Case Report

Early pediatric palliative care involvement in a child with a large deletion of the short arm (p) of chromosome 10: a case report

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Background: We present a case of a Chinese child with one of the largest terminal deletions (21 Mb) of the short arm of chromosome 10 (10p) reported to date. Distal monosomy 10p is a rare chromosomal disorder characterized by intellectual disability, postnatal growth retardation, structural birth defects and dysmorphisms. Mutations in certain 10p regions have been associated with distinct clinical features, but the real weight of each component cannot be estimated in a large deletion like that of our child; therefore, long-term prognosis is difficult to predict precisely, although it certainly foresees a severe impact on the psychomotor development of the child.

Case Description: Diagnosis was made in the early neonatal period because of several dysmorphic features and multiple organ involvement. Since the patient's care needs were complex, the Pediatric Palliative Care (PPC) and Pain Service team was involved as a case manager and coordinator from the beginning. In the Veneto region of Italy, our PPC center offers a palliative care approach, through the national health system, embedded with curative-restorative care providing many support activities (such as physiotherapy, physiological support and home assistance) valuable for patients and their families' quality of life. Despite overlap in many characteristics of our child and other children who receive PPC services, the experience of children who have rare genetic conditions and undetermined prognosis with PPC services is still largely unknown. Periodic hospitalization for multidisciplinary follow-up and reassessment of patient's needs were arranged and any rehabilitation program focused on improving her skills was followed. At 5 years of age, her medical condition is controlled and well managed.

Conclusions: This case represents a good example of complex care management by the PPC team, which takes into account the patient's and family's needs enhancing their quality of lives, as reported and underlined by parents themselves. This approach could be considered for other children with rare medical conditions without a definite prognosis.

Keywords: Chromosome 10 deletions; genetics; palliative care; case report

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Introduction

Distal monosomy 10p is a rare chromosomal disorder due to the deletion of the terminal portion of the short arm of chromosome 10; the phenotype varies according to the size of the chromosomal loss, but is usually characterized by intellectual disability, postnatal growth retardation, structural birth defects and dysmorphisms (1-3).

Specifically, 10p15.3 deletions involving *ZMYND11* gene cause a syndrome characterized by neurodevelopmental disorder, hypotonia, seizures and craniofacial dysmorphisms (4,5); 10p14 deletions involving *GATA3* gene are typically associated with varying degrees of Hypoparathyroidism, sensorineural Deafness and Renal disease (the HDR syndrome; OMIM#146255, also known as Barakat syndrome) (6,7), while more centromeric deletions, in the DiGeorge syndrome type 2 (DGS2) locus, are responsible for a phenotype resembling DiGeorge syndrome (2). Information about prognosis has been described only in the HDR syndrome. We present a new case of approximately 21 Mb 10p terminal deletion which encompasses all the above-mentioned critical regions in a Chinese child, who had been referred to our regional Pediatric Palliative Care (PPC) and Pain Service, in Veneto region of Italy, at 2 months of life. Our PPC center offers children with complex chronic conditions (CCCs) (8) a palliative care approach combined with curative-restorative care and provides coordination between the specialist teams involved. Our in and outpatient service has supported more than 800 families over the past 15 years, providing medical, psychological and nursing home care, a dedicated sub-intensive ward for acute conditions and a pain service for the management of acute, procedural and chronic pain.

Through this experience, which reflects parents' and clinicians' point of view, we want to highlight how early access to the PPC program for children affected by complex genetic diseases without a definite prognosis may positively impact their quality of life (QoL) and parental satisfaction. We present the following case in accordance with the CARE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-356/rc).

Case presentation

Our patient is the second female child born to Chinese, healthy, non-consanguineous parents who presented with a complex medical condition since birth due to a large chromosome deletion.

Prenatal ultrasound was significant for intrauterine growth restriction and polyhydramnios but no further prenatal genetic testing was done. She was born at 37 gestational weeks and was admitted to the Neonatal Intensive Care Unit for respiratory distress and received non-invasive ventilation. Anthropometric birth measurements were: weight 2,120 g (<3rd centile), length 46.5 cm (10th–25th centile), head circumference 32 cm (10th–25th centile). Dysmorphic features were noted during the first physical examination including small palpebral fissures, left blepharophimosis, malar hypoplasia, small mouth with thin lips, small, low-set and posteriorly rotated ears, preauricular pits, crumpled helices and camptodactyly of the 5th fingers. Anterior anus displacement was also detected. During the first few days, for difficulties in feeding and failure to thrive, a nasogastric tube was placed and a complete cardiological assessment was performed revealing a subaortic ventricular septal defect (VSD), patent foramen ovale (PFO) and hypoplasia of the pulmonary valve. Laboratory investigations detected hypoparathyroidism. Abdominal ultrasound revealed mild left hydroureteronephrosis, but no other renal anomalies. Head ultrasonography showed a large cavum septum pellucidum and hyperechogenic halo about the lateral ventricles, confirmed by magnetic resonance imaging (MRI) scan. No diffusion-weighted signal abnormalities were detected. Ophthalmological assessment revealed bilateral retinal hemorrhages and amplitude reduction in left eye visual evoked potentials. Evoked otoacoustic emissions (EOAEs) were absent and the auditory brainstem response (ABR) test didn't record any peripheral and central activity at a stimulus level of 90 dBnHL. Muscular hypotonia, mainly axial, and psychomotor retardation were observed from the first month. In view of all these clinical findings, standard karyotype analysis was performed and a large terminal deletion of 10p, with a breakpoint in band 10p12, was detected. The array-CGH analysis confirmed the presence of a single copy terminal loss of 10p spanning approximately 21 Mb and breakpoint in band 10p12.31 {46,XX,del[10]p12.arr[GRCh37] 10p15.3p12.31(136361_21057840)×1 dn}. No chromosomal anomalies involving chromosome 10 were identified in her parents. At 2 months, the child was admitted to our tertiary care hospital to undergo heart surgery. Complementary dysphagia workup confirmed swallowing difficulties and diagnosed major reflux, then a percutaneous endoscopic gastrostomy (PEG) tube and a Nissen fundoplication were performed. Since the patient's care needs were complex, the PPC and Pain Service team was involved as a key coordinator in the Pediatric Department from

the first month. The team's initial task was to organize community discharge in preparation for the postponed cardiac surgery, in order to give her the possibility to gain weight and decrease the risk related to the surgery. At this point the native family, after giving the consent to the surgery, faced the difficulties in the long-term management of a child with a life-limiting condition without a definite prognosis, severe global developmental delay and difficulties in feeding. Despite the support offered, they decided to place the child in foster care. The PPC team represented a reference point for clinical decision-making processes from native family to foster care one especially on pertinence of invasive interventions. Adoptive parents received appropriate training for the management of medications and feeding pumps. Periodic hospitalizations for multidisciplinary follow-up and reassessment of patient's needs were arranged. The PPC team supported foster parents who embraced palliative care as a first choice from the beginning, including any physical therapy focused on improving the child's skills. Foster parents, aware of the undetermined prognosis, expressed their wish not to expose the child to further invasive interventions but to focus on her QoL.

From 6 months of age, she started physiotherapy twice a week in a physiotherapy center. Cardiac surgery for VSD patch closure and PFO closure was performed at 12 months and during the operation thymic hypoplasia was detected. The pulmonary hypertension residual from the surgery required oxygen for the following 24 months. At 18 months of age the physiotherapy sessions were suspended during the summer period, as the patient didn't tolerate heat and her parents had the impression that muscle hypotonia was worsening. At 24 months she was put on hearing aids.

At the annual follow-up hospitalization at 5 years, she presented a reduction in the need for regular hospitalization and an increased involvement in the social dimension (kindergarten and activity with peers). These achievements were reached thanks to the adherence to rehabilitation and the efforts done by the foster family. She was 95 cm tall (<1st centile), her weight was 9.9 kg (<1st centile) and head circumference was 45 cm (<1st centile). Neurological evaluation still showed a severe global psychomotor retardation. Spontaneous movements were still mainly jerky, and no fine motor skill was developed. However, muscular hypotonia had improved and some motor milestones were achieved (even if later in life): she was able to sit with support and walk with a medial walker for a few months, she started to slither but no crawling, she transferred objects between hands and to the mouth, she attended regularly the kindergarten, and enjoyed her peers. She also presented great difficulties in expressive speech but, thanks to weekly speech therapy starting from 3.5 years, she was able to communicate disappointment, pain or distress using augmentative and alternative communication. Last otorhinolaryngologic evaluation confirmed profound hearing loss with a conductive component due to bilateral auditory canal stenosis. Follow-up assessments showed good kidney and heart functions, normal electrolytes levels, but revealed hyperuricemia so allopurinol 10 mg/kg per day was started. From 2 months of age, she was fed exclusively through PEG and she didn't take any food or drink orally. Dysphagia workout was performed and she swallowed small amounts of semi-solid food without any complication, so a program of oral rehabilitation and reeducation was considered and started, in order to enhance the pleasure of eating (*Table 1*).

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was taken from the patient's foster parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Geneticist's perspective

This case describes the clinical picture of a child with one of the largest 10p deletions reported to date and highlights main clinical issues and challenges over time related to a rare chromosomal abnormality with complex phenotype.

While several correlations between specific 10p regions and peculiar clinical features have been proposed (1-7), the rarity of these disorders and the paucity of a systematic follow-up and reassessment of patients' needs throughout years makes it difficult to establish specific long-term outcomes and life-expectancy. Information about prognosis has been reported only for patients with Barakat syndrome, according to the degree of renal insufficiency (6). The large deletion observed in our proband involves more than 200 genes including those related to HDR, DiGeorge type 2 and 10p15.3 deletion syndromes. Our child shows a HDR phenotype with DGS2 and 10p15.3 deletion syndromes features including hypoparathyroidism, hearing loss, vesicoureteral reflux (VUR), cardiac anomalies, thymus

Table 1 Timeline of clinical evolution from birth to 5 years of age accordingly to the different systems, social and rehabilitation interventions

Aspect involved	Period of life				
	Birth to 5 months	6 months	12 months	2 years	5 years
Setting of care	Hospital	Hospital	Hospital	Home	Home
Cardiovascular	Diagnosis of subaortic VSD with PFO and hypoplasia of the pulmonary valve	Clinical stability	Corrective heart surgery Residual mPAP	Oxygen support to keep mPAP within normal range	No oxygen support Normal mPAP
Respiratory	No support needed	Occasional nocturnal desaturations	Frequent infections requiring non-invasive ventilation	No respiratory support	No respiratory support
Gastrointestinal	Oral feeding difficulties, poor weight gain PEG and Nissen fundoplication	Poor weight gain (<3rd %centile)	Poor weight gain (<3rd %centile)	Poor weight gain (<3rd %centile)	Poor weight gain (<3rd %centile) Fed by PEG + test meals (pleasure)
Genitourinary	Urosepsis	VUR grade III/ IV → antibiotic prophylaxis	Antibiotic prophylaxis, no acute infections	Antibiotic prophylaxis, no acute infections	Antibiotic prophylaxis, no acute infections
Metabolic	Hypoparathyroidism Calcium and Vitamin D Supplemental	Clinical stability	Severe hypocalcemia requiring ev supplemental	Oral supplementation No acute decompensation	Oral supplementation No acute decompensation
Neurologic	Ultrasound: large cavum septum pellucidum and hyperechogenic halo about the lateral ventricles. No MRI abnormalities	Muscular hypotonia and psychomotor retardation	Muscular hypotonia and psychomotor retardation	Improved muscular hypotonia, psychomotor retardation	She is able to walk with a medial walker and to sit down, psychomotor retardation
ENT/speech	EOAEs were absent and ABR test didn't recorded any peripheral and central activity	Oral feeding and swallowing difficulties	Clinical stability	Hearing aids Augmentative and alternative communication	Training for swallowing Hearing aids Augmentative and alternative communication training
Social	Neonatal intensive care unit; hospitalizations	Custody	Foster family	Foster family and kindergarten	Foster family and kindergarten
Rehabilitation interventions	–	–	Intensive physiotherapy 2–3 times/week	Intensive motor physiotherapy twice/week	Intensive motor physiotherapy twice/week Augmentative and alternative communication therapy once/week Logopedic training for swallowing

ENT, ear, nose, and throat; VSD, ventricular septal defect; PFO, patent foramen ovale; mPAP, mean pulmonary artery pressure; PEG, percutaneous endoscopic gastrostomy; VUR, vesicoureteral reflux; ev, endovenous; MRI, magnetic resonance imaging; EOAEs, evoked otoacoustic emissions; ABR, auditory brainstem response.

hypoplasia, dysmorphisms, cognitive disability and language delay. However, the real weight of each component cannot be estimated in a large deletion like that of our child. In 2009 Benetti *et al.* (9), reported one similarly large deletion of the short arm of chromosome 10 (p12.1-pter) detected by a high resolution cytogenetic analysis in a girl with hypodysplastic kidneys, bilateral grade 3 VUR, deafness, facial dysmorphisms and mental retardation. Unlike our patient, the girl did not present the clinical features of DGS2. In 2017, Kim *et al.* described a female infant with the most similar 10p deletion (16 Mb) to our child detected by microarray analysis, who presented with craniofacial dysmorphisms, genitourinary and cardiac anomalies, hypoparathyroidism, hearing loss, thymus hypoplasia and relatively small kidneys (10). For both cases, no long-term follow-up was reported.

It is clear that planning a care pathway is more difficult when prognosis is unknown and when the child has complex care needs. The decision to refer this child to the PPC service, regardless the prognostic uncertainty, was based on specific eligibility criteria recently developed with the ACCAPED (Accertamento dei bisogni Clinico-Assistenziali Complessi in PEDiatria; assessment of complex clinical-care needs in pediatrics), a tool which helps PPC providers to recruit children with rare and often poorly understood diseases (11). In our clinical practice, the use of this tool is very effective in order to individuate patients with CCCs (8) who can benefit from a PPC support. The result of this evaluation is also discussed in multidisciplinary meetings with all the subspecialists involved in order to plan and define the goals of care for each eligible child.

Limited experience of PPC with children affected by complex genetic disease is reported in literature (12-14), but a closer collaboration among genetic and PPC services is suitable, in order to maintain an ongoing consistent discussion about the goals of care.

Pediatric palliativist clinician's perspective

Neurodevelopmental delay and feeding difficulties represent the major aspects that impacted patient's and parents' QoL. The recent improvements in swallowing encourage continuing the physiotherapy and exercises for speech and oral dysphagia provided within community care, as long as this is accepted and beneficial for the child.

Children with genetic conditions usually have more than one team or clinic that follows them. However, there is often a lack of support system for parents or siblings provided in an ongoing, organized fashion, and families may feel highly isolated. Some studies suggest that families appreciate a "diagnosis" even when it does not lead to any treatment (15,16). Since our patient was referred to the PPC service, the PPC team provided her family the adequate support to face the resulting complexity in making decisions (11). Parents were always actively involved in clinical decision processes, contributing to create a positive therapeutic alliance necessary to provide the best QoL for them and their child (17). The support in treatment decision-making processes was tightly imbricated with an ongoing care addressing even minor daily problems or choices.

The PPC team is often recognized by parents and different subspecialists as the true "case manager" of children with CCCs, having the role of coordination through the hospital follow-up and home care needs, including social, psychological, ethical and spiritual support, if needed. This is why PPC teams have an added value in the care of these children (14,16,17). Furthermore, to ensure continuity of care, regular meetings are held with all the figures involved, whenever necessary.

The importance of providing such comprehensive care is also emphasized by the American Academy of Pediatrics (18) and this is particularly true for rare genetic conditions as the disease trajectory is often unknown. More than 20 million children are estimated to be eligible for PPC worldwide and this number is expected to increase over the next decade, resulting in intensive healthcare use (19,20). In Italy, Benini *et al.* estimated the actual prevalence of children with PPC needs is 34–54 per 100,000 inhabitants of any age, accounting for a total of 20,540–32,864 children (20). In this perspective, promoting the integration of the PPC into the healthcare systems may help reduce the pressure on it and improve the resources allocation (21). We therefore feel the importance to embed very early palliative care in curative-restorative care to enhance patients and parent's QoL. Acting as case manager and coordinator of multiple subspecialties teams together with the availability of nurses and doctors 24/7 is the key of the PPC team's job.

Parents' perspective

Foster father: "Our adopted daughter introduced us to a world we didn't know, but taught us to face life in small steps. She makes you taste any moment, the small progress she achieves and we fix them in our mind. The beauty of dealing with the PPC team is having someone who takes the little one in hand at 360°. The PPC team is a sort of "glue"

among the various departments of the Pediatric Hospital".

Foster mother: "The PPC team helped me particularly in giving a certain lightness to handicap, difficulty, suffering. I found an environment very warm, very close and that helped me to stay closer to her with naturalness, without panic and fear. We always found incredible helpfulness even when we called at night. We don't know where we are going exactly but we know that we are not alone".

Conclusions

Our patient's foster family also welcomed other children with disabilities and complex genetic conditions after her arrival. They felt supported and strengthened in this decision thanks to the integrative approach of our center. Parents' thoughts are at the core of our work: single coordination between specialist teams and continuity of patients' care, even at home and at any time, daily assessment of treatment goals and the life project of the child together with his family. All these aspects, as part of a holistic approach, are important in helping children reach their potential. We also want to highlight the importance of patient future follow-up since no data about outcomes in children with large 10p deletions are available.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-356/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-356/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was taken from the patient's foster parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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