 GCA = 34) with age equivalents around 5 to 6-years-old. Consistent with cognitive estimates, academic skills were also around 5 to 6-years-old. Language and fine motor skills were a bit lower with age equivalents between 4 to 5-years old.

3.6.5 | 8p Mosaic Ring

We again only saw one child (age 32 months) with this genetic change in 8p. Parent report indicated Low Average to Average level of independence (Vineland-3 Adaptive Behavior Composite = 86). Performance-based testing showed only mild delays, with the weakest skills in gross motor (17-month age equivalent) and expressive language skills (20-month age equivalent). Both fine motor and receptive language skills were the strongest at 27-month age equivalent.

4 | Discussion

In this report, we add to the clinical description of Chromosome 8p patients according to their specific chromosomal rearrangement, report neurodevelopmental, and neuropsychological attainment, and propose surveillance care guidelines for caregivers and medical providers of patients with 8p differences. Previous work has attempted to match the specific break points and size of the rearrangements to clinical phenotype and therefore we focused on presenting clinical presentation especially from functional and performance-based testing [2–11]. These clinical care guidelines are novel in this population.

4.1 | Clinical Presentation

Our findings are generally consistent with prior literature with less than half of children having seizures, a high percentage

of children with abnormal brain MRI findings (most common being hypoplasia/aplasia of the corpus callosum), and high rates of cardiac findings [2, 3]. Overall, 80% of patients had brain abnormalities on MRI (92% in the Invdupdel group). As reported by Okur et al., corpus callosum abnormalities were most frequent in 8p patients with the Invdupdel change; this was the most common brain MRI finding in the current patient cohort. Okur et al. also describes this subgroup having high rates of seizure (55% in their series), but which was notably lower (7%) in our series and in Vibert et al. (34%). Our overall rate of any seizure disorder history was 25% which is lower than Okur et al. (48%). CVI was reported in our patients but at a higher prevalence (29%) than was reported by Okur et al. (12%), which may reflect a heavy emphasis on screening and diagnosis of CVI at our center.

A single patient with an 8p deletion in our cohort had an arrythmia that required a pacemaker. Okur et al. suggests evidence of arrythmias in children with 8p imbalances, as supported by our reporting. Left ventricular cardiomyopathy was diagnosed in one patient at 2 years of age, along with mitral value regurgitation and aortic sinus dilation. Four patients required surgical cardiac intervention including the aforementioned pacemaker for arrythmia, PDA coiling, ASD closure, and repairs for Tetralogy of Fallot. The patient with the severe conotruncal malformation sequence was the patient with the unbalanced translocation that shares cytogentic overlap with recombinant 8 syndrome, also known as the San Luis Valley syndrome, but for this patient it did not include GAGTA4 [13, 14]. For this patient, their rearrangement was smaller in size than typical rearrangements in this syndrome. Aside from the patient with Tetralogy of Fallot, there were no other patients with reported pulmonary stenosis, which is different than what was seen in the series by Okur et al. Sleep disorders were prevalent but not associated with sleep apnea.

4.2 | Activities of Daily Living

Activities of daily living are the life activities needed to function in society including bathing, toileting, dressing, feeding, functional mobility, and hygiene. Children with Chromosome 8p often require assistance in order to complete these activities thoroughly due to difficulty with motor planning, lack of initiation, decreased body awareness, and low tone. In addition, most children had developmental delays and many children reported sensory processing disorders which impacted their ADL independence.

4.2.1 | Developmental Supports

Occupational, physical, and speech therapy play an important role for individuals with 8p, due to the helpful impact on functional mobility, activities of daily living, and communication. While interventions are highly dependent on the individual, we recommend focusing on strategies that will assist their navigating and interacting with their environment(s) as independently as possible. Various settings can support their needs along the developmental trajectory, and include early intervention services as well as home-based, school, and outpatient therapies. While ongoing lifelong therapy is not recommended, oversight by these therapeutic disciplines is.

Other more consistent findings include lack of initiation/motor planning, decreased endurance, impaired body awareness, high pain tolerance, and sensory dysregulation. Regulation strategies and compression garments can help with body awareness and quality of movement to improve participation in activities.

4.3 | Communication

"Will my child speak" is often a pressing question for caregivers of children with Chromosome 8p disorders. To address these concerns, speech therapy is recommended to increase communication for individuals with difficulty speaking, understanding, learning, and communicating. To assess for the need for hearing augmentation, a formal evaluation by an audiologist is recommended.

4.4 | Mental and Behavioral Health, Neuropsychology, and Development

Mental and behavioral health concerns were prevalent consistent with prior reports.

Changes in 8p affected development in all children, manifesting in developmental delays with persisting cognitive impairment, and/or challenges in learning, social–emotional and behavioral functioning. Across 8p changes, overall level of independence as rated by parents revealed the highest needs in individuals with 8p Invdupdel followed by our patient with 8p/8q Unbalanced Translocation and then, 8p Deletion, 8p Duplication, and 8p Mosaic Ring.

Interestingly, performance-based testing revealed that age did not necessarily predict developmental level. Children who completed out-of-age measures were generally happy to engage with examiners. Given the wide range of abilities, evaluators should not assume that an individual would require administration of an out-of-age measure; however, clinics should have multiple test options available. Further, psychiatric and/or behavioral difficulties often resulted in lower estimates of level of independence than expected given cognitive level. Ideally, evaluation should not include solely parent report; however, parent report is helpful should questionnaires be the only option. Overall, a child's developmental profile may be driven and maintained by multiple factors.

In terms of mental and behavioral health concerns or diagnoses for our cohort, we found differences based on genetic subtype (noting that our sample size is small). Generalizations were further limited by not having complete data on all patients in terms of behavioral health diagnoses or caregiver impressions. Table 2 summarizes relevant behavioral health diagnoses for those patients for whom we were able to gather both Neuropsychiatric testing and caregiver reports of behavioral health outcomes.

4.5 | Limitations

Several limitations must be considered. Our sample is reflective of patients who could access our multidisciplinary clinic. This could be limited due to insurance coverage, location of care,

TABLE 4 | 8p clinical care recommendations.

Neurological	• Electroencephalogram (EEG) if seizures are suspected. • MRI brain (without contrast) to evaluate for brain malformations if seizures are present, if head circumference is not progressing steadily, or if there are focal abnormalities on the neurologic exam prior to age 3. • Screening MRI brain after age 3 in the absence of focal findings.
Cardiovascular	• Cardiology referral for consideration of echocardiogram (ECHO) to assess congenital heart disease and electrocardiogram (ECG) for arrhythmia assessment.
Oral Health	• Routine dental care every 3 to 6 months [2].
Musculoskeletal	• Assess for scoliosis clinically. Image with plain X-rays if concerns [2].
Gastrointestinal	• Many children with 8p may require modified feeds, but often this might not go beyond parent-led food choices. • Assess safety of feeding when clinical concern arises, through clinical feeding evaluation with a trained therapist (a speech or occupational therapist with training in swallowing disorders). • Assess nutritional adequacy, consider nasogastric or gastrostomy tube placement if needed. • Assess for and manage constipation [2].
Genitourinary	• Assessment for undescended testes and hypospadias in males. Refer to urologist as needed [2].
Endocrine	• Assess for short stature and track linear growth at each visit. If linear growth falters and/or if stature < 3% ile, recommend assessment by a pediatric endocrinologist to consider testing and treatment options [2].
Hearing	• Audiologic evaluation with an Audiologist is recommended if speech delay or clinical concerns, rates of hearing loss are not reported as elevated in this population.
Eyes	• Ophthalmologic evaluation annually with an ophthalmologist, specifically requesting a comprehensive examination that includes testing for cortical vision impairment. If present, ensure vision instruction for school, including inclusion of a Teacher for the Visually Impaired providing input in Individualized Education Plan assessments and planning.
Development	• Initiate evaluation for developmental therapies and services including Early Intervention. • Neuropsychological evaluation is recommended serially to guide therapies at periods of transition (preschool, Kindergarten, 2nd grade, 6th grade, 9th grade, 11/12th grade and in the 6 months before the child turns 21.
Mood and Behavior	• Screen or ask about psychiatric or behavioral concerns including ADHD. Evaluation for more severe behavioral issues may be required. Depending on the mood or behavioral issue, screening/evaluation is best completed by a pediatrician, child psychiatrist, developmental pediatrician, child psychologist, or behavioral specialist (or a combination thereof).
Adult Transition	• Begin planning for adult medical and community support needs around age 12 years [18]. • Plan for transition to adult medical providers around age 18–21 years. • Connect with Community Center Board to facilitate benefits access.
Genetics	• Consultation with a clinical geneticist and/or genetic counselor helps the family to understand the diagnosis and consider implications for family planning. • Considering updating testing when the clinical picture does not match the molecular diagnosis or if previous cytogenetic analysis was below the resolution of 180 kb chromosomal oligoarray.

family interest, or awareness of our program. Second, our data is limited by being retrospective and therefore the only information available is what was clinically pertinent to the visit and documented. Retrospective data collection is impacted by bias which is why the data was collected by a team member not involved in the data analysis and interpretation. Further, some patients received care outside of our healthcare system and not all clinical care reports were available to review. Finally, our small sample size limits the generalizability of our findings including for 8p subtypes. We only used our sample to add to the description of patients with 8p including areas not previously reported on such as certain clinical findings, activities of daily living, functional and performance-based testing which all provide an important family-centered perspective previously not published.

4.6 | Proposed Management Guidelines

The era of personalized medicine is upon us. We find ourselves now tasked with delivering well-coordinated, highly specialized care to patients with rare and ultra-rare neurogenetic conditions. Since 2021, Children's Hospital Colorado has conducted visits with patients with Chromosome 8p rearrangements (along with other rare neurogenetic diagnoses) in a Multi-Disciplinary Clinic

format. With a large team of specialists experienced in the care of patients with complex epilepsies and neurodevelopmental disabilities, we can promptly share symptom management guidance with families and their local medical team. Having considered the clinical findings and needs of the 24 patients presented here and the prior relevant literature, we propose these management and surveillance care guidelines for 8p patients (Table 4).

4.6.1 | Growth Assessment

Growth parameters should be obtained at each visit, including length (height if able to stand after age 3) and weight. Prior literature reports short stature is common in this group; however, a plateauing or cessation of growth from the patient's prior percentiles should prompt further evaluation (i.e., for nutritional inadequacy and possible endocrinopathy) [2]. Consider a formal swallowing evaluation if any signs or symptoms of dysphagia or changes in diet are present.

4.6.2 | Imaging

A prior report demonstrated a high prevalence of abnormalities on brain imaging in patients with Chromosome 8p differences [2, 3]. The highest incidence is in hypoplasia or aplasia of the corpus callosum, which was consistent with our findings. We recommend neuroimaging at the point of any focal neurological symptoms, seizures, or evidence of craniomegaly in children under 3 years with 8p differences. If there are neither focal changes nor concerning patterns of head growth, imaging may be deferred until approximately age 3 to reduce the risks of anesthesia and to allow the assessment of complete myelination. Similarly, EEG studies have a high probability of showing abnormalities; however, we would recommend that the timing of this study be based on symptoms or clinical concerns for seizure activity (as management will more depend on clinical symptoms than EEG findings per se).

We recommend a screening echocardiogram at the point of diagnosis to assess for congenital heart malformations given the high incidence of cardiac structural malformations in our population (in agreement with the prior series by Okur et al.).

Regarding the risk of scoliosis, which is high in many populations of patients who have hypotonia and/or atypical ambulation, we recommend clinical screening and observation for signs of significant scoliosis at each visit and if present, imaging with plain x-rays. If significant scoliosis emerges, we recommend consultation with orthopedic specialists. We did not specifically look at scoliosis in this study.

4.6.3 | Other Co-Morbidities

In terms of vision and ophthalmologic needs, we found a rather high incidence of some vision differences, with 7 out of 24 patients having a formal diagnosis of cortical vision impairment, and several others having astigmatism, myopia, strabismus, small optic nerves. Given this heterogeneity combined with overall high incidence of abnormalities and limited ability in this population for patients to complete vision screening tests in the pediatrician's office, we would recommend screening ophthalmologic exam at the point of diagnosis and then ongoing annual assessments by a pediatric ophthalmologist. CVI is undertested even by ophthalmologists so providers should specifically refer for comprehensive exam including CVI testing or refer to ophthalmologists known to perform CVI testing [15, 16].

In male patients, physical exam should carefully evaluate for fully descended testes and the presence of hypospadias. If abnormalities are noted, the patient should consult with a pediatric urologist [2].

We noted sporadic incidence of other medical diagnoses, but at this time, do not have the data to recommend broader screening. We do recommend assessing for mental and behavioral health disorders, though with concurrent developmental delays or intellectual disabilities including communication disorders, traditional screening tools may not identify needs and patients may require a formal evaluation with a provider [4, 17].

As with all populations experiencing a high incidence of developmental differences, we recommend referral to Early Intervention or other developmental support services for all patients at the point of 8p diagnosis. These services should be available in all communities in the United States until age 3 through Early Intervention and thereafter through the public school system through Individualized Education Plans.

Transitioning to Adult Care: As with all chronic medical conditions, particularly for children with intellectual disabilities, the transition from pediatric to adult health care systems is a daunting task for families to navigate. The American Academy of Pediatrics has published guidelines for supporting patients and families as they transition to adult medical care [18]. This process should be discussed early, by age 12 years, and discussed by both primary care and specialty care providers. Discussion should include anticipated medical and community/educational support needs that will extend into adulthood, guardianship and/or supported decision making planning, and financial benefits planning. Connecting with the patient's local Community Center Board is helpful to coordinate disability benefits and adult supports.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Peer Review

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